On the Variability of Ligand pK_a during Homogeneously Catalyzed Aqueous Methanol Dehydrogenation

Nitish Govindarajan, Hugo Beks, and Evert Jan Meijer*

Amsterdam Center for Multiscale Modeling and Van 't Hoff Institute for Molecular Sciences, University of Amsterdam, Science Park 904, 1098XH, Amsterdam, The Netherlands

E-mail: e.j.meijer@uva.nl

Abstract

Using DFT based molecular dynamics simulations incorporating explicit water solvent, we elucidate the varying behaviour of the ligand pK_a of a molecular catalyst for methanol dehydrogenation, using the Ru(PNP) catalytic system as a case study. The pK_a of the amido ligand moiety in this catalytic system is highly sensitive to the species adsorbed on the metal center, resulting in a substantial variation of the ligand pK_a along the catalytic cycle. Since the ligand pK_a is an important characteristic that determines the exact role of the ligand during aqueous methanol dehydrogenation, this characteristic has important implications on metalligand cooperative pathways.

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Introduction

Aqueous methanol dehydrogenation that involves the conversion of methanol and water to three equivalents of molecular hydrogen and one equivalent of CO_2 is an attractive method for the storage and transport of molecular hydrogen (H_2) .¹ Recently, several highly active molecular complexes based on both precious metals like Ru, Ir^{2-5} and earth abundant metals like Fe, Mn^{6,7} have been reported for aqueous methanol dehydrogenation under mild conditions. An important example is the Ru(PNP) complex 1 (Scheme 2), that was the first reported molecular complex that could perform methanol dehydrogenation under mild conditions (90 °C, 1 atm) with high activity and selectivity, albeit requiring large amounts of inorganic base (8M KOH) for optimal activity.² Most of these catalysts are commonly assumed to operate via outer-sphere Novori-Morris type mechanisms,^{8–10} involving proton transfer to the ligand moiety and hydride transfer to the metal center in the C-H activation step. Similarly, the cooperative action of the ligand proton and the metal hydride is generally assumed to be involved in H_2 production, resulting in the regeneration of the catalyst and one equivalent of H_2 as shown in Scheme 1a. As aqueous methanol dehydrogenation involves the dehydrogenation of three molecules: methanol (MeOH), methanediol and formic acid (FA), there are three eq. of H_2 generated in the entire reaction, along with the formation of 1 eq. of CO₂. Since the metal (as a hydride acceptor) and the ligand (as an internal acceptor base) act in a cooperative manner in the key steps of the catalytic cycle, metal-ligand cooperativity has been used as an important strategy for the design of active and additive free methanol dehydrogenation catalytic systems.¹¹ However, in recent years computational studies have provided evidence that that metal-ligand cooperativity might not be crucial for some systems.¹²⁻¹⁴

For the Ru(PNP) catalytic system addressed in this work, Meijer and co-workers recently proposed a modified metal-centered mechanism as shown in Scheme 1b in solution owing to the high pK_a of the ligand amido moiety at the associated stage on the catalytic cycle.¹⁵ Due to its high pK_a in solution, the ligand moiety is not directly involved in reversible protonation/deprotonation, and therefore cannot act as an internal acceptor base as proposed in earlier studies.^{16,17} The ligand NH moiety remained protonated throughout the catalytic cycle (1b) and only seemed to interact with the reactive species via hydrogen bonding interactions. This picture is supported by the fact that in the experimental setup, large amounts of a strong base is needed (8M KOH):.^{2,17} The presence of a strong base is required for generating the methoxide (CH_3O^-) species, as there is no deprotonated ligand (N^{-}) acting as an internal acceptor base.



Scheme 1: (a) Commonly proposed Noyori-Morris mechanism for aqueous methanol dehydrogenation. Both the metal (M) as a hydride acceptor and ligand (L) are directly involved in the C-H activation and hydrogen production steps, and (b) revised metal-centered mechanism proposed for the Ru(PNP) complex **1** where the ligand nitrogen stays protonated throughout the catalytic cycle due to its high pK_a . The ligand does not directly participate in the catalytic cycle.

These results suggested that the pK_a of the ligand moiety is an important characteristic, that determines the exact role of the ligand (as an acceptor base/hydrogen bond donor) and the nature of the operating reaction mechanism (metal-centered or Noyori-Morris type). The importance of the ligand pK_a for the nature of the operating mechanism was further substantiated in a more recent study for the [Ru(trop)₂dad] catalytic system.¹⁸

In an earlier study,¹⁵ we computed the pK_a of the ligand moiety for one of the complexes in the Ru(PNP) catalytic system $(1-H_2O^+)$. However, as the species adsorbed on the metal center changes along the various stages of the catalytic cycle (Scheme 2), one can anticipate that the pK_a of the ligand nitrogen moiety will also vary along the catalytic cycle. In view of the previous discussion (*vide supra*), this implies that it is important to quantify this pK_a variation, in order to assess and understand the exact role of the ligand along the various stages of the catalytic cycle.



Scheme 2: Complexes involved during different stages of aqueous methanol dehydrogenation catalyzed by the Ru(PNP) complex 1 including (a) methanol dehydrogenation, (b) formic acid dehydrogenation and (c) hydrogen production. The structure of complex $1-H_2O^+$ is also shown.

Here, we present a computational study using density functional theory based molecular dynamics (DFT-MD) incorporating explicit water solvent. We elucidate a varying nature of the ligand pK_a (ligand- pK_a) along various stages of the catalytic cycle of homogeneous aqueous methanol dehydrogenation, catalyzed by a Ru(PNP) complex 1. The ligand- pK_a appears to be highly sensitive to the species adsorbed on the Ru metal center, that is constantly changing along (various stages of) the catalytic cycle (Scheme 1). Importantly, we argue that the variability of the ligand pK_a has important implications on metal-ligand cooperative pathways, as it is a crucial factor that determines the exact role of the ligand (either as a proton donor/acceptor or as a hydrogen bond donor) during homogeneously catalyzed aqueous methanol dehydrogenation. In addition, the implications of the varying nature of the ligand on the role of external additives are discussed.

Computational Methods

Our setup consists of complexes 1-X, where X = vacant site, OCH₃, HCH₂O, H, H₂, OCHO,

HCOO and H_2O as shown in Scheme 2 explicitly solvated by 156 water molecules a cubic periodic box (L = 16.96 Å). The properties required to compute the ligand pK_a were determined from molecular dynamics trajectories that were generated with Born-Oppenheimer based DFT-MD as implemented in the CP2K package.¹⁹ The DFT electronic structure was computed using the $BLYP^{20,21}$ functional with Grimme's D3²² dispersion corrections, and using the hybrid PBE0 functional supplemented with the D3 dispersion correction. For the latter the ADMM method as implemented in $CP2K^{23}$ was used. The temperature was controlled with a CSVR thermostat²⁴ and set to 360K corresponding to the experimental conditions. Goedecker-Teter-Hutter (GTH) pseudopotentials were used to account for the interactions of the valence electron with the nuclei and core electrons.²⁵ Triple ζ basis sets were used for all atoms except ruthenium, where a double ζ basis set was used. A plane wave cutoff of 280 Ry was used in all calculations. Note that if X = vacant site, H_2 or H_2O the complexes are cationic (charge = +1), while they are neutral in all other cases.

The central quantity of interest for the present study is the ligand pK_a . These were determined from DFT-MD simulations that are outline above. Here it is important to note that the simulations represent a realistic setup incorporating thermal motion and an explicit description of the aqueous solvent. This setup yields true free energies, including both the energetic (enthaplic) and entropic contributions. In this regard, we note that the typical accuracy of using such a model for pK_a estimations is around 1-2 pK_a units.^{26–29}

To determine the pK_a , we employ the insertion-deletion technique (I-D) developed by Sprik and co-workers that combines DFT-MD and thermodynamic integration for the computation of the ligand pK_a of these complexes.^{27,30,31} In the I-D technique, the pK_a is obtained by considering transfer of the proton from the NH-species to aqueous solution in the two separate stages (Figure 1a). In the first step, the free energy associated with removing (deleting) the proton from the ligand

nitrogen is determined. This is implemented by converting the ligand proton (NH) to a (non-interacting) dummy atom (Nd^{-}) . The free energy change is determined by calculating the vertical energy gap (ΔE) along the deletion pathway from DFT-MD trajectories. In the second step, the free energy associated with introducing the proton in the aqueous part of the system that is spatially far away from the catalyst is computed. In line with the deletion step, this is done by inserting a (noninteracting) dummy atom that is converted into a proton. The pK_a value is the difference in the absolute deprotonation free energy for the acid under consideration and the solvated proton (modeled as a H_3O^+). Note that we have used a variation of the original I-D method (the proton transfer variant), not inserting the proton in a reference system consisting of only water molecules. A similar approach was also used in previous studies,^{32,33} and suppresses spurious contributions to the calculated pK_a that arise if the "deletion" and "insertion" systems differ substantially.^{31,34} The I-D technique has been successfully used to estimate the pK_a values of a variety of compounds including organic molecules, $^{27}\mathrm{amino}\ \mathrm{acids}, ^{28}\mathrm{TiO}_{2}{}^{32}$ and $\mathrm{Fe_{2}O_{3}}{}^{33}$ with accuracies of around 1-2 pK_a units compared to experimental values (where available).

In order to validate the I-D method for pK_a estimations for transition metal complexes, we considered it useful to estimate the pK_a of a Ru based water oxidation catalyst complex $([Ru(II)Py_5OMe(H_2O)]^{2+})$ with a known experimental pK_a (in water) equal to 11 units.^{29,35} Our obtained value of 9 pK_a units for this complex using the I-D method provides a first indication that the accuracy of this method for transition metal complexes is $\approx 2 pK_a$ units, similar in magnitude to other systems investigated with this technique.^{27,28} Further details of the calculation is provided in the Supporting Information (SI).

The thermodynamic scheme employed in the I-D technique for the pK_a calculation along with a snapshot of the simulation box used for the calculations is shown in Figure 1.



Figure 1: (a) Thermodynamic cycle used in the calculation of the deprotonation free energy $(\Delta_{\rm pt}A_{\rm NH})$ and the resulting p $K_{\rm a}$ with the insertiondeletion technique modeled as a proton transfer reaction. Here, d represents the non-interacting dummy atom, and (b) A representative snapshot of the simulation cell used in the insertion-deletion simulations for complex **1-vacant**⁺. The ligand proton and the dummy atom on a solvent water molecule are enlarged and highlighted in grey.

The crucial step in Figure 1a is the proton transfer involving the deprotonation of the ligand amido moiety:

$$\equiv \mathrm{NH}_{(aq)} + \mathrm{H}_2\mathrm{Od}_{(aq)} \rightarrow \equiv \mathrm{Nd}_{(aq)}^- + \mathrm{H}_3\mathrm{O}_{(aq)}^+ \quad (1)$$

Here "d" indicates the non-interacting dummy atom. The expression to evaluate the free energy $\Delta_{\rm pt} A_{\rm NH}$ for the reaction 1 is given by:

$$\Delta_{\rm pt} A_{\rm NH} = \int_0^1 \frac{\partial A(\eta)}{\partial \eta} d\eta = \int_0^1 \langle \Delta E \rangle_\eta d\eta, \quad (2)$$

where

$$\Delta_{\rm pt} E_{\rm NH} = E_1 - E_0 \tag{3}$$

and

$$E_{\eta} = (1 - \eta)E_0 + \eta E_1$$
 (4)

In equations 2-4, η is the coupling parameter which can take values from 0 to 1. Here, $\eta = 0$ corresponds to the system with the protonated state of the ligand $(\equiv NH)$ and H_2Od , while $\eta = 1$ corresponds to the system with a deprotonated ligand $(\equiv Nd^{-})$ and the hydronium ion (H₃O⁺), and intermediate values of η correspond to a mixture of these states. The vertical energy gap $\Delta_{\rm pt} E_{\rm NH}$ is calculated directly from the DFT-MD simulations, where E_0 is the potential energy surface (PES) of the system with $\eta = 0$, while E₁ is the PES of the system with $\eta = 1$. The PES for a given value of η is defined by the mapping potential E_n in equation 4. The final expression used in the calculation of the ligand pK_a is:

$$pK_{a} = \frac{1}{k_{\rm B}T\ln 10} \left(\Delta_{\rm pt}A_{\rm NH} + \Delta A_{\rm H_{3}O^{+}} \right) \quad (5)$$

$$\Delta_{pt}A_{\rm NH} = \frac{5}{18} \Big(\langle \Delta_{\rm pt}E_{\rm NH} \rangle_{0.1127} + \langle \Delta_{\rm pt}E_{\rm NH} \rangle_{0.8873} \Big) \\ + \frac{4}{9} \langle \Delta_{\rm pt}E_{\rm NH} \rangle_{0.5} \tag{6}$$

Here, $\Delta_{pt}A_{NH}$ is evaluated using thermodynamic integration according to equation 2. To evaluate the integral given in equation 2, we employ the Gauss-Legendre quadrature (equation 6) using three values of η (0.1127, 0.5) and 0.8873) to numerically evaluate the integral. The advantage of using the Gauss-Legandre quadrature is that it does not consider the (problematic) end points (i.e. $\eta = 1$) in the integral evaluation, in addition to having a higher numerical accuracy than other integration schemes, as discussed in an earlier study by De Meyer and co-workers.³⁶ For each value of η , a \approx 10-15 ps equilibration followed by \approx 30-40 ps production run is performed. The term $\Delta A_{H_3O^+}$ is the correction for the standard translational free energy of the proton and is a constant value equal to -0.19 eV (-3.2 pK_a

units). Note that the free energies associated with the dummy atom insertion (ΔA_{Nd} and ΔA_{H_2Od}) in Figure 1a and quantum corrections (ΔA_{ac}) are typically small as shown in previous studies (≈ 0.5 -1 pK_a units).^{28,32} In the present study they are neglected. Snapshots from the I-D simulations corresponding to $\eta = 0.1127$ and $\eta = 0.8873$ for the **1-vacant**⁺ species are shown in Figure 2a,b. Based on these snapshots, it is clear that $\eta = 0.1127$ is representative of the situation corresponding to the protonated amido ligand moiety (NH) where the ligand donates a hydrogen bond to a solvent water molecule (Figure 2a), while $\eta = 0.8873$ is representative of the deprotonated amido ligand moiety (Nd⁻) where it is seen accepting a hydrogen bond from a solvent water molecule (Figure 2b). In addition, the values of ΔE , and its time average, for the three values of η used to obtain $\Delta_{\rm pt} A_{\rm NH}$ for 1-vacant⁺ is shown in 2c. Note that a number of constraints had to be enforced in order to sample well-defined protonated (NH) and deprotonated (Nd⁻) states of all the complexes in this study. Further details on these aspects and the time-averaged ΔE plots used to calculate pK_a -ligand for all complexes considered in this study are provided in the SI.



Figure 2: Representative snapshots corresponding to (a) $\eta = 0.1127$ and (b) $\eta = 0.8873$ in the insertion-deletion simulations for complex **1vacant**⁺. For $\eta = 0.1127$, the ligand moiety donates a hydrogen bond to a solvent water molecule, while for $\eta = 0.8873$ the ligand moiety accepts a hydrogen bond from a solvent water molecule, (c) Running average of the vertical energies (ΔE) for different values of η (0.1127, 0.5 and 0.8873) used to compute the pK_a-ligand for complex **1**-vacant⁺. Instantaneous values of ΔE are shown in grey and exhibit large fluctuations, therefore requiring relatively long DFT-MD simulations. Color coding in this study: Ru (pink), O (red), N (blue), C (black) and H (silver).

Results and Discussion

For the Ru(PNP) catalytic system, the complexes that are involved during various stages of the catalytic cycle for aqueous methanol dehydrogenation are shown in Scheme 2. The ligand pK_a in solution (pK_a -ligand) for these complexes, computed using the I-D technique in combination with a Gauss-Legendre quadrature (Equation 6), is shown in Figure 3. Evidently, pK_a -ligand is strongly dependent on the nature of species adsorbed on the metal center. i.e. X. From Figure 3, the variation in the ligand pK_a as a function of the species adsorbed on the metal center (X) is ≈ 10 units (ranging between 17-27). Since these complexes are all present in the catalytic cycle, the large variation of the pK_a -ligand indicates that its vari-

ability is an important characteristic of the catalytic cycle. Complex **1-vacant**⁺ has the lowest p $K_{\rm a}$ -ligand = 17.4 \pm 0.5, indicating that the deprotonation of the amido moiety is the easiest when there is no species adsorbed on the metal center, i.e X = vacant. As soon as a species (X) is adsorbed on the Ru metal center resulting in complexes 1-OCH₃, 1-HCH₂O, 1-H, 1- H_2^+ , 1- H_2O^+ , 1-OCHO and 1-HCOO, there is a large increase in pK_a -ligand (Figure 3), indicating that these 18 valence electron complexes are very stable species, as observed in our previous study.¹⁵ Importantly, the resting species of the catalytic cycle for the Ru(PNP) system: **1-OCH**₃ has a very high pK_a -ligand $= 24.8 \pm 0.5$, indicating that the deprotonation of the amido ligand moiety is unlikely even under very basic conditions present in experiments (8M KOH). These observations are consistent with our previous work¹⁵ where we found that the amido ligand moiety does not participate actively along during the entire catalytic cycle for methanol dehydrogenation, in contrast to its commonly assumed role as reversible proton donator/acceptor in the Novori-Morris type mechanisms 1a.

In order to assess the effect of inaccuracy due to the approximate nature of the exchangecorrelation (XC) functionals on the computed pK_a -ligand, we also determined the pK_a -ligand for complex **1-vacant**⁺ using a hybrid (PBE0) functional. We find a good agreement (within 2 pK_a units) between the BLYP-D3 and PBE0-D3 values for this complex (see SI for more details) indicating that the calculated pK_a ligand values are not very sensitive to the level of theory employed, consistent with an earlier study.²⁷



Figure 3: Calculated pK_a -ligand in increasing order as a function of the nature of species (X) adsorbed on the Ru metal center for the complexes involved during aqueous methanol dehydrogenation catalyzed by the Ru(PNP) catalytic system.

To provide a clear picture of the variation in pK_a -ligand along the catalytic cycle, we plot the pK_a -ligand as a function of the progress of the catalytic cycle involving methanol (MeOH) dehydrogenation, formic acid (FA) dehydrogenation and H₂ production (Scheme 2a-c) in Figure 4.



Figure 4: Calculated variation of the pK_a -ligand along the catalytic cycle for MeOH dehydrogenation, FA dehydrogenation and H₂ production for the Ru(PNP) complex in aqueous solution.

Our findings on the variable nature of the pK_a -ligand can provide important novel insights on the the importance and nature of metal-ligand cooperativity. In the originally proposed bifunctional Noyori-Morris type mechanism,^{10,37} the metal and ligand act in a cooperative manner in the key steps involving C-H activation and hydrogen production during methanol dehydrogenation (Scheme 1a). The

metal acts as a hydride acceptor and the ligand acts as an internal acceptor base that is involved in reversible protonation/deprotonation. For the Ru(PNP) complex, we found a metalcentered mechanism distinct from the Novori-Morris mechanism owing to the high proton affinity of the ligand amido moiety.¹⁵ This is further validated in the current study, where most complexes along the catalytic cycle have a high p $K_{\rm a}$ -ligand (> 20), indicating that the amido ligand is unlikely to be directly involved in the C-H activation and hydrogen production steps via reversible protonation/deprotonation. Since the pK_a -ligand is highly sensitive to the chemical nature of the species adsorbed on the metal center, this may imply that the ligand can participate directly (via reversible protonation/deprotonation) in some stages of the catalytic cycle, while it does not participate directly in other parts of the catalytic cycle, depending on the magnitude of pK_a -ligand. This is a novel notion, that can be of significant importance in new design strategies for catalysts, as a ligand pK_a can be a determining factor in the mechanism and energetics of the catalytic cycle. In our view, these findings demonstrate the importance of considering the pK_a -ligand and its variability along the catalytic cycle as an important characteristic in the study and design of molecular catalyst for (de)hydrogenation reactions in protic environments. Our study also demonstrates that it is important to assess the pK_a of the potential proton donating/accepting ligand along the full catalytic cycle. Limiting oneself to a single stage of the catalytic cycle, e.g complex 1- OCH_3 (the resting state) with the assumption that the other complexes in the catalytic cycle have a similar pK_a -ligand might provide an incomplete and possibly a misleading picture of the reaction mechanism.

In a recent work, Beller and co-workers used density functional theory calculations to address the role of an inorganic base (KOH) in aqueous methanol dehydrogenation catalyzed by the Ru(PNP) complex $1.^{17}$ They proposed that the role of the base is to help in the deprotonation of the ligand NH moiety that results in an anionic pathway involving the ligand N⁻ during the key C-H activation step that has a lower barrier compared to the previously proposed (neutral) pathways involving the NH moiety.¹⁶ However, in our previous work based on DFT-MD simulations, we concluded that the ligand amido moiety for the Ru(PNP) system had a high pK_a in solution, and therefore the anionic pathway is unlikely to operate under catalytic conditions as the deprotonation of the amido moiety from complex $1-OCH_3$ even by a strong base like OH^- is highly endergonic (Δ $G = +12.3 \text{ kcal mol}^{-1}$.¹⁵ While the high pK_aligand for all the complexes belonging to the Ru(PNP) catalytic system considered in this work further support our previous observations, it is interesting to note that due to the dynamic nature of the pK_a -ligand, there could be parts in the catalytic cycle where the pK_a -ligand is low enough for deprotonation by a base like OH⁻, in which case the base can play a direct (positive) role in the catalytic cycle by triggering the anionic pathway. This is particularly important in the case of the aqueous methanol dehydrogenation reaction that involves a number of stages including methanol and formic acid dehydrogenation (Scheme 2), and it can be beneficial in understanding the exact stages where an external base can affect the reaction. Therefore, in addition to the need to accurately estimate and consider the dynamic nature of the p $K_{\rm a}$ -ligand to understand the exact role of the ligand in the reaction mechanism, it can also be used to understand the role of external additives like OH⁻ in various stages of the catalytic cycle during aqueous methanol dehydrogenation.

Conclusion

In summary, we have used DFT based molecular dynamics with an explicit description of the aqueous solvent to elucidate the substantial variability of the pK_a of the ligand amido moiety along the catalytic cycle of aqueous methanol dehydrogenation catalyzed by a Ru(PNP) molecular complex. We find the pK_a of the ligand to be strongly sensitive to the nature of the adsorbed species on the metal cen-

ter along the catalytic cycle. For the complexes involved in the Ru(PNP) catalytic system, the variation in pK_a-ligand is ≈ 10 units, with most complexes having a high pK_a -ligand (> 20). The substantial variability of the ligand pK_{a} has important implications on metal-ligand cooperative pathways, as it is a crucial factor that determines the exact role of the ligand (either as a proton donor/acceptor or as a hydrogen bond donor) during homogeneously catalyzed aqueous methanol dehydrogenation. In addition, the implications of the varying chemical nature of the ligand on the role of external additives are discussed. We anticipate that our findings can motivate future computational and experimental studies for accurate ligand pK_a estimations of complexes involved in homogeneous (de)hydrogenation reactions, and may provide new directions for the rational design of molecular catalysts in protic solvents.

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Author Contributions

N. G. conceived the idea and designed the research. H. B. and N. G. performed the calculations and analysis of the results under the supervision of E. J. M. We thank Prof. Michiel Sprik and Dr. Vivek Sinha for insightful comments and suggestions. All authors discussed the results and wrote the manuscript.

Notes

The authors declare no competing financial interest.

Supporting Information Available

Time averaged Δ E plots for all complexes, validation of the insertion-deletion method, effects of the XC functional and constraints used in the insertion-deletion DFT simulations.

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