Bifunctional Activation of Methane by Bioinspired Transition Metal Complexes. A Simple Methane Protease Model

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Introduction

Methane, the primary component of natural gas, is an abundant domestic hydrocarbon feedstock. In addition to its use in power generation and home heating, methane is a tremendous resource as a C_1 feedstock for value-added chemicals, especially liquids such as methanol that are more easily transportable for so-called remote or stranded gas formations.[1] Given the current bounty of methane due to advances in extraction technology, the search for efficient routes to upgrading of methane – as well as other light alkanes found in natural gas – has garnered considerable interest in the catalysis community.[2]

As a substrate for catalysis, methane offers many well-known challenges. It is a small, symmetric molecule with no lone pairs. Its C–H bonds are apolar and both thermodynamically strong[3] as well as kinetically inert. With a pKa value estimated to be ~ 50 - 55,[4] methane is an extremely poor Brønsted-Lowry acid. It is also very poor base with a high ionization potential of ~12.6 eV.[5] Researchers have shown, however, that superacids and superbases can react with methane and other light alkanes. Most notable among these are the efforts of Olah and coworkers with conjugate superacids[6] and the Streitwieser group with alkali metal amide superbases.[4] However, in general, the reactivity of "super" systems with alkanes has been largely confined to stoichiometric rather than catalytic transformations.

Nature uses cooperative acid-base interactions to amplify the reactivity of weak acids, for example, as in cysteine and serine proteases.[7] In such enzymes, a functionality such as a histidine-aspartate (H-D) is utilized to effectively reduce the pKa of S–H and O–H bonds, respectively, making them more available for further reactivity. Valence bond calculations by Raimondi *et al.* suggest a significant contribution to the ground state of methane from so-called bi-ionic resonance structures, *e.g.*, (H—)$_2$C(H$^+$)(H$^-$).[8] Nazemi and Cundari have reported the computational machinery — DFT reinforced by high-accuracy composite *ab initio* methods - for calculating pKa(C—H) as a descriptor for the intrinsic acid/base properties of hydrocarbon/hydrocarbyl C—H bonds within an organometallic milieu.[9,10] Their research borrowed heavily from pioneering work by Ho and Coote[11] on weak, organic carbon acids. In other work in our laboratory, modeling — density functional and high-level *ab initio* theory (complete basis set/CCSD(T) methods) — demonstrate that ligation of hydrocarbon and hydrocarbyl C—H bonds within the coordination sphere of a metal can greatly impact the acid/base properties of even apolar methane and methyl C—H bonds.[12,13] Moreover, preliminary evidence from our lab suggests that both metal (M) identity and supporting ligand (L_n) donor/acceptor properties greatly affect the pKa(C—H) of methane in weakly bound σ-complexes.[13] The same factors, M and L_n, also greatly influence the pKa of C—H bonds of methyl complexes that would be formed upon initial metal-mediated activation of methane. [12] Indeed, M and L_n effects upon methane/methyl pKa(C—H) values are commensurate with, if not greater, than well-known inductive and resonance effects in organic acids.

Given the foregoing precedents it was hypothesized whether it should be possible to effect cooperative, bifunctional activation of methane. Of course, the C—H bond in methane has an estimated pKa of ~50 — 55, a far cry from the titratable side chain of serine (pKa(O—H) ~ 10) and cysteine (pKa(S—H) ~ 8)). Hence, a model His-Asp (H-D) dyad is utilized as a base to deprotonate methane; a metal complex acts as a Lewis acid to capture in the unstable methyl anion formed in this reaction. To this end, the impact of metal, supporting ligand and H-D modification upon the barriers for methane activation by this simple "methane protease" model was studied. Preliminary results are reported herein.

Computational Methods

The Gaussian 16 code[14] was used for quantum chemical calculations. Initial optimizations and evaluations of conformations were carried out using the LSDA functional in conjunction with the 6-31G(d) basis set. All optimizations were carried out with continuum solvent effects incorporated via the SMD[15] model. To mimic a polar, but not inordinately so, enzyme active site, acetone (ε ~ 20) was chosen. The optimized geometries obtained at the LSDA/6-31G(d) level of theory were then refined with the ωB97xD functional[16] and a larger 6-31+G(d) basis set. The reported energetics assume a temperature of 298.15 K and 1 atm, and entropic and enthalpic corrections utilized unscaled vibrational frequencies determined at the ωB97xD/6-31+G(d) level of theory. All species were characterized via the computation of their energy Hessian; note that the weakly bound nature of these bifunctional activators led to, in a few cases, to extra small imaginary frequencies. Previous experience suggests such cases typically impact computed enthalpies by 1 kcal/mol or less. For these reasons and given the sensitivity of the entropic correction to the lowest vibrational modes, which can be decidedly anharmonic, we focused on enthalpic barriers in this research given our goal was to study trends among highly related models.

Results and Discussion

A representative transition state (TS) for bifunctional methane activation is depicted in **Figure 1.** As we sought to compare and contrast Earth abundant, divalent 3d metal ions from the later portion of the transition series, a mixed N_2S motif was selected for the present calculations, as opposed to alternatives with harder or softer ligand sets. The active site C--H (1.33 Å) and N--H (1.38 Å) bonds are both significantly stretched from typical covalent ground state values, ~20% and ~40%, respectively, implicating a TS that is somewhat "early" on the reaction coordinate for methane activation Furthermore, the optimized bond lengths of the O--H--N hydrogen bond, **Figure 1**, suggest that H-D is better described a carboxylic acid/imidazolate as opposed to a carboxylate/imidazole tautomer.

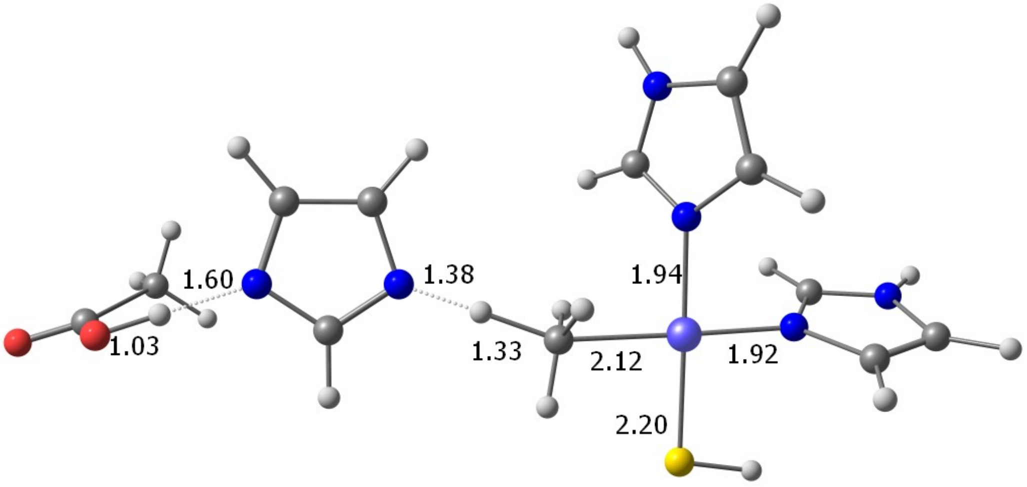

Figure 1. Representative ωB97xD/6-31+G(d)-optimized transition state – singlet spin state - for bifunctional methane activation by a $[Ni^{II}(imidazole)_2(SH)]^+$ and a model $[H\text{-}D]^-$ base. Pertinent bond lengths are quoted in Angstrom units. Carbon = gray; hydrogen = white; oxygen = red; nitrogen = blue.

The baseline system in **Figure 1** has a computed enthalpic barrier ($\Delta H^{\#}$) of 37.3 kcal/mol relative to separated methane, the H-D anion and a cationic aqua precursor complex, $[Ni(N_2S)(OH_2)]^+$. This is a high barrier, but more important for the present study is to investigate how the enthalpic barriers for methane activation by the above model would change as a function of the various chemical components, *viz* the metal ion (M = Fe^{II}, Co^{II}, Ni^{II}, Cu^{II} or Zn^{II}), the coordination geometry at the metal (*e.g.*, a *cis* versus *trans* arrangement of the imidazole ligands), or the substituents on the H-D base (H → F replacements were investigated).

The Impact of Metal Identity and Coordination Geometry

Taking the baseline system in **Figure 1**, variants in which all of the M^{II} ions from iron through zinc were evaluated to see how this impacted the barrier to methane activation. All plausible spin states were evaluated at the ωB97xD/6-31+G(d) level of theory. Results in **Table 1** are with respect to the lowest spin states found for the pertinent stationary states.

Table 1. Bifunctional Methane Activation by $[M(N_2S)(OH_2)]^+$ Lewis Acids and a Model Histidine-Aspartate Base[a]

Metal	**$\Delta H^{\#}$ (kcal/mol)**
Co^{II}	30.5
Ni^{II}	37.3 (cis), 35.9 (trans)
Cu^{II}	32.4 (cis), 33.1 (trans)
Zn^{II}	31.4 (cis), 32.3 (trans)

[a] See **Figure 1** for the structure of the activating complex. *Cis* and *trans* refer to the relative orientation of the imidazole ligands on the activating metal complex, although for metal ions whose coordination geometry is closer to tetrahedral, these are better described as conformational rather than geometric isomers.

From the results in **Table 1**, it is obvious that the metal has a major impact on the barrier to C–H activation, ranging from a low of 30.5 kcal/mol for Co^{II} to a high of 37.3 kcal/mol for Ni^{II} when the imidazole ligands are in a *cis* arrangement. Intriguingly, the trend is not monotonic from iron to zinc. Attempts to find simple descriptors such as ionic radii, covalent radii, *etc*. to explain these trends are underway. One obvious metric, the strength of the M—CH3 bond being formed does not correlate with the computed ΔH$^{\#}$, at least insofar as the gas-phase metal-carbon bond energies reported by Armentrout and co-workers for $[M—CH_3]^+$ are any indication.

The data in **Table 1** indicate that the disposition of the ligands about the metal, and hence their position relative to the N--H--C--M active site play a secondary role in determining the barrier to methane activation. In the *cis* complexes, one of the imidazole ligands is *trans* to the N--H--C--M catalytic active site, while for the *trans* geometric isomer, the thiolate ligand is *trans* to the catalytic active site. For several of the ions, the coordination geometry at the metal is intermediate between tetrahedral and square planar exemplars, so the assignment of geometric isomers using the labels *cis* and *trans* is more nebulous in those cases. Overall, re-orientation of the metal coordination sphere has a calculated impact on ΔH$^{\#}$ of *ca.* ±1 kcal/mol. For the metal ions in **Table 1**, the metal impact on ΔH$^{\#}$ of roughly ±3 kcal/mol.

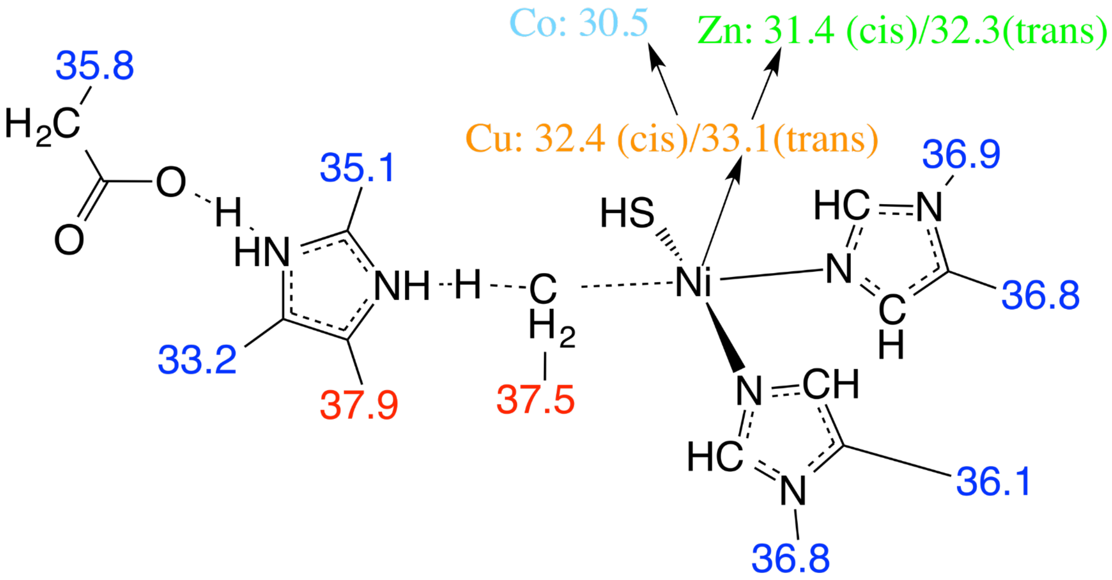

Figure 2. Changes show the computed enthalpic barrier (in kcal/mol) at STP to methane activation when a particular H is replaced by a F. The "baseline" per-protiated system has a computed ΔH$^{\#}$ = 37.3 kcal/mol. ωB97xd/6-311++G(d,p)/SMD-acetone. Red = higher than baseline; blue = lower than baseline. Note: Moving the imidazolate from cis to trans configuration yields ΔH$^{\#}$ = 35.9 kcal/mol. Per-protiated copper version in bronze; zinc in green; cobalt in light blue.

The Impact of Substituent Modifications to the H-D Base

To assess the sensitivity of the enthalpic barriers for bifunctional methane activation to modification of the basic (H-D) and acidic (metal complex) components, it was decided to take the parent complex and systematically substitute H with F atoms. This choice was motivated by making changes that would not introduce additional conformational complexity and for which steric considerations would not be expected to override electronic factors, such as the intrinsic acidity of $M(N_2S)$ or the basicity of H-D. For these same reasons, we did not fluorinate the C–H bonds that flank the ligating nitrogen of the imidazole ligands. Ni^{II} was chosen as the metal ion for these studies to see if such modifications could reduce its relatively high barrier to methane activation. The results are summarized in **Figure 2.**

Several interesting observations in regard to the sensitivity of this simple bifunctional methane activator emerge from **Figure 2.** Most of the H→F modifications serve to lower the barrier to methane activation (blue text in **Figure 2**). Only fluorination of the substrate ($CH_4 \rightarrow CH_3F$) or one of the C–H bonds proximal to the basic N raises the barrier (red text in **Figure 2**) versus the baseline Ni^{II} system, and in these cases by only 0.2 and 0.6 kcal/mol, respectively. In fact, most of the "organic" modifications have a much more modest than the "inorganic" modifications, with the impact on $\Delta H^{\#}$ computed to be a range of ± 1 - 2 kcal/mol relative to the baseline per-protiated system.

One notable set of calculations comes from changing the H on the imidazole of the model H-D. Fluorinating the C–H that resides between the two nitrogens yields $\Delta H^{\#}$ = 35.1 kcal/mol. This is contrasted by fluorination of the other imidazole C–H bond that is proximal to the active site, calculated $\Delta H^{\#}$ = 37.9 kcal/mol, which is the <u>highest</u> barrier for this set of models by more than 1 kcal/mol. Changing the C–H distal to the active site to C–F yields the <u>lowest</u> barrier, $\Delta H^{\#}$ = 33.2 kcal/mol, which is lower than any other mono-fluorinated Ni(II) model by nearly 2 kcal/mol. Since these are isomeric transition states that differ little in conformation and geometry, it is reasonable to assume that the relative energetic differences are meaningful. As such, they point to the ability to tailor the activity of such bifunctional activators through judicious modification of substituents. Whether the origin of this effect is steric and/or electronic is not clear.

Summary, Conclusions and Prospectus

Reported herein are calculations of simple bifunctional methane activators. The models chosen couple a histidine-aspartate (H-D) base to formally deprotonate methane, and several metal motifs acting as the Lewis acid to capture the methyl anion. These acid and base motifs are chosen as simple models of entities one might find within the active site of an enzyme. Several interesting conclusions have been reached as a results of this research, which are summarized here.

- The impact of the metal among the late 3d metal M^{II} ions is quite pronounced with a range of ~7 kcal/mol from Co^{II} on the low end to Ni^{II} at the high end. For the models tested, the metal ion has the greatest impact on the computed enthalpic barriers to methane activation.
- Alteration of the metal's coordination environment – without changing the supporting ligand types – for example, comparing *cis* and *trans* coordination isomers, has an impact on the barriers to methane activation of *ca.* ± 1 kcal/mol.
- The impact of metal coordination environment upon methane activation barriers is commensurate with modification of the supporting ligand substituents. In the present research, fluorination of N–H and C–H bonds was utilized as a simple probe of electronic effects so as not to introduce overriding steric factors into the modulation of the transition state energies. Surprisingly, changing the substrate from CH_4 to CH_3F (thus, a spectator H is replaced with F) raised the barrier by only 0.2 kcal/mol versus methane. Fluoromethane has a homolytic C–H bond dissociation enthalpy (BDE) of 107.4 kcal/mol slightly stronger than the 105.0 kcal/mol BDE measured for methane. The pKa of methane is estimated at roughly 50 – 55; utilizing the published recipe for pKa(C–H) in DMSO, we estimate pKa(C–H) ~ 51 for methane while that for fluoromethane is modestly more acidic, pKa(C–H) ~ 48½. The small difference in calculated $\Delta H^{\#}$ for methane vs. fluoromethane may imply a more modest degree of charge build-up than one may have supposed on the active hydrogen of the methane C–H bond being activated in these model transition states.
- One extremely interesting result involves the varying impact of fluorination of the imidazole, which serves as a simple mimic of the side chain of histidine. Sequentially fluorinating the 3 C–H bonds of imidazole produces a range in the calculated $\Delta H^{\#}$ of ~4½, an effect greater than any other modeled herein apart from the impact of changing the central metal ion of the active site. Our initial hypothesis is that these fluorination is changing the intrinsic basicity of the resulting H-D base, and on this way modulating the barrier to methane activation.

The present computations on a simple bifunctional model provide some insight into novel, bioinspired methane activators. This research suggests that the relative impact follows the trend: M ion > H-D base substitution ~ M coordination geometry > L_n substitution. While promising, the barriers computed here are still quite high, especially when taking into consideration the entropic penalty expected for the modeled termolecular reaction. In a protein or peptide assembly one would expect some degree of pre-organization to partially mitigate this penalty. Additionally, the present simulations utilized a relatively polar active site, while other calculations suggest that the enthalpic barriers such as these are significantly reduced in a more hydrophobic environment. Current work is focused on making more significant modification to the supporting ligands of the Lewis acidic metal as well as the base.

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