

Dihydropyridines for the Catalytic Conversion of CO₂ to CH₃OH:

A Thermodynamic and Kinetic Study

by

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Dihydropyridines for the Catalytic Conversion of CO_2 to CH_3OH : A Thermodynamic
and Kinetic Study

Thesis directed by Professor Charles B. Musgrave

ABSTRACT

Rising atmospheric CO_2 concentration and rapid depletion of fossil fuels necessitates the search for competent methods for CO_2 conversion to fuels. Various studies demonstrate the ability of pyridinic derivatives to photoelectrochemically reduce CO_2 to methanol. Here the thermodynamic and kinetic aspects of pyridines as hydride-donating catalytic reagents that transfer hydrides via their dihydropyridinic form are analyzed. We investigate the effects of functionalizing pyridinic derivatives with electron-donating and electron-withdrawing groups on hydride transfer catalyst strength – assessed via their hydricity and nucleophilicity – and the catalyst recyclability – assessed via reduction potential. We find that pyridines with electron-donating groups have stronger hydride-donating ability, but are less efficiently recycled (having more negative reduction potentials). In contrast, pyridines substituted with electron-withdrawing groups are more efficiently recycled but are weaker hydride donors. Functional group modification favorably tunes hydride strength or efficiency, but not both. This problematic coupling between the strength and recyclability of pyridinic hydrides is attributed to their aromatic nature. Several avenues are suggested for overcoming this difficulty.

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CHAPTER I

INTRODUCTION

Concerns about the impact of atmospheric carbon dioxide (CO_2) on climate and increasing global energy demands have motivated efforts towards efficient conversion of CO_2 into useful products, such as fuels.¹⁻³ More than 30 billion tons of CO_2 are released into the atmosphere annually, but only half of this CO_2 is naturally recycled by photosynthesis, resulting in a net accumulation of CO_2 in the atmosphere.⁴ One possible solution is to supplement nature's carbon economy with artificial photosynthesis by photochemically reduced CO_2 to store solar energy and sequester carbon.⁵ However photosynthesis is exquisitely complex and not yet fully understood such that imitating natural CO_2 reduction has proven an elusive goal. Even the less ambitious goal of developing catalysts that efficiently transform CO_2 into valuable products via non-photochemical means has proven to be extremely difficult.^{3, 6-10} In this work, we investigate various organic catalysts and screen for catalysts that can mimic nature's ability to convert CO_2 to simple fuels, such as methanol, and close the carbon cycle shown in Fig 1. The goal of this project is to find molecular catalysts that have (1) favorable thermodynamics for CO_2 reduction, (2) fast reaction kinetics, and (3) can be recycled efficiently; this will hopefully provide alternative fuel production methods and aid in the battle against global warming.

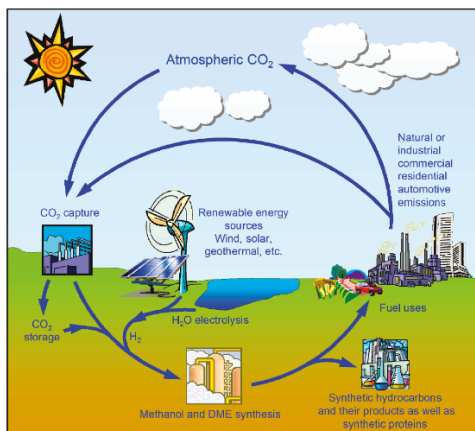


Figure 1. The Carbon Cycle. Obtained from REF 4.

SCOPE OF THE STUDY

Many novel methods have been explored for the conversion of CO₂ to fuels, such as bifunctional catalysts and plasma technology. Here we limit ourselves to a strictly homogeneous system that is electrochemically driven by pyridine-based catalysts. This is inspired by the system devised by Bocarsly and coworkers, which remains for more than a decade the most efficient photoelectrochemical system for methanol generation from CO₂. The pyridine molecule is a biomimetic catalyst; it mimics the role of NADPH in reducing CO₂ in the Calvin cycle of photosynthetic organisms, as shown in Fig 2. Quantum chemical methods are utilized to analyze the viability and efficiency of the systems under study in addition to dihydropyridine strength and recyclability characterization, which is of increasing interest for various hydride transfer reactions in the organic chemist community.

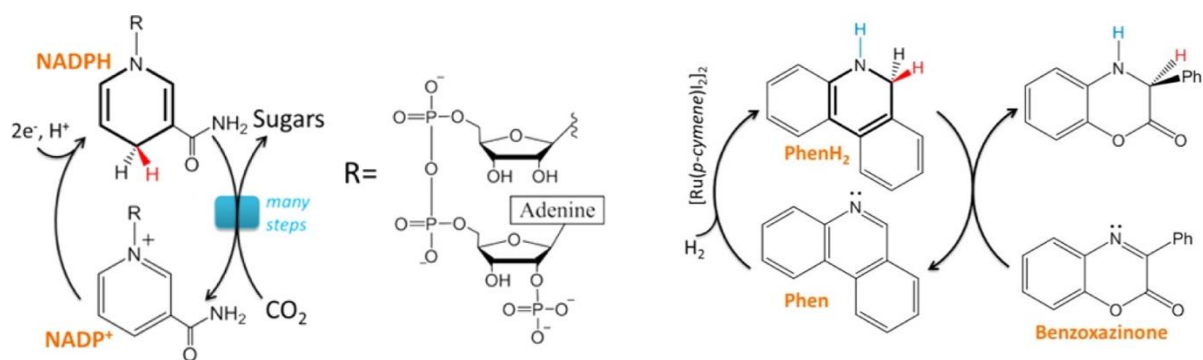


Figure 2. Dihydropyridine PhenH₂, a pyridine derivative, is a biomimetic hydride donor and regenerates similarly to NADPH. Modified from REF 28.

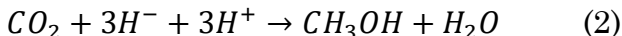
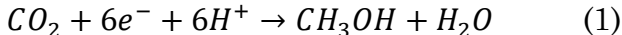
ARRANGEMENT OF THESIS

The outline of the remainder of this thesis is as follows. In Chapter II, recent relevant advances pertaining to CO₂ reduction via pyridinic catalysts are reviewed and the hypothesis is detailed. In Chapter III, computations of the quantum chemical simulations performed are detailed. In Chapter IV, methodologies for the calculation of significant chemical properties are presented. Chapter V offers an analysis and discussion of the accumulated results. The observed trends are then explored, and future works involving pyridinic catalyst applications are suggested in Chapter VI, followed by conclusions in Chapter VII. The Bibliography and Appendix sections proceed the main text of the thesis.

CHAPTER II

BACKGROUND

CO₂ conversion to the simplest fuels is tricky. The conversion of CO₂ into reduced product via a series of one-electron transfers (ETs) and proton transfers (PTs) inevitably produces high-energy radical intermediates at every odd electron reduction, resulting in slow kinetics and low selectivities unless these radicals are stabilized.¹¹ The challenge of producing these high-energy reduction intermediates by odd electron reductions is quantified by the one-electron reduction of CO₂ to CO₂^{•-}, which involves a highly unfavorable reduction potential of -2.14 V vs. the standard calomel electrode (SCE).¹²⁻¹³ Nature avoids this issue by utilizing closed-shell, stable intermediates generated by two electron/one proton transfers, also known as hydride transfers (HTs).¹⁴ Consequently, the six ETs and six PTs that reduce CO₂ to methanol could theoretically be accomplished as three HTs and three PTs,¹⁵ as shown by equations (1) and (2):



Bocarsly and coworkers have shown that a simple pyridinium ion catalyzes photoelectrochemical CO₂ reduction to methanol at a p-GaP photocathode.¹⁶ They observed that this system achieved near 100% Faradaic efficiency operating at 220 mV of underpotential of an illuminated p-type GaP electrode in water – the most successful reported photoelectrochemical conversion of CO₂ to methanol to date. While their initially proposed mechanism involved the pyridinyl-COOH intermediate,¹⁶⁻¹⁸ it has been discarded due to several inconsistencies associated with the reduction potentials and pKa values of relevant intermediates.¹⁸⁻²² Subsequent computational studies have shown that a likely mechanism involves the photoelectrochemical formation of dihydropyridine, which then drives CO₂ reduction via a hydride transfer mechanism.^{18, 20-23}

Indirect evidence that pyridine analogs play a key role in electrocatalytic CO₂ reduction has been provided using operando reflectance FTIR experiments, which showed that the electrochemical reduction of pyridinium ion on a Pt electrode generates piperidine, a fully reduced derivative with formula C₅NH₆.²⁴ While dihydropyridine was not detected in this study, it is a likely intermediate in the reduction of pyridinium ion to piperidine. Another set of experiments that confirms the role of NADH analogs were performed in a study of the electrocatalytic reduction of CO₂ to methanol on Pt and carbon electrodes, where it was shown that electrocatalysis improves in the presence of dihydrophenanthridine and dihydroacridine derivatives.²⁵

Despite the evidence these results provide, direct experimental proof of the homogeneous catalytic reduction of CO₂ by metal-free hydrides has not yet been obtained. For example, attempts to chemically reduce CO₂ using dihydrophenanthridines, dihydroacridines and dihydropyridines did not observe reduction products.²⁵⁻²⁶ Furthermore, electrocatalytic CO₂ reduction by aromatic N-heterocycles exhibits strong dependence on the type of working electrode.^{16-17, 25} These results indicate that the electrode may play a role in the catalysis, either indirectly, for example by influencing competing reactions, such as proton reduction, or directly, for example by interacting with the catalytic species or by catalyzing CO₂ reduction itself. Keith and Carter proposed that the catalysis of CO₂ reduction by pyridines occurs heterogeneously, where CO₂ is reduced by hydride transfer from surface-bound PyH₂ species.²⁰ Kronawitter and coworkers propose a competing mechanism where piperidinium-like species, formed through heterogeneous interactions with a Pt electrode, perform the hydride transfer reactions.²⁴

Recently, Lim and co-workers reported the first detailed theoretical mechanism of converting CO_2 to methanol in aqueous solution assisted by 1,2-dihydropyridine (PyH_2) as a renewable organo-hydride.²⁷⁻²⁸ Dihydropyridines (DHPs) are very interesting molecules because their structures resemble the active site of the NADPH hydride species of photosynthesis.²⁹ The reactions by which methanol is formed by successive HT-PT processes is illustrated in Fig 3.

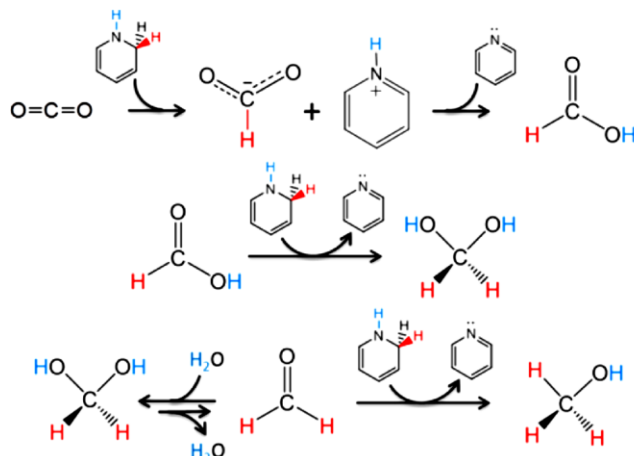


Figure 3. Mechanism of methanol formation by hydride transfers from 1,2-dihydropyridine to CO_2 . CO_2 is reduced to formate by HT, followed by protonation to formic acid. Similarly, sequential HT-PT to formic acid produces methanediol, which is then dehydrated to formaldehyde. Lastly, formaldehyde is reduced to methanol by HT-PT. Edited from REF 15.

Lim et al. show that the overall conversion of CO_2 to methanol in aqueous solution is thermodynamically favorable by ~ 44 kcal/mol.²⁸ In the first step, a hydride is transferred by the catalyst to CO_2 , creating a formate intermediate, which then abstracts a proton from the oxidized product (PyH^+) and forms formic acid. Formic acid undergoes another HT followed by a PT to form methanediol. Methanediol loses a water molecule via hydrolysis to form formaldehyde. One last HT-PT step is required to convert formaldehyde to the methanol fuel. The HT reactions to form formic acid, methanediol, and methanol are thermodynamically downhill by approximately 5, 12, and 31 kcal/mol, respectively.²⁸ Because the reduction of CO_2 to formic acid is the least thermodynamically favorable, it will be the focus of the thermodynamic study – a hydride that can reduce CO_2 to formic acid will very likely be able to perform the other two reductions.

Upon sequential HT-PT, PyH_2 turns into pyridine (Py), the inactive form of the catalyst. The Py/ PyH_2 cycle, shown in Fig 4, outlines the processes by which the DHP catalysts react and recycle. Lim et al. predicted that the DHP catalyst could be formed via sequential PT-ET-PT-ET to Py in electrochemical, photochemical and photoelectrochemical systems.²⁸ Formation of the active catalyst via proton-coupled electron transfers (PCETs) is a possible pathway given that the pK_a of the XH^+ or $\text{XH}_2^{+\bullet}$ is too low (<5) to be in equilibrium with water.

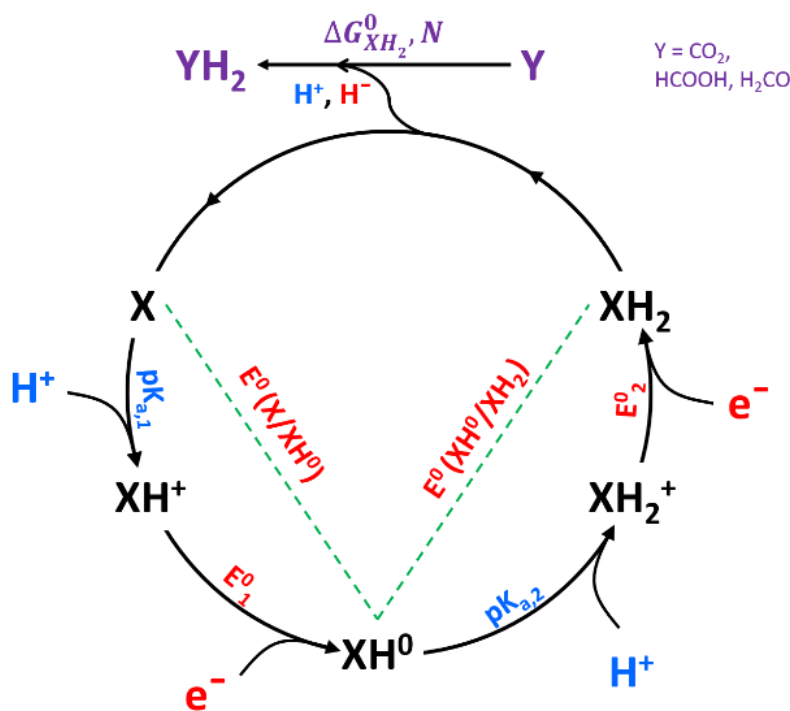


Figure 4. The possible routes for the formation of XH_2 by the reduction of X and the reduction of a target oxidant Y by hydride and proton transfer from XH_2 . The black route represents the most likely mechanism of consecutive PT-ET-PT-ET. The green route would be the most likely at low $\text{pK}_{a,1}$ and $\text{pK}_{a,2}$, where PCET is favored. The route in blue indicates a double concerted PCET, a phenomenon observed in reducing pteridines but is a highly debated mechanism.³⁰ The catalyst can donate its hydride to a hydride acceptor Y (in this work $\text{Y} = \text{CO}_2$). Edited from REF 15.

HYPOTHESIS

While DHP is a promising catalyst, it is expensive to recycle. The first reduction E_1^0 shown in Fig 4 requires -1.3 V vs. SCE and,¹⁵ even though it is a significant improvement from the single electron reduction of CO_2 to a $\text{CO}_2^\bullet$ radical (-2.24 V vs. SCE), much lower (less negative) reduction potentials are desired for increased efficiency of catalyst regeneration. Tuning the properties of the DHP catalyst requires a better understanding of its behavior. As such, this work is tailored to studying derivatives of the DHP molecule – shown in Figure 5 – substituted by various electron withdrawing groups (EWGs) and electron donating groups (EDGs). We hypothesize that functionalizing DHPs with EDGs will produce stronger hydrides due to better charge stabilization after the hydride donation. We study the effects of these derivatives and functional groups on various essential properties – hydricity, nucleophilicity, pKa, and reduction potential – which quantitatively describe pyridinic catalysts. Catalyst reactivity is defined by the thermodynamic hydricity and kinetic activation free energy, whereas its recyclability is described by pKa and reduction potential values.

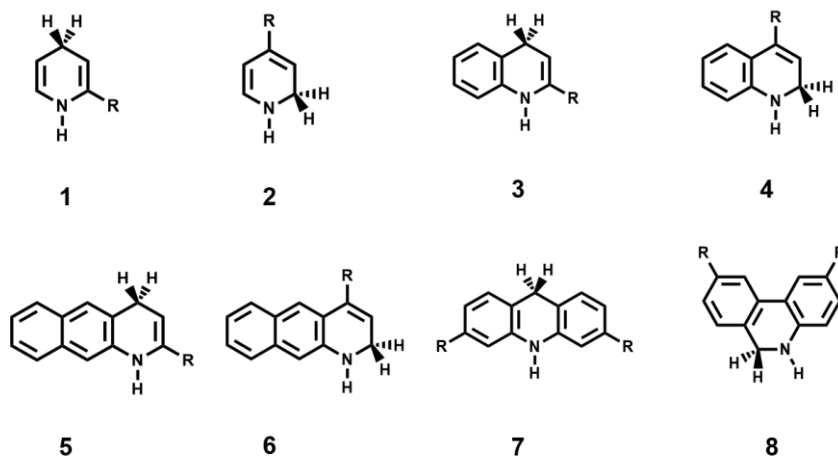


Figure 5. List of dihydropyridine families examined in this work. 1) 1,4-dihydropyridine. 2) 1,2-dihydropyridine. 3) 1,4-dihydroquinoline. 4) 1,2-dihydroquinoline. 5) 1,4-dihydrobenzoquinoline. 6) 1,2-dihydrobenzoquinoline. 7) dihydroacridine. 8) dihydrophenanthridine. 5 functional groups have been studied: $-\text{H}(\text{R}=\text{a})$, $-\text{COOH}(\text{R}=\text{b})$, $-\text{CN}(\text{R}=\text{c})$, $-\text{CH}_3(\text{R}=\text{d})$, $-\text{NMe}_2(\text{R}=\text{e})$. DHP derivatives are coded XR, where X is the family number from 1-8, and R is the functional group.

CHAPTER III

COMPUTATIONAL DETAILS

Quantum chemical calculations were used to evaluate hydricities, nucleophilicities, and reduction potentials of the molecules of interest. Density functional theory (DFT) based on the M06 exchange correlation functional³¹ combined with the 6-31+G(d,p) basis set was employed.³² This level of theory should provide a reliable description of the properties of the molecules and reactions of interest – hydride transfers – since the M06 functional has been parameterized with experimental data for similar molecular systems.³¹ To validate the M06/6-31+G(d,p) method we performed calculations on a subset of five of the smallest hydrides (entries 1a-1e in Table 1) with the wB97XD/6-311++G(d,p) method.³³ All calculations were conducted within the Gaussian 16 software package.³⁴

Solvation effects were considered using a conductor-like polarizable continuous model (CPCM)³⁵⁻³⁶ for water, the primary solvent of interest as explained in the Introduction, but also for acetonitrile, and dichloromethane solvents (as will be seen, different solvents are relevant for different properties); explicit inclusion of several hydrating water molecules is used for certain purposes. We obtained hydricities agreeing within 3 kcal/mol for the two methods, with M06 tending to estimate lower hydricities, by approximately 2.5 kcal/mol relative to the wB97XD functional (see Table A.1 in the Appendix). Our methods also accurately reproduce experimental nucleophilicity, reduction potential, and pKa values, as indicated in the respective chapters which follow.

For all properties, and free energies in particular, we define the reference state of all reactions as the isolated reactants in solution.³⁷ The calculated vibrational force

constants were used to compute the zero-point energy and vibrational entropy contributions to free energies, and the vibrational heat capacity contributions to enthalpies at 298 K. Such force constants also confirmed that reactants and products have only positive vibrational modes and that transition states have only one imaginary mode, corresponding to hydride transfer to CO₂.

DFT calculations tend to incorrectly approximate the activation free energy of bimolecular reactions, due to complications associated with implicit solvation. Solvation affects the contributions to the free energy from the molecular modes of motion. The commonly employed entropy evaluation within the rigid rotor, harmonic oscillator, and ideal gas approximations generally overestimates any entropic penalty for solution phase reactions since hindered translations, rotations, or vibrations of the solvated solute molecule are not accounted for. DFT-based methods using the CPCM solvent model have been shown to overestimate the transition state (TS) entropic contributions to the free energy at 298 K by 4-12 kcal/mol compared to experimental values.^{28, 38-40} This exceeds the typical errors in predicted activation barriers mainly because the translational motion is incorrectly approximated as the significantly large gas-phase translational entropy. Assorted correction methods are proposed;⁴¹⁻⁴⁴ here we add an experimentally determined entropic contribution ($-T\Delta S^\ddagger$) for HT for a similar system to our calculated activation enthalpy ($\Delta H^\ddagger$) to produce an approximate $\Delta G^\ddagger \approx \Delta H^\ddagger_{Calc} - T\Delta S^\ddagger_{Exp}$. Srinivasan et al. showed that for the HT from BNAH to Δ^1 -pyrroline-2-carboxylic acid in water, the experimentally determined entropic contributions $-T\Delta S^\ddagger$ at 298 K are ~ 2.3 kcal/mol;⁴⁵ We add this value of $-T\Delta S^\ddagger$ to the calculated $\Delta H^\ddagger$ to predict $\Delta G^\ddagger$.

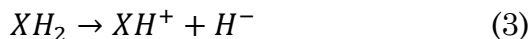
CHAPTER IV

THEORETICAL DETAILS

This chapter outlines how each of the chemical properties studied in this work – thermodynamic hydricity, nucleophilicity, pKa, and reduction potential – aids in understanding dihydropyridine reactivity. Theoretical details explaining calculation procedures for each property are provided. Additionally, new methodology is presented allowing the calculation of nucleophilicity and aqueous hydricity values of dihydropyridines via quantum chemical methods.

HYDRICITY

The thermodynamic hydricity of a dihydride XH_2 ($\Delta G_{XH_2,a}^0$), which is typically measured in acetonitrile solvent (hence the ‘a’ subscript), quantifies a hydride donor’s strength via its heterolytic dissociation free energy of X-H, i.e. the hydricity $\Delta G_{XH_2,a}^0$ of XH_2 is defined as the heterolytic dissociation free energy, so that more negative values indicate greater hydride donor strength:⁴⁶⁻⁴⁸



$$\Delta G_{XH_2,a}^0 = G_{XH^+} - G_{XH_2} + G_{H^-} \quad (4)$$

Current DFT-based methods do not generally calculate the free energy of the solvated hydride G_{H^-} accurately.⁴⁹ We have therefore employed instead two different indirect approaches to estimate the hydricity: 1) the isodesmic approach (IA)⁵⁰⁻⁵¹ and 2) the linear scaling approach (LSA).⁵² The former avoids a free energy calculation for the solvated hydride ion, but instead requires knowledge of the experimentally determined hydricity value of a reference molecule. We select BNAH as reference because it has a structure very similar to the dihydropyridinic molecules that we consider. The difference between eq. (4) and its equivalent for the hydride dissociation of BNAH yields the isodesmic eq. (5), in which the G_{H^-} term is eliminated. Equation (5) enables the IA estimation of the hydricity of XH_2 via calculation of the free energies of BNAH, BNA⁺, XH_2 , and XH^+ .

$$\Delta G_{XH_2,a}^0 = \Delta G_{BNAH,a}^0 + (G_{XH^+} - G_{XH_2}) + (G_{BNAH} - G_{BNA^+}) \quad (5)$$

The LSA, proposed by Muckerman, requires fitting a linear model to experimentally determined hydricity values against the quantum chemically computed quantity ($G_{XH^+} - G_{XH_2}$) – the free energy difference between oxidized species XH^+ and the

hydrides XH_2 . The fit, plotted in Fig 6, is then used to interpolate/extrapolate hydricities of hydrides which do not yet have an experimentally determined value.

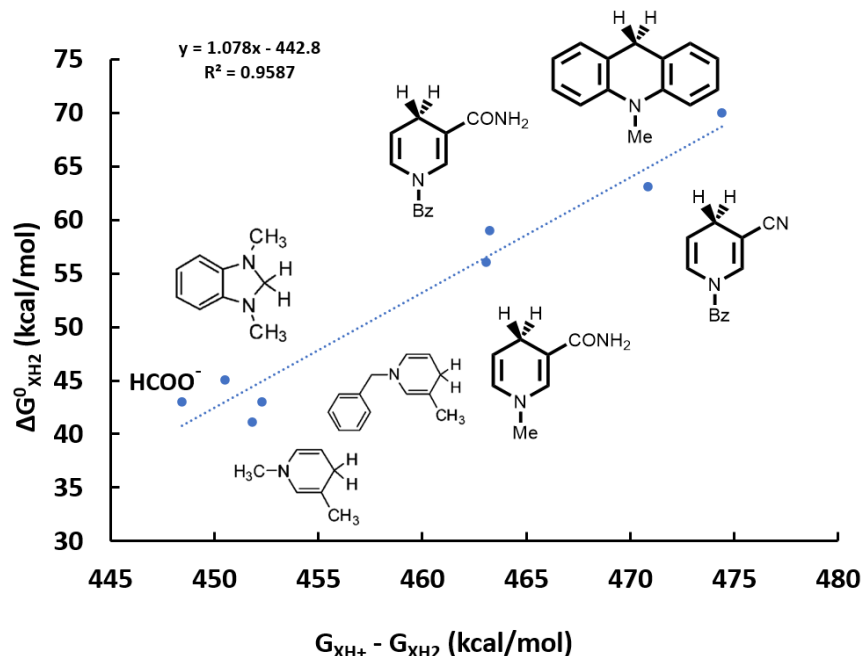


Figure 6. The Linear Scaling Approach. Experimentally determined hydricities in acetonitrile solvent versus the computed free energy differences ($G_{\text{XH}^+} - G_{\text{XH}_2}$).

For a test set of 8 hydrides, we find that the IA predicts hydricities more accurately than does the LSA, as shown in Table 1. The mean absolute deviation between experimental and calculated hydricities is approximately 0.5 kcal/mol and 2 kcal/mol for IA and LSA respectively. Accordingly, we will employ IA hydricity values for the thermodynamic screening of DHPs.

Table 1. Comparison of hydricity values (kcal/mol) obtained experimentally and via the IA and LSA with experimentally determined hydricity values.

Molecule*	Hydricity (Literature)	Hydricity (IA)	Hydricity (LSA)
BNAH	59 ^a	59.0	56.7
BNcyanoH	63 ^a	66.6	64.9
methylacridine	70 ^a	70.2	68.8
MNAH	56 ^a	58.9	56.6
1,4-BMPyH	43 ^b	48.1	44.9
1,2-BzImH	45 ^b	46.3	43.0
1,4-DMPyH	41 ^b	47.6	44.4
HCOO [−]	43 ^b	44.2	40.8
Mean Abs Dev	-	0.54	1.92

a) REF 46

b) REF 52

AQUEOUS HYDRICITY

Hydricity values are most commonly reported in acetonitrile solvent and thus provide only a limited description of hydride donor strength. As noted earlier, we are more interested in reactions of DHPs in water solvent and, as a result, require the aqueous hydricity ($\Delta G_{XH_2,w}^0$) to measure the thermodynamic strength of these hydrides. Unfortunately, aqueous hydricity determination is more challenging due to the lack of experimental data for benchmarking calculations. Further challenges are illustrated by the following. Creutz et al. predict based on experimental observations that the shift (difference) in the hydride anion’s solvation free energy in acetonitrile and water solvents ($\Delta G_{H-}^{solv} = G_{H-}^w - G_{H-}^a$) is 16-22 kcal/mol in magnitude.⁵³ IA aqueous hydricity prediction using formate as reference yields $\Delta G_{H-}^{solv} \sim 9$ kcal/mol, lying well outside this range (see Appendix A for details). This deviation can be attributed to (1) errors in the reference formate molecule’s hydricity determination or (2) failure of the IA in aqueous media. Whatever the error source, we consider that the isodesmic approach with a reference hydricity measured in water cannot be assumed to accurately predict aqueous hydricities.

To overcome this difficulty, we propose an alternative aqueous hydricity calculational approach which contains elements from the IA as well as the well-known experimental potential-pKa approach.⁴⁹ We begin with the reaction of the dihydride XH_2 with CO_2 in water to produce X and formic acid



with the reaction free energy

$$\Delta G_{rxn,w}^0 = G_X + G_{HCOOH} - G_{XH_2} - G_{CO_2} \quad (7)$$

This equation can be manipulated, using the definitions of $pK_a(XH^+)$, $pK_a(HCOOH)$, $\Delta G_{XH_2}^0$ and $\Delta G_{HCOO^-}^0$ to relate the free energy of reaction to the hydricities of XH_2 and $HCOO^-$ via eq. (8) and its equivalent eq. (9)

$$\Delta G_{rxn} = (G_X + G_{H^+} - G_{XH^+}) + (G_{HCOOH} - G_{HCOO^-} - G_{H^+}) + (G_{XH^+} + G_{H^-} - G_{XH_2}) + (G_{HCOO^-} - G_{CO_2} - G_{H^-}) \quad (8)$$

$$\Delta G_{rxn,w}^0 = 1.36pK_a(XH^+) - 1.36pK_a(HCOOH) + \Delta G_{XH_2,w}^0 - \Delta G_{HCOO^-,w}^0 \quad (9)$$

We have selected reaction eq. (6) for the approach employing eq. (9) – which we will refer to as the ‘pKa-isodesmic’ approach (PIA) – because formic acid and the formate intermediate have pKa and hydricity values which are well-defined in the literature. Equation (9) requires the pKa value of formic acid (3.8)⁵⁴ as well as formate’s aqueous hydricity (35 *kcal/mol*).⁵³ PIA predicts $\Delta G_{H^-}^{soln}$ to be of magnitude 20 *kcal/mol*, in good agreement with the Creutz et al. result given above.⁵³ As is to be discussed, thermodynamically capable catalysts possess $\Delta G_{XH_2,w}^0$ lower than that of formate in water solvent; formate has a hydricity of 43 *kcal/mol*⁵⁵ in acetonitrile and 35 *kcal/mol* in water.⁵⁶⁻⁵⁷

NUCLEOPHILICITY

Efforts to quantify the hydride donor abilities of hydrides to effect reductions have been reported and can significantly aid the selection of appropriate hydride donors for CO₂ reduction. For example, Mayr and coworkers have discussed a method to quantify the kinetic hydride nucleophilicity (N) of various hydrides including boranes, silanes and carbon-based hydrides.⁵⁸ Specifically, these authors proposed that, as shown in the definition relation eq. (10), the logarithm of the (dimensionless numerical value of the) rate constant ($M^{-1}s^{-1}$) of a HT reaction at 20°C is equal to the sum of N and the electrophilicity (E) of the hydride acceptor, multiplied by a sensitivity parameter (s_N) that depends only on the nature of the nucleophile:

$$\log k_{20^\circ\text{C}} = s_N(N + E). \quad (10)$$

By measuring the rates of HT from a hydride donor (nucleophile) to various hydride acceptors (electrophiles) with known electrophilicities E , the desired N and s_N values can be determined for the hydride donor of interest from equation (10) via linear regression. The sensitivity parameter s_N is typically within the range 0.5-1.2,⁵⁹ and is approximately constant within each class of hydride donors (vide infra); N typically spans the range 0 to 15, with larger values indicating stronger nucleophiles. We emphasize that as a kinetic parameter, N is distinct from the often employed thermodynamic hydricity parameter.⁵⁵ N and the hydricity of a molecule thus provide different measures for quantifying the strength of the hydride in HT reactions.¹⁵

A calculation procedure is proposed to allow the determination of N values from quantum chemical calculations. Specifically, we relate the N to the activation free energy of a hydride transfer reaction. A simple algebraic manipulation shows that N

and $\Delta G^\ddagger$ are linearly related to each other (i.e. $N \propto \Delta G^\ddagger$) when the proportionality coefficient s_N is approximately constant within a given class of hydride donors being analyzed. To demonstrate this, we combine the well-known Transition State Theory-based equation⁶⁰ for the exponential dependence of the rate of reaction on the activation free energy,

$$k = c_0 \frac{k_B T}{h} \exp(-\Delta G^\ddagger / RT), \quad (11)$$

where k_B and h are the Boltzmann and Planck constants and c_0 is a factor to guarantee units of $M^{-1}s^{-1}$ for the dimensional k , with the Mayr group's definition of nucleophilicity, eq. (10), to yield eq. (12).

$$N = -\frac{1}{2.3RTs_N} \Delta G^\ddagger + \frac{1}{s_N} \log_{10} \left(u c_0 \frac{k_B T}{h} \right) - E. \quad (12)$$

Equation (12) connects N and $\Delta G^\ddagger$ and relates three unknowns: $\Delta G^\ddagger$, N , and E . u has units of $M \cdot s$, hence the argument of the log is dimensionless. All the reactions are considered at the constant temperature $T = 298$ K. The strictly linear relationship between N and the computed $\Delta G^\ddagger$ only holds for a constant electrophilicity value E ; we ensure this constancy by selecting CO_2 as the electrophile hydride acceptor for all reactions we consider. The last two terms in eq. (12) can be combined into an intercept N_0 term such that the relationship takes the linear form shown in eq. (13)

$$N = -\frac{1}{2.3RTs_N} \Delta G^\ddagger + N_0 \quad (13)$$

Mayr and coworkers have effectively already demonstrated this because $\ln k$ is linear in $\Delta G^\ddagger$; with the novel feature that we calculate $\Delta G^\ddagger$, we show in Fig 7 that the linear relationship between N and $\Delta G^\ddagger$ holds for a given fixed acceptor – specifically for the

carbon-based class of hydride donors. Similar to the linear scaling approach for hydricity value calculations, the approach described here allows the prediction of *N* values of hydride donors based on quantum chemical calculations of the activation barrier of hydride transfers to CO₂.

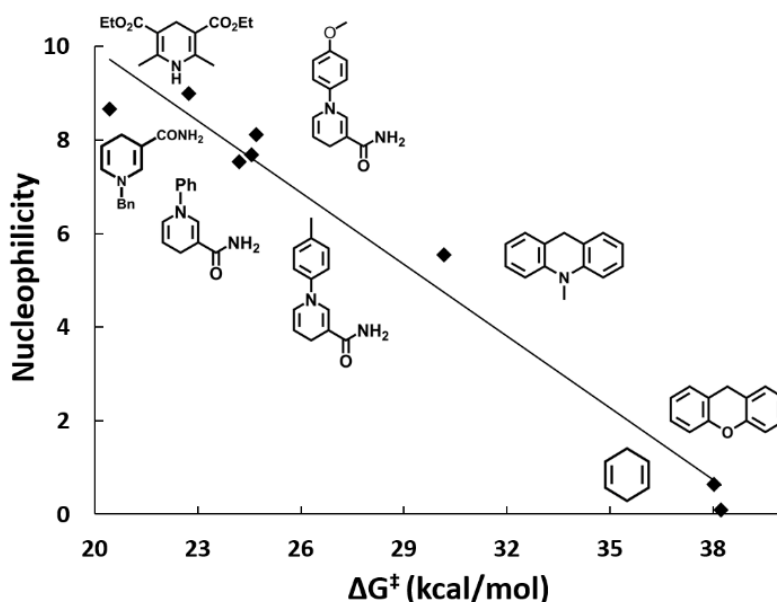


Figure 7. Nucleophilicity *N* vs. activation free energy of reaction $\Delta G^\ddagger$ for carbon-based hydride donors with CO₂ as the hydride acceptor in dichloromethane solvent. Experimental data are labeled as diamonds while the line represents calculated *N* values based on eq. (12), $N = -0.51\Delta G^\ddagger + 20.2$ and computed $\Delta G^\ddagger$ for hydride transfers. Effective *S_N* and *E* values of 1.44 and -11.3 are obtained. The Mean Absolute Deviation (MAD) of the differences between experimental and calculated nucleophilicity values is 0.26. A paired t-test on each set of the experimental and recovered *N* values to determine the effectiveness of the model results in a 95% confidence interval of (-0.52, 0.52) and a p-value of 1.0; a p-value greater than 0.05 indicates that no significant difference exists between recovered and experimentally inferred nucleophilicity values, which is validated by the inclusion of 0 in the 95% confidence interval.⁶¹

pKa

The pKa is an important property for characterizing the reactivity of pyridinic hydrides for two main reasons. First, it indicates which DHP formation route – shown in Fig 4 – is most likely to occur. Species with very low pKa values are thermodynamically favored to form the DHP via a proton-coupled ET (PCET). Conversely, moderate-to-high pKa values indicate that species can be easily protonated at mild reaction conditions, and the likely DHP formation route is through sequential PTET. Second, the pKa of XH^+ species is required for aqueous hydricity calculations via eq. (9). We calculate pKa values, after Schlegel,⁶² from the deprotonation reaction $AH \rightleftharpoons A^- + H^+$, using eqs. (14) and (15)

$$pK_a = \frac{\Delta G_{aq}}{2.303RT} \quad (14)$$

$$\Delta G_{aq} = G_{A^-} + G_{H^+} - G_{AH} \quad (15)$$

This approach requires the free energy of a proton in water G_{H^+} , determined experimentally to be -265.9 kcal/mol .⁶³⁻⁶⁶

The remaining species’ free energies required in eq. (15) for pK_a calculations are computed using a hybrid explicit/implicit solvation model. Five explicit water molecules are configured around the relevant solute and that cluster is embedded in CPCM- H_2O implicit solvent; this approach directly describes important hydrogen bonding interactions as well as the far-field solvation effects to provide a reasonable description of hydration effects in HT thermodynamics.⁶² Table 2 demonstrates that this approach reproduces experimental pKa values more accurately than does the CPCM-only model, with a mean absolute deviation from experiment of 0.33 pKa units.

Table 2. Comparison between literature pKa values and our calculated pKa values using two different models. The largest deviation in this sample set is approximately 1.6 pKa units for phenanthridine.

Molecule*	Reference pKa	0W Model ^a	5W Model ^b
Pyridine	5.14 ⁵⁴	2.9	5.14
Quinoline	4.85 ⁵⁴	3.12	5.33
Benzoquinoline	5.05 ⁵⁴	3.59	4.80
Acridine	5.6 ⁵⁴	4.9	5.73
Phenanthridine	3.3 ⁵⁴	2.73	4.87
1e	6.86 ⁶⁷	4.75	6.79
2e	9.17 ⁶⁷	8.28	8.30
1d	5.97 ⁶⁸	3.82	6.23
2d	6.02 ⁵⁴	4.32	5.69
3d	5.42 ⁵⁴	4.45	5.53
3e	7.25 ⁵⁴	5.73	8.17
4d	5.2 ⁵⁴	4.47	5.54
4e	9.08 ⁵⁴	8.82	9.29
HCOOH	3.8 ⁵⁴	9.73	4.72
Mean Absolute Deviation		0.58	0.33

*Codes for molecular identities can be found in Fig 5.

^aThe '0W' model estimates pKa using M06/6-31+G(d,p)/CPCM-H₂O with no explicit water molecules.

^bThe '5W' model estimates pKa using M06-2X/6-31+G(d,p)/CPCM-H₂O with five explicit water molecules.

REDUCTION POTENTIAL

The efficiency of DHP catalysts can be quantified by the reduction potential required to generate these catalysts from their inactive pyridinic form. Efficient catalysts are characterized by low negative reduction potentials (close to 0 V), thus requiring minimal free energy expenditure for catalyst regeneration. The calculation of reduction potentials E^0 (vs. SCE) in water follows the approach proposed by Tossell, which uses eqs. (16) and (17):⁶⁹

$$\Delta G_{red} = G_{XH} - G_{XH^+} \quad (16)$$

$$E^0 = \frac{-100.5 - \Delta G_{red}}{23.05} - 0.24 \quad (17)$$

We obtain good agreement of our calculated reduction potentials with reported experimental values: the mean average deviation = 0.14 V, see Table 3.

Table 3. Comparison between experimental and theoretical E^0 values (V versus SCE).

Molecule ^a	E^0_{exp} ^b	E^0 (M06) ^c
Pyridinium	-1.37 ²⁶ , -1.44 ⁷⁰ , -1.31 ²⁷	-1.32
CO ₂	-2.18 ⁷¹ , -2.31 ⁶⁹	-2.42
Benzene	-3.46 ⁷²	-3.43
Nitrobenzene	-1.19 ⁷³	-1.08
CH ₂ O	-2.53 ¹³	-2.56
CH ₃ CHO	-2.65 ¹³	-2.93
(CH ₃) ₂ CO	-2.82 ¹³	-3.15
Mean Absolute Deviation		0.139

^aMolecules selected from literature for E^0 comparisons.

^bExperimentally determined E^0 values (V versus SCE).

^cReduction potential values (V versus SCE) computed using M06/6-31+G(d,p)/CPCM-H₂O level of theory.

^dReduction potential values (V versus SCE) computed using M06-2X/6-31+G(d,p)/CPCM-H₂O level of theory.

CHAPTER V

RESULTS AND DISCUSSION

Here we first explore the effects on HT effectiveness of functionalizing pyridinic derivatives – with electron-donating and electron-withdrawing groups – on pKa and reduction potential values, parameters related to HT catalyst recyclability. In particular, the pKa values provide clues of probable pathways by which dihydropyridines are formed from their respective pyridinic forms, while the reduction potential values indicate the efficiency of these hydrides as catalysts. The functionalization effects on aqueous hydricity and nucleophilicity values of dihydropyridines – which characterize the thermodynamic and kinetic HT strengths – are studied. These studies reveal a linear tradeoff between catalyst strength and efficiency, a competition that we attribute to the aromatic nature of these pyridine-based hydrides. Several suggestions for avoiding this limitation for practical reduction processes are presented.

SUMMARY OF HYDRICITY, NUCLEOPHILICITY, pKa, AND E⁰ VALUES

Table 4 summarizes all computationally obtained hydricity, nucleophilicity, pKa, and reduction potential values of the pyridinic compounds examined in this work via the methods discussed in Chapters III and IV.

Table 4. Summary of hydricity $\Delta G_{XH_2,a}^0$, aqueous hydricity $\Delta G_{XH_2,w}^0$, nucleophilicity N, reduction potential E^0 , and pKa values related to the formation of and hydride transfer by DHPs. HT reaction: $XH_2 + CO_2 \rightarrow XH^+ + HCOO^-$.

XH_2^a	R^b	Hydricity (a) ^c	Hydricity (w) ^d	N ^e	E ⁰ ₁ ^f	E ⁰ ₁ (PCET) ^g	E ⁰ ₂ ^h	E ⁰ ₂ (PCET) ⁱ	pKa _{a,1} ^j	pKa _{a,2} ^k
1	H	50.5	30.9	10.5	-1.32	-1.15	0.29	0.28	5.14	1.05
	CONH ₂	59.8	39.1	9.2	-0.71	-0.78	-0.15	-0.56	1.89	-6.40
	CN	63.4	40.5	7.0	-0.56	-0.90	0.76	0.07	-1.08	-11.63
	CH ₃	47.8	28.0	11.1	-1.44	-1.22	0.23	0.28	6.23	2.11
	NH ₂	41.8	18.7	12.4	-1.73	-1.45	-0.17	0.15	6.79	6.13
2	H ^l	48.6	27.7	11.8	-1.32	-1.15	0.06	0.15	5.14	2.65
	CONH ₂	54.6	35.0	10.1	-0.79	-0.75	0.33	-0.08	2.79	-6.69
	CN	60.8	39.2	8.5	-0.49	-0.62	0.51	-0.16	0.57	-9.89
	CH ₃	45.8	26.2	12.3	-1.49	-1.24	-0.01	0.20	5.69	3.20
	NH ₂	37.4	14.1	13.9	-2.03	-1.54	-0.50	0.13	8.30	10.02
3	H	59.3	39.3	8.1	-0.97	-0.78	0.41	0.29	5.33	-0.75
	CONH ₂	64.8	46.7	6.6	-0.56	-0.44	0.54	0.07	1.87	-8.24
	CN	71.5	49.1	4.4	-0.27	-0.57	0.84	0.12	-1.16	-10.42
	CH ₃	56.6	37.9	8.9	-1.09	-0.82	0.34	0.28	5.53	-0.02
	NH ₂	48.3	24.1	10.8	-1.46	-1.12	-0.10	0.14	8.17	6.19
4	H	56.8	36.8	9.5	-0.97	-0.78	0.39	0.19	5.43	-3.31
	CONH ₂	60.9	41.0	9.0	-0.63	-0.56	0.55	0.05	3.88	-8.57
	CN	67.0	45.2	6.9	-0.26	-0.35	0.70	-0.10	1.69	-13.53
	CH ₃	54.2	35.5	10.1	-1.09	-0.83	0.33	0.18	5.54	-1.83
	NH ₂	44.9	21.2	11.6	-1.55	-1.03	-0.12	-0.01	9.29	-0.39
5	H	62.8	45.7	7.0	-0.74	-0.53	0.42	0.22	3.69	-3.35
	CONH ₂	67.7	52.1	5.5	-0.54	-0.38	0.53	0.18	0.93	-10.09
	CN	74.5	56.4	3.3	-0.12	-0.38	0.78	0.09	-3.78	-14.44
	CH ₃	59.3	42.1	7.8	-0.87	-0.56	0.35	0.19	5.27	-3.04
	NH ₂	50.2	35.5	10.1	-1.26	-0.87	0.10	0.21	5.32	2.14
6	H	61.3	42.7	8.2	-0.74	-0.53	0.46	0.15	4.80	-5.24

	CONH ₂	65.0	46.9	7.4	-0.47	-0.37	0.55	0.06	2.85	-8.30
	CN	70.5	50.7	5.8	-0.12	-0.19	0.65	-0.07	0.94	-13.53
	CH ₃	58.5	40.9	8.9	-0.85	-0.56	0.41	0.14	5.25	-4.81
	NH ₂	48.7	32.1	10.6	-1.24	-0.70	0.32	0.13	9.24	-4.97
7	H	69.3	50.5	4.9	-0.63	-0.34	0.51	0.36	5.73	-1.51
	CONH ₂	76.5	58.5	2.6	-0.37	-0.23	0.89	0.46	3.52	-6.07
	CN	83.2	60.7	0.6	-0.10	-0.14	1.07	0.42	2.63	-9.48
	CH ₃	66.4	48.3	5.9	-0.73	-0.40	0.36	0.38	6.76	0.80
	NH ₂	61.4	44.1	6.8	-0.89	-0.52	-0.24	0.33	6.98	8.83
8	H	64.0	42.4	7.5	-0.97	-0.81	0.47	0.42	4.87	-1.24
	CONH ₂	70.7	47.9	5.5	-0.60	-0.58	0.76	0.35	3.47	-6.81
	CN	76.9	53.7	3.8	-0.32	-0.47	1.01	0.36	1.20	-10.02
	CH ₃	61.2	38.9	8.5	-1.11	-0.87	0.25	0.36	5.30	1.49
	NH ₂	51.4	34.2	10.3	-1.52	-1.05	-0.05	0.53	8.53	9.60

^aNumbers designate the family of DHP derivatives found in Figure 1: 1) 1,4-dihydropyridine, 2) 1,2-dihydropyridine, 3) 1,4-dihydroquinoline, 4) 1,2-dihydroquinoline, 5) 1,4-dihydrobenzoquinoline, 6) 1,2-dihydrobenzoquinoline, 7) dihydroacridine and 8) dihydrophenanthridine. ^bFunctional groups attached to corresponding family of DHPs. ^cHydricity values (kcal/mol) calculated in acetonitrile solvent using IA. ^dHydricity values (kcal/mol) calculated in water solvent using PIA. Candidate molecules for CO₂ reduction in water are highlighted in blue, with $\Delta G_{XH_2}^W < 35$ kcal/mol. ^eNucleophilicity values calculated in DCM solvent. All reported pK_a and E⁰ values correspond to a pH of 7 in aqueous solvent at 298.15 K and 1 atm. ^fFirst reduction potential values (versus SCE) for the electron transfer $E^0(XH^+/XH^0)$. ^gFirst reduction potential values (versus SCE) for the net proton and electron transfer $E^0(X/XH^0)$. ^hSecond reduction potential values (versus SCE) for the electron transfer $E^0(XH_2^{+\bullet}/XH_2)$. ⁱSecond reduction potential values (versus SCE) for the net proton and electron transfer $E^0(XH^0/XH_2)$. ^jpK_a values of XH^+ species. ^kpK_a values of $XH_2^{+\bullet}$ species. ^lThe hydricity and nucleophilicity values of **2-H** (1,2-PyH₂) should replace the numbers previously reported in REF 28.

DIHYDROPYRIDINE FORMATION

Here we consider the effects of functionalizing dihydropyridines with electron-donating and electron-withdrawing groups on the pKa and E^0 values in order to determine the overall influence these groups would have on XH_2 catalyst regeneration. A promising catalyst would optimally i) possess protonated intermediates XH^+ and $XH_2^{\bullet+}$ with sufficiently high pKa values to facilitate formation of XH_2 via PTs in the PT-ET-PT-ET route, while ii) having reduction potentials that are not too negative, thus not requiring excessive free energy to access the active hydride state XH_2 , and all iii) resulting in an adequately strong hydride donor that performs HT reductions at practical rates.

The first reduction of XH^+ to XH requires significantly more energy (that is, a more negative reduction potential E_1^0) for the hydrides considered here than does the second reduction E_2^0 of $XH_2^{\bullet+}$ to XH_2 . Since this might appear surprising because a cation is reduced in both reductions, we discuss this in detail. The first reduction dearomatizes XH^+ and creates a radical species. The high free energy required to dearomatize XH^+ in turn supplies the driving force for HT, driven by re-aromatization of the dihydropyridinic species XH_2 .²⁸ In contrast, the second reduction to form XH_2 involves no dearomatization because $XH_2^{\bullet+}$ is not aromatic, and instead only reduces a radical cation. Consequently, once the applied potential is sufficiently negative to initiate the first reduction, the second reduction following protonation of XH proceeds with relative ease.¹⁵ A similar trend is observed by Cao et al for dihydropyridine-type compound experiments.⁷⁴

The calculated E^0 and pKa values associated with sequential ETs and PTs to form hydrides from their aromatic state X are compiled in Table 4 and exhibit a clear trend

as we now discuss. Functionalizing DHPs with electron-donating groups (EDGs) produces species with more negative reduction potentials, as shown in Fig 8a, larger pKa values and – as also seen in Fig 8a – ultimately stronger hydricities. In contrast, functionalization with electron-withdrawing groups (EWGs) leads to species with lower pKa values and less negative reduction potentials, the latter also seen in Fig. 8a. Concerning the pKa effects, EDGs increase the electron density in the conjugated π -system, allowing for easier protonation of X and XH^0 species, which explains the larger pKa values relative to EWG-functionalized species. The effects on E_1^0 are related to the increased electron density with EDGs which also destabilizes the reduced π -system of XH . As a result, the addition of the 7th electron into the aromatic ring that breaks the aromaticity must also overcome repulsive coulombic interactions with the EDG-provided electron density. Thus, reduction of XH^+ in the case of EDG-functionalized DHPs requires more energy (produces lower reduction potentials) than does reduction of XH^+ for EWG-functionalized DHPs. In addition to these inductive effects on reduction potentials, the size of the π -space affects the reduction potentials of XH^+ ; Larger π -systems containing multiple fused aromatic rings, such as quinoline (3-H, Table 4) and benzoquinoline (5-H, Table 4), delocalize the electrons in the π -space, thus providing effects similar to EWGs to produce less negative reduction potentials, as shown in Fig 8b. That also results in lower pKa values.

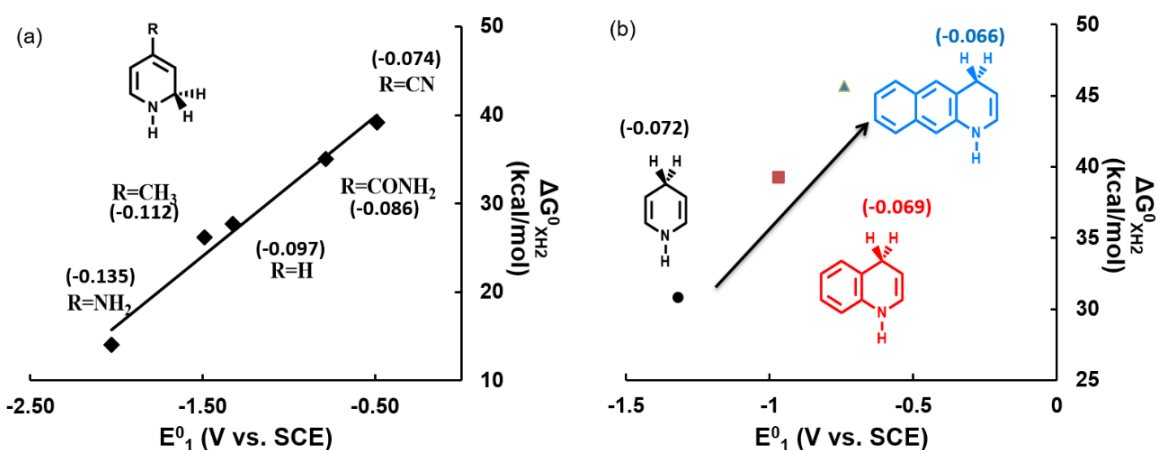


Figure 8. Aqueous hydricity (kcal/mol) vs. the first reduction potential E^0_1 (V versus SCE). (a) Effects of functionalizing 1,2-dihydropyridine (entry 2-H, Table 4) with EDGs (R= NH₂ and CH₃; lower $\Delta G^0_{XH_2,w}$ and more negative E^0_1) and EWGs (R= CN and CONH₂; larger $\Delta G^0_{XH_2,w}$ and less negative E^0_1). (b) Comparison of multiple-ring systems: 1,4-dihydropyridine (one ring; entry 1-H, Table 4) with 1,4-dihydroquinoline (two rings; entry 3-H, Table 4) and 1,4-dihydrobenzoquinoline (three rings; entry 5-H, Table 4). The arrow indicates the direction of increasingly fused aromatic rings, which have an effect similar to that of the EWGs in (a). Lower magnitude hydricities (y-axis) represent stronger hydrides, while more negative reduction potentials (x-axis) indicate less energy-efficient catalysts. The charge density of the hydridic hydrogen calculated via APT population analysis⁷⁵ is displayed in parentheses.

It is important to stress that both pK_a and E^0 depend on experimental conditions. For example, E^0 depends on both the solvent and solution pH. Table 4 tabulates the aqueous pK_a's and E^0 s of all the DHPs we have examined for $pH = 7$. E^0 values can be adjusted for other pH values using the Nernst equation.⁷⁶ Consequently, Table 4 provides a useful guide for determining which steps are likely to be active for different pyridine analogs.

DIHYDROPYRIDINE STRENGTH

We have calculated, via the methods discussed in Chapter IV, the hydricities, aqueous hydricities and nucleophilicities of DHPs, summarized in Table 4, to analyze the impact of functionalization on hydride donor strength. The driving force for HT reactions by DHPs is rearomatization; upon hydride donation, DHPs regain their aromaticity. The thermodynamic and kinetic strengths of DHPs are governed by the electron densities on the active ring or, more precisely, on the hydridic hydrogen; EDGs increase the electron density in the ring, creating stronger hydrides with lower $\Delta G_{XH_2}^0$ and larger N, whereas EWGs have the opposite effect. These interpretations are supported by the Fig 8 charges on the hydride calculated via atomic polar tensor (APT) population analysis,⁷⁵ (see also: Appendix C).

The HT reaction characterized by $XH_2 + CO_2 \leftrightarrow XH^+ + HCO_2^-$ favors the side with larger $\Delta G_{XH_2,w}^0$. Consequently, the forward reaction to generate formate by HT to CO_2 is favored in water if $\Delta G_{XH_2,w}^0$ of XH_2 is lower than that of formate ($\Delta G_{XH_2,w}^0(HCO_2^-) = 35$ kcal/mol for the reaction $HCO_2^- \rightarrow CO_2 + H^-$).⁵⁶ 10 of 40 DHPs considered in this work are identified as thermodynamically competent in reducing CO_2 , with $\Delta G_{XH_2,w}^0 < 35$ kcal/mol, and are highlighted in Table 1. In contrast, only 2 DHPs from the studied set are deemed capable of CO_2 reduction in acetonitrile, with $\Delta G_{XH_2,a}^0 < 43$ kcal/mol. We also find, as shown in Fig 9, that the DHPs' thermodynamic and kinetic parameters correlate linearly. Such trends within the same class of molecules are often identified in physical organic chemistry as quantitative structure-property (or activity) relationships or, more broadly, linear free energy relationships.⁷⁷⁻⁸¹ In Appendix B, we show that $N = 9$ is the minimum N value required for feasible kinetics of CO_2 reduction by DHPs. Figure 9 shows that all thermodynamically capable DHPs ($\Delta G_{XH_2,w}^0 < 35$ kcal/mol) are also kinetically strong ($N > 10$). As such,

the thermodynamic criterion is sufficient in determining a DHP catalyst's capability in reducing CO₂.

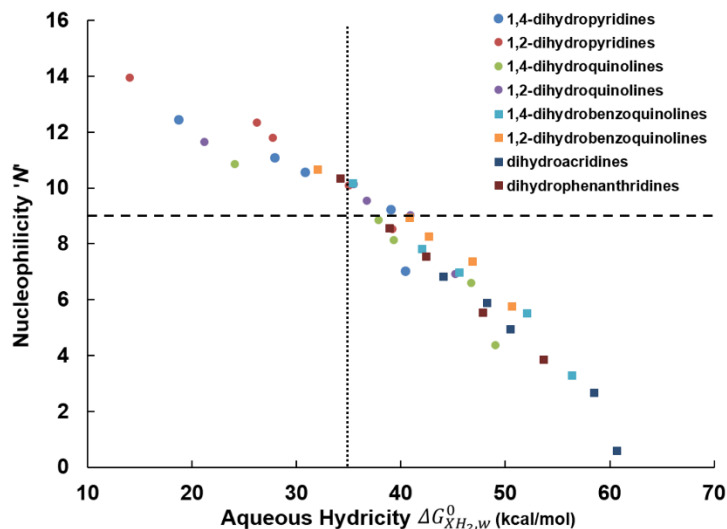


Figure 9. Predicted nucleophilicity N values plotted against predicted aqueous hydricity values (kcal/mol). The plot shows a clear LFER trend for HT reactions within the DHP class of hydrides. The dotted vertical line represents the aqueous hydricity of formate (35 kcal/mol). The dashed horizontal line crosses the y -axis at $N = 9$, an approximate threshold for the kinetic competence of the catalyst at 298 K. DHPs in the upper-left quadrant are considered capable of reducing CO₂ ($N > 9$ & $\Delta G_{XH_2,w}^0 < 35$ kcal/mol).

CHAPTER VI

LIMITATIONS AND FUTURE OUTLOOKS

While our analysis just concluded has found many hydrides to possess hydricities and nucleophilicities indicating capability to reduce CO₂, the recycling of the catalyst remains a considerable challenge. In this chapter, we consider this issue and suggest strategies which may circumvent this limitation.

Our results collected in Fig 10 demonstrate that a strong correlation exists between the first (and most free energy-demanding) reduction potential E_1^0 and the aqueous hydricities $\Delta G_{XH_2,w}^0$ of DHPs. We have also indicated in that Figure that only all DHPs with $\Delta G_{XH_2,w}^0 < 35$ kcal/mol (the hydricity of formate) are theoretically capable of reducing CO₂. This $\Delta G_{XH_2,w}^0$ - E_1^0 correlation – which is approximately linear for each DHP type – reveals the essential recycling challenge: stronger catalysts require more free energy to recycle them in order to produce their active hydride forms.

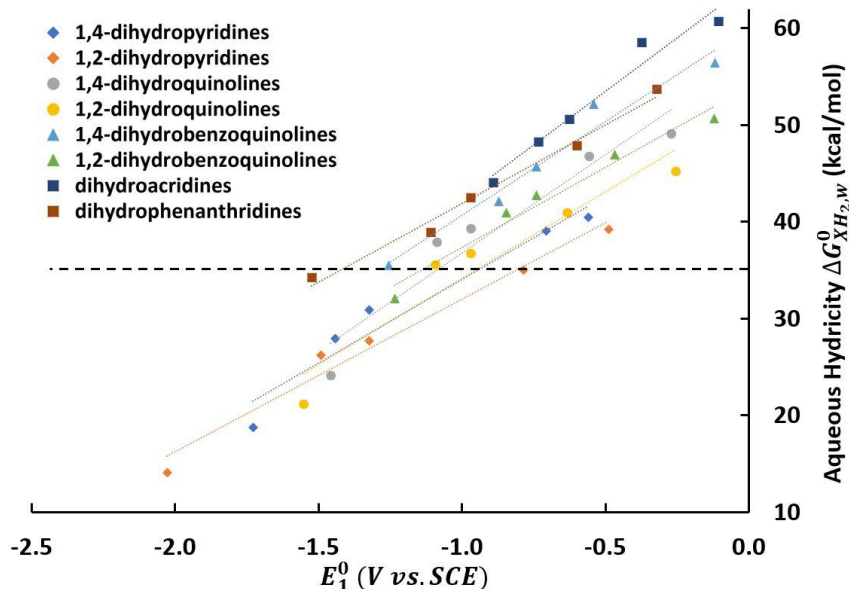


Figure 10. Aqueous hydricity $\Delta G_{XH_2,w}^0$ (kcal/mol) – defined by the reaction eq. 9 in water solvent – versus the first reduction potential E_1^0 (V versus SCE) – defined by eqs. 16 and 17 – for all 40 DHPs considered in this work. Linear regression is performed to obtain the dotted lines for each family of DHPs. The dashed horizontal line corresponds to formate’s aqueous hydricity $\Delta G_{XH_2,w}^0 = 35$ kcal/mol. As discussed in text, there is a tradeoff (linear within each DHP family) between the strength of the hydride (increasing with smaller $\Delta G_{XH_2,w}^0$) and free energy required to recycle it (increasing with more negative E_1^0). The best catalysts would optimally lie in the lower region of Fig 10 as much as possible towards the right.

Overcoming the restrictions resulting from the $\Delta G_{XH_2,w}^0$ - E_1^0 correlation would be of significant help in the effort to achieve conversion of CO_2 into fuels effected by molecular catalysts. We will suggest various possible approaches below that might avoid such a $\Delta G_{XH_2,w}^0$ - E_1^0 correlation. While heterogeneous CO_2 catalysis is obviously also of great interest, here we limit ourselves to offering general suggestions – some based on recent work⁸²⁻⁸³ – for improving homogeneous CO_2 reduction efficiency.

As discussed in Chapter V, the strength of the hydride donor – which stems from re-aromatization²⁸ – scales linearly with the free energy required to de-aromatize the XH^+ species. Because the $\Delta G_{XH_2,w}^0$ - E_1^0 correlation in pyridines is fundamentally governed by aromaticity issues ($\Delta G_{XH_2,w}^0$ and E_1^0 correlate with rearomatization and

de-aromatization, respectively), one might be tempted to avoid the correlation's difficulty by completely avoiding aromatic compounds in the search for molecular CO₂ reduction catalysts. However, a more nuanced solution might lie in suitably changing the nature of the hydride rather than simply evading aromaticity. The search for catalysts need not be limited to carbon-based hydrides, but could also include other classes of potentially regenerable hydrides, such as nitrogen-based hydrides (i.e. nitrogen-bound hydride). An encouraging example is provided by the biological cofactor flavin adenine dinucleotide (FAD), which commonly participates as a hydride transfer reagent in its fully reduced FADH₂ state;⁸⁴ remarkably the nitrogen-based FADH₂'s hydricity is on par with that of the carbon-based cofactor NADPH.⁵⁰ Moreover, FAD reduction requires a less negative reduction potential than does NADPH, further motivating consideration of nitrogen- or Flavin-based hydrides.^{49, 85} In this connection, Lim et al. recently predicted that the carbon-based flavin derivative 6,7-dimethyl-4-hydroxy-2-mercaptopteridine is thermodynamically capable of reducing CO₂, but is kinetically slow.⁸⁶ But the electron density arguments discussed in Chapter V, indicate that functionalizing analogs of pteridines with EDGs would likely favorably affect the HT kinetics since the hydride's electron density increases.

A more pronounced difference in approach to overcoming the restrictions imposed by the $\Delta G_{XH_2,w}^0 - E_1^0$ relationship would be the use of transition metal molecular catalysts, as illustrated by the ruthenium-based molecular catalyst examined by Tanaka and coworkers.⁸⁷⁻⁹³ These authors showed that the Ru complex with the organic ligand 1,5-dihydro-2-(2-pyridyl)-benzo[b]-1,5-naphthyridine (which is analogous to pyridine) catalyzes HTs to CO₂ for methanol production via this catalysis with the assistance of carboxylate bases. Additionally, Tanaka's catalyst was found to be recycled purely photochemically.⁹⁰ Muckerman and coworkers proposed that the Tanaka catalyst is

sufficiently strong in reducing CO₂ after accessing higher reduced states via photoexcitation.^{52-53, 94} Photochemistry's role in the Tanaka system is then to produce a highly reducing electron in an excited state of the molecular catalyst by photoexcitation to aid the CO₂ reduction. Although ruthenium is expensive – and thus likely not economic for industrial-scale CO₂ reduction applications – understanding the Tanaka catalyst's nature can provide key insights into novel alternative strategies for reducing CO₂ and catalyst regeneration.

Another approach to CO₂ reduction could involve devising systems where photoelectrochemical phenomena are exploited without involving prohibitively expensive metals. For example, a photocatalyst might act to regenerate DHPs by shuttling electrons from an electrode to the pyridinic forms *X*. Here long-lived high energy excited states of the photocatalyst possessing highly reducing electrons could be accessed by photoexcitation, thus overcoming the difficulty that direct electrochemical photocatalyst reduction occurs at considerably more negative potentials. In conjunction with this approach, a molecular bridge between pyridine and the photocatalyst could be utilized to facilitate electron transfer to pyridine, an approach often used for charge transfer in nanoparticle systems.⁹⁵⁻⁹⁶

Lastly, in addition to improving the hydride donor strength, CO₂ activation needs to be investigated. Various molecular approaches have been shown to be effective in activating CO₂ for reduction; here we present a few selected examples to discuss CO₂ activation. Rhodium pincer catalysts can activate CO₂ via a Rh-O bond, allowing easier HT to the carbon atom, yielding formate product. This catalyst, however, lacks the capability to transfer protons and allow further reduction to more desired products such as methanol.⁸² Frustrated Lewis pairs (FLPs) have also been shown to enhance the thermodynamics and kinetics of HT to CO₂ by Ammonia-Borane,

although the irreversible binding of FLPs on CO₂ hinders the production of more useful products.⁸³ FLP chemistry involving the simultaneous activation of CO₂ and the reducing agent is a promising approach, as shown by Fontaine and coworkers.⁹⁷ Most CO₂ reductions by FLPs, however, require HTs from hydroborane or hydrosilane reagents, although some recyclability issues will need to be overcome.

CHAPTER VII

CONCLUSIONS

Quantum chemical methods based on DFT have been exploited herein to quantify the effects of solvation and functionalization on the hydride donor strength of dihydropyridine species, and the feasibility of their formation. We have focused on hydride transfer (HT) to CO_2 , of importance for both energy and environmental concerns. We also focus on HT reactions in water solvent, since HT by dihydropyridines is thermodynamically and kinetically more favorable in water than in e.g. acetonitrile, due to solvent stabilization of the ionic reduced products, specifically hydrogen bonding between the solvent and products. The hydricity and nucleophilicity concepts are used to evaluate hydrides' thermodynamic and kinetic activity, which stems from the stabilizing effects of re-aromatization. The reduction potential associated with de-aromatizing pyridines (and recycling the active form of the catalyst) is used as metric for catalyst efficiency. To better understand dihydropyridine catalysts, a systematic study was performed to observe the effect of functional groups on the hydricity, nucleophilicity, and reduction potentials of pyridinic derivatives.

An important feature of our findings is that electron-donating groups create stronger hydrides, as indicated by lower hydricity values and higher electron densities localized on the hydridic hydrogen. This advantage, however, comes at the expense of larger free energy requirements (more negative reduction potentials) to recycle dihydropyridinic catalysts; this effect is due to the feature that the pyridinic ring – considering an increased electron density in the π -system by electron-donating groups – must be de-aromatized. Multiple ring systems and electron-withdrawing functional groups, in contrast to electron-donating groups, produce more efficient but

weaker hydrides as the electron density is delocalized across the molecule. This HT strength-efficiency relationship between the catalyst hydricity and the free energy required to recycle it restricts the capability of such recyclable organic hydrides for HT, and thus presents a major challenge for the design of hydrides to catalyze CO₂ reduction. We have presented several suggestions for circumventing this limitation which could prove to be of interest in the catalytic conversion of CO₂ to fuels.

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APPENDIX

Appendix A. Hydricity

Benchmark Hydricity Calculations

Here we validate the M06/6-31+G(d,p)³¹⁻³² level of theory (Chapter III) used to calculate hydricity values $\Delta G^0_{\text{XH}_2, \text{a}}$ in acetonitrile with a more reliable wB97XD/6-311++G(d,p).³²⁻³³ Table A.1 shows that hydricity values obtained via both methods are within 3 kcal/mol. The latter theory level tends to overestimate hydricity values by 2.5 kcal/mol relative to the former. This is within acceptable DFT error, so we continue to use the M06/6-31+G(d,p) for hydricity calculations.

Table A.1. Hydricity $\Delta G^0_{\text{XH}_2}$ Predictions for Different Electronic Structure Theory Levels: M06/6-31+G(d,p) versus wB97XD/6-311++G (d,p) in CPCM-acetonitrile solvent. The hydricities have been calculated using the isodesmic approach.

Molecule*	Hydricity (kcal/mol)		Δ Hydricity
	M06 ^a	wB97XD ^b	
1a	50.54	53.42	2.88
1b	59.77	61.92	2.15
1c	63.38	66.04	2.66
1d	47.82	50.25	2.43
1e	41.76	44.38	2.62
Average deviation			+2.55

*Codes for molecular identities can be found in Fig 5.

^aHydricity values in acetonitrile solvent (kcal/mol) calculated via the M06/6-31+G(d,p)/CPCM-CH₃CN electronic structure level of theory.

^bHydricity values in acetonitrile solvent (kcal/mol) calculated via the wB97XD/6-311++G(d,p)/CPCM-CH₃CN electronic structure level of theory.

Hydricity Shift Calculations.

Creutz et al. report the shift in the solvated hydride anion free energy G_{H^-} on going from acetonitrile to water solvents as approximately 16-22 kcal/mol. Using the PIA method described in Chapter IV, we find that G_{H^-} is -424.6 kcal/mol in water, approximately 20 kcal/mol more favorable than in acetonitrile, in good agreement with the literature.⁵³ Extrapolation of the G_{H^-} value in water using the PIA is shown in Fig A.1. Using the IA with formate as the reference hydride (whose aqueous hydricity $\Delta G^0_{XH_2,w}$ is 35 kcal/mol) yields a lower G_{H^-} shift of ~ 9 kcal/mol on going from acetonitrile to water, which is unacceptably outside the 16-22 kcal/mol range predicted by Creutz. These results lend confidence in the viability of the PIA.

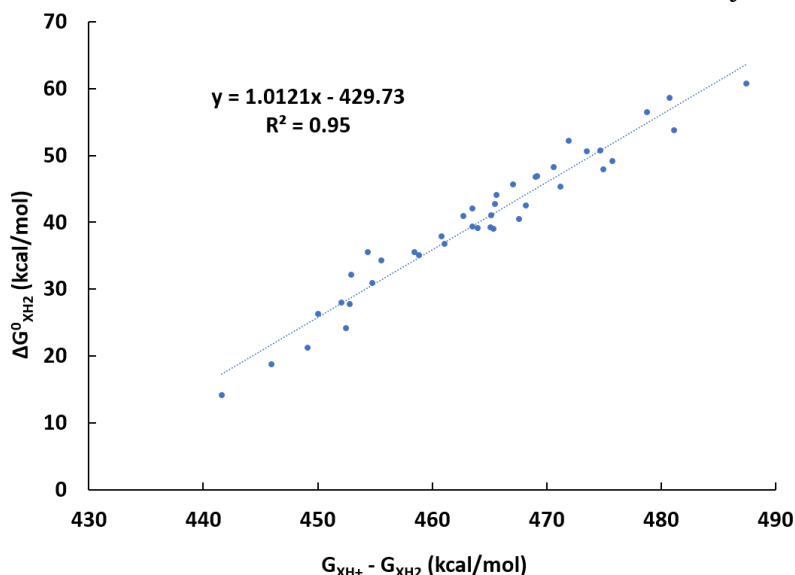


Figure A.1. Aqueous hydricity $\Delta G^0_{XH_2}$ (kcal/mol) using the ‘pKa-isodesmic’ approach versus the computed free energy difference ($G_{XH^+} - G_{XH_2}$). The value of the hydride free energy G_{H^-} can be found by taking the ratio of intercept to slope

Appendix B. Nucleophilicity

Evaluating the Value of N for Kinetic Threshold

This section outlines how we determine the target N value to analyze the kinetic viability of hydrides at room temperature, where hydrides with hydride transfer barriers less than 20 kcal/mol are defined as kinetically active. We first show that the relationship between N in DCM solvent and the activation free energy in water solvent remains linear (with some deviations) in Fig B.1. Although the activation free energies of HT in water are lower than in DCM, they maintain they scale roughly similarly, with a slight shift to the left (lower activation free energies) in Fig B.1.

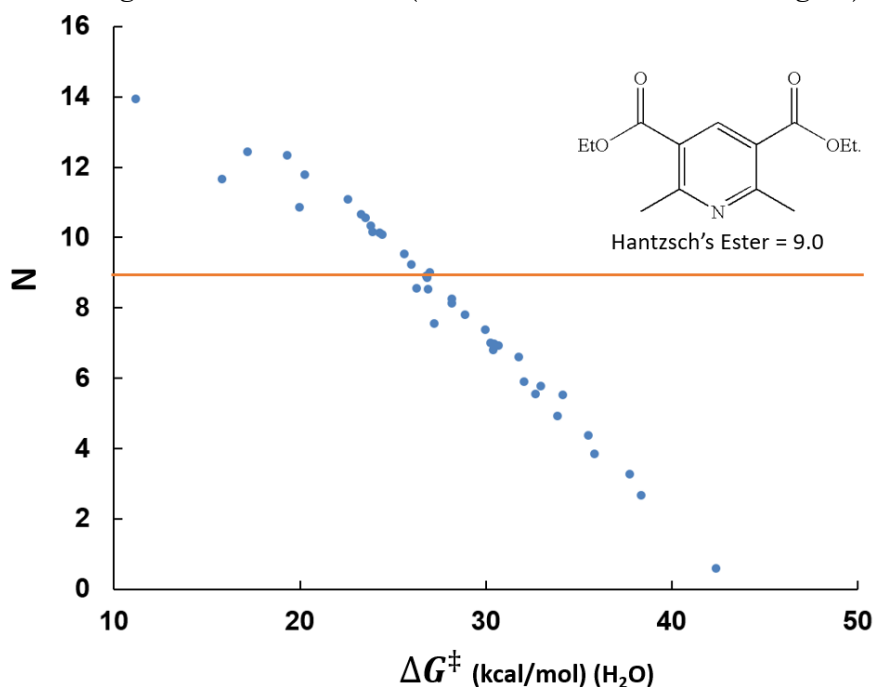


Figure B.1. N values in DCM solvent are plotted versus the computed $\Delta G^\ddagger$. N depends linearly on the activation free energy $\Delta G^\ddagger$ of HT of DHPs with CO₂ in water media.

In a detailed study by Lim et al.²⁸ using CCSD(T) level of theory and 2 solvating waters, 1,2-DHP has been shown to have an activation free energy of ~14.3 kcal/mol in water at room temperature. Reactions at room temperature can proceed at practical rates if their activation barriers are below ~20 kcal/mol.²⁸ Our calculations

indicate that the activation free energies of HT reactions by DHPs are systematically lower in water than in acetonitrile solvent. This can be explained by the polar nature of the transition state of the HT reaction, which is more stabilized by the more polar water solvent relative to acetonitrile. Our calculations using M06 – a lower level of theory compared to CCSD(T) – indicate that 1,2-DHP has an N value of 11.8 corresponding to an activation free energy of 22.3 kcal/mol in DCM. This clearly indicates that our activation free energies calculated in water are overestimated by ~8 kcal/mol. By shifting the activation free energies of 1,2-PyH₂ and all other DHPs by 8 kcal/mol (the difference between the DCM and REF²⁸ models) we obtain that a 20 kcal/mol free energy activation barrier corresponds to an 8.9 N value (Fig B.1). We thus determine that an N value of ~9 is a reasonable cutoff for kinetic viability of DHPs as HT catalysts.

Appendix C. APT Charge Analysis

We analyze the hydride strength for DHPs as a function of charge density on their hydridic by performing APT charge density analyses. We find that EDGs increase the electron charge density (more negative charge) on the hydrides. In contrast, EWGs are found to delocalize the electron away from the hydridic hydrogen, inducing a less negative charge on the hydride. A larger negative charge indicates that the hydrogen has a more hydridic character and thus lower hydricities, as shown in Fig C.1. This is in agreement with our deduction in Chapter V of the text, which associates EDGs with stronger hydrides and EWGs with weaker hydrides. Table C.1 lists the hydride charge obtained via APT charge analysis for all 40 DHPs in this work.

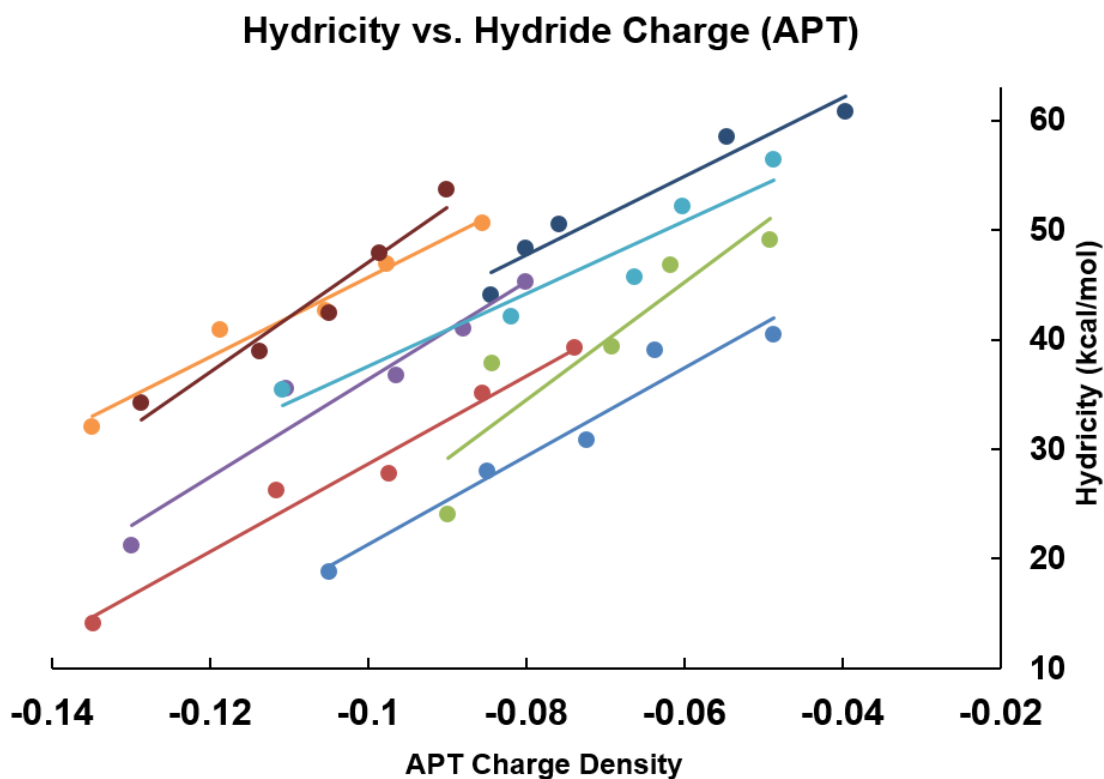


Figure C.1. Aqueous hydricity versus the charge density localized on the hydridic hydrogen. A linear correlation can be drawn for each subclass of DHPs. Generally, stronger hydrides have a more negative charge.

Table C.1. Charge density on the hydridic hydrogen of all DHPs calculated via the APT method.

Molecule*	Charge (H^-)	Molecule*	Charge (H^-)
1a	-0.072	5a	-0.066
1b	-0.064	5b	-0.060
1c	-0.049	5c	-0.049
1d	-0.085	5d	-0.082
1e	-0.105	5e	-0.111
2a	-0.097	6a	-0.105
2b	-0.086	6b	-0.098
2c	-0.074	6c	-0.086
2d	-0.112	6d	-0.119
2e	-0.135	6e	-0.135
3a	-0.069	7a	-0.076
3b	-0.062	7b	-0.055
3c	-0.049	7c	-0.040
3d	-0.084	7d	-0.080
3e	-0.090	7e	-0.085
4a	-0.097	8a	-0.105
4b	-0.088	8b	-0.099
4c	-0.080	8c	-0.090
4d	-0.110	8d	-0.114
4e	-0.130	8e	-0.129

*Codes for molecular identities can be found in Fig 5.