Thermodynamic Parameters of Elementary Steps for 3,5-Disubstituted 1,4-Dihydropyridines To Release Hydride Anions in Acetonitrile

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ABSTRACT: A series of 3,5-disubstituted 1,4-dihydropyridine derivatives including the derivative with two chiral centers, 6H (R² = CH₃, CH₂Ph), as a new type of organic hydride source were synthesized and characterized. The thermodynamic driving forces (defined as enthalpy changes or standard redox potentials) of the 6 elementary steps for the organic hydrides to release hydride ions in acetonitrile were measured by isothermal titration calorimetry and electrochemical methods. The impacts of the substituents and functional groups bearing the N1 and C3/C5 positions on the thermodynamic driving forces of the 6 elementary steps were examined and analyzed. Moreover, the results showed that the reaction mechanism between the chiral organic hydride and activated ketone (ethyl benzoylformate) was identified as the concerted hydride transfer pathway based on the thermodynamic analysis platform. These valuable and crucial thermodynamic parameters will provide a broadly beneficial impact on the applications of 3,5-disubstituted 1,4-dihydropyridine derivatives in organic synthesis and pharmaceutical chemistry.

INTRODUCTION

Organic hydrides (also called as metal-free hydrides) are one of the most important organic compounds that can provide a hydride ion to the reaction partner in chemical reactions.1−4 Because of having many special chemical properties compared with the metal hydrides (also called as inorganic hydrides, such as KH, NaH, NaBH₄, LiAlH₄, etc), organic hydrides have been receiving extensive applications in biomimetic chemistry,5,6 organic synthetic chemistry,7,8 energy chemistry,9 green chemistry,10,11 materials chemistry,12,13 and many others.14 Below are listed some representative examples (Scheme 1).

Scheme 1. Structures of the Three Well-Known Organic Hydride Donors (BNAH, HEH, and AcrH₂)

Benzy1,4-dihydrornicotinamid (BNAH) is a well-known organic hydride. Because of having the same core structure with NADH coenzyme, BNAH has been widely used as the model of NADH coenzyme to examine the mechanism of NADH oxidation in vivo.5−25 Hantzsch ester (3,5-diester substituted 1,4-dihydropyridine, HEH) is a typical organic hydride. Because of easily releasing one hydrogen molecule or two hydrogen atoms, Hantzsch ester has been extensively used as reducing agent to make aldehydes, ketones, imines, alkenes, and ketroesters become the corresponding saturated forms.26−30 N-Methyl-9,10-dihydronacridine (AcrH₂) is also another well-known organic hydride. Owing to possess very good fluorescence properties, AcrH₂ has been widely used in optical materials.31,32 In recent years, the 3,5-disubstituted 1,4-dihydropyridine derivatives have drawn great attention33−37 because these compounds have shown versatile applications in organic synthesis, particularly in asymmetric synthesis. For example, various activated ketones (the activated ketones were defined as strong electron-withdrawing groups attached to the carbonyl group in this work) could be asymmetric reduced to chiral alcohols in acetonitrile at room temperature by using the (L)-valine derivated 3,5-disubstituted 1,4-dihydropyridine (6H, R² = CH₃) via hydride transfer manner in the presence of MgClO₄·1.5H₂O.38−41

Although organic hydrides have received extensive attention, the focus of many chemists is mainly on the applications, the reports on the thermodynamic driving forces to scale their hydride-donating ability, especially the thermodynamic driving forces of elementary steps to evaluate the mechanism of hydride transfer reactions in solution have so far been scarce (Scheme 2).42−44 Because the development of the potential

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Scheme 2. Six Elementary Steps of 3,5-Disubstituted 1,4-Dihydropyridines (XH) To Release Hydride Anions

Scheme 3. Structures of 3,5-Disubstituted 1,4-Dihydropyridines (XH) in This Work

R¹ = p-OCH₃, p-CH₃, p-H, p-Br, p-CN; R² = CH₃, CH₂Ph

Figure 1. Electrochemical methods (CV and OSWV) for measurement of the oxidation potential of 2H (R¹ = p-H) (a) and the reduction potential of 2⁺ (R¹ = p-H) (b) in anhydrous deaerated acetonitrile solution.
applications of organic hydrides demands the guidance of the related thermodynamic parameters in solution, evidently it should be an urgent task for chemists to acquire those exact values.

As our continuous interest in the determination of the thermodynamic parameters of organic hydrides to release hydride anions, we, in this paper, have synthesized a new type of organic hydrides (XH), namely 3,5-disubstituted 1,4-dihydropyridine compounds as shown in Scheme 3, and the related thermodynamic driving forces for 6 elementary steps of XH to PhXn+ClO4⁻ (eq 3) were measured by using isothermal titration calorimetry (ITC) in acetonitrile at 298 K. The detailed experimental results were summarized in Table 1.

### RESULTS

The oxidation potentials of 3,5-disubstituted 1,4-dihydropyridines (XH) and reduction potentials of the cations (X⁺) were detected by using the electrochemical method, including cyclic voltammetry (CV) and Osteryoung square wave voltammetry (OSWV) in acetonitrile at 298 K (Figure 1, SI-3). Molar reaction enthalpy changes (ΔH_rxn) of hydride transfer from 3,5-disubstituted 1,4-dihydropyridines (XH) to PhXn+ClO4⁻ (eq 3) were measured by using isothermal titration calorimetry (ITC) in acetonitrile at 298 K (Figure 2, SI-4). The detailed experimental results were summarized in Table 1.

![Figure 2. ITC for detection of the reaction heat between 2H (R\textsuperscript{1} = p- H) and PhXn⁺ClO\textsubscript{4}⁻ in acetonitrile at 298 K. Titration was conducted by addition of 2H (R\textsuperscript{1} = p-H) (10 μL, ca. 2.63 mM) every 400 s into the PhXn⁺ClO\textsubscript{4}⁻ (ca. 25.0 mM).](image)

| (XH) | R\textsuperscript{1}/R\textsuperscript{2} | ΔH\textsubscript{rxn} | E\textsubscript{ox}(XH) | E\textsubscript{red}(X⁺) |
|------|-----------------|-----------------|-----------------|-----------------|
|      |                  | CV    | OSWV  | CV    | OSWV  |
| 1H   | (R\textsuperscript{1} = ) | -28.4 | 0.402 | 0.371 | -1.323 | -1.299 |
| p-OCH₃ | | -27.9 | 0.408 | 0.380 | -1.316 | -1.287 |
| p-CN | | -26.7 | 0.426 | 0.395 | -1.289 | -1.263 |
| p-CN | | -25.5 | 0.452 | 0.428 | -1.261 | -1.235 |
| 2H   | (R\textsuperscript{1} = ) | -28.6 | 0.376 | 0.354 | -1.335 | -1.305 |
| p-OCH₃ | | -28.2 | 0.385 | 0.362 | -1.327 | -1.299 |
| p-CN | | -27.7 | 0.390 | 0.370 | -1.318 | -1.288 |
| p-CN | | -27.0 | 0.400 | 0.378 | -1.313 | -1.279 |
| 3H   | (R\textsuperscript{1} = ) | -25.8 | 0.438 | 0.410 | -1.281 | -1.258 |
| p-OCH₃ | | -29.3 | 0.365 | 0.338 | -1.340 | -1.312 |
| p-CN | | -28.9 | 0.373 | 0.346 | -1.333 | -1.302 |
| p-CN | | -28.3 | 0.382 | 0.354 | -1.319 | -1.294 |
| 4H   | (R\textsuperscript{1} = ) | -26.0 | 0.626 | 0.602 | -1.180 | -1.156 |
| p-OCH₃ | | -25.5 | 0.633 | 0.608 | -1.170 | -1.145 |
| p-CN | | -25.2 | 0.641 | 0.618 | -1.159 | -1.134 |
| 5H   | (R\textsuperscript{1} = ) | -24.7 | 0.655 | 0.630 | -1.142 | -1.117 |
| p-CN | | -23.9 | 0.681 | 0.653 | -1.110 | -1.086 |
| 6H   | (R\textsuperscript{1} = ) | -37.6 | 0.628 | 0.605 | -1.149 | -1.129 |
| CH₂Ph | | -38.7 | 0.457 | 0.429 | -1.268 | -1.246 |
| CH₃ | | -42.4 | 0.397 | 0.374 | -1.352 | -1.318 |
| 7H   | (R\textsuperscript{1} = ) | -26.0 | 0.889 | 0.861 | -0.741 | -0.707 |
| 8H   | (R\textsuperscript{1} = ) | -20.3 | 0.689 | 0.665 | -1.058 | -1.029 |

The unit is kcal mol\textsuperscript{-1}. Each trial was repeated at least three times and reproducible to ±0.05 kcal mol\textsuperscript{-1}. The values of ΔH\textsubscript{rxn} are listed in Table 1, while ΔH\textsubscript{H→A} (PhXn⁺) is the hydride affinity of PhXn⁺ClO\textsubscript{4}⁻. The definition for the thermodynamic driving forces of XH to release hydride anions in acetonitrile was formulated as the molar enthalpy changes ΔH\textsubscript{H→A}(XH) as shown in eqs 1 and 2, which could be easily accessed from eq 4. In eq 4, the values of ΔH\textsubscript{rxn} are listed in Table 1, while ΔH\textsubscript{H→A} (PhXn⁺) is the hydride affinity of PhXn⁺ClO\textsubscript{4}⁻ (~96.8 kcal mol\textsuperscript{-1}) in acetonitrile at 298 K.
Besides these 3 elementary steps thermodynamic parameters [ΔH_{\text{H-d}}(\text{XH}), E_{\text{oa}}(\text{XH}), \text{and } E_{\text{oa}}(\text{X}^+)], the remained 3 thermodynamic parameters are also defined as the relevant enthalpy changes of XH to release hydrogen atoms ΔH_{\text{H-d}}(\text{XH}), the radical cation intermediates XH^+ to release hydrogen atoms ΔH_{\text{H-d}}(\text{XH}^+), and protons ΔH_{\text{PD}}(\text{XH}^+) in acetonitrile, respectively.46 Because these values could not be measured by the experimental technique directly, our group designed a three thermodynamic cycles based on the possible hydride transfer process of 3,5-disubstituted 1,4-dihydropyridines in acetonitrile at 298 K (Scheme 4).

\[
\begin{align*}
\Delta H_{\text{H-d}}(\text{XH}) &= \Delta H_{\text{H-d}}(\text{XH}) - F[E_{\text{oa}}(\text{X}^+)-E^0(H^+/\text{g})] \\
\Delta H_{\text{H-d}}(\text{XH}^+) &= \Delta H_{\text{H-d}}(\text{XH}) - F[E_{\text{oa}}(\text{XH})-E^0(H^+/\text{g})] \\
\Delta H_{\text{H-d}}(\text{XH}^+) &= \Delta H_{\text{H-d}}(\text{XH}) - F[E_{\text{oa}}(\text{XH})-E^0(H^+/\text{g})]
\end{align*}
\]

Scheme 4. Construction of Three Thermodynamic Cycles for 3,5-Disubstituted 1,4-Dihydropyridines (XH) and Their Related Intermediates in Acetonitrile

According to the thermodynamic cycles and Hess’s law, eqs 5−7 were well established.53 In eqs 5−7, \( E_{\text{oa}}(\text{XH}) \) and \( E_{\text{oa}}(\text{X}^+) \) are the standard oxidation potentials of XH and X^+ in acetonitrile, which were adopted the OSWV values instead of CV values as they were closer to the standard redox potentials. \( E^0(H^+/\text{g}) = -1.137 \) (V vs Fe^{+5/0}) and \( E^0(H^+/\text{g}) = -2.307 \) (V vs Fe^{+50}) are known data and available from the literature.53 \( \Delta H_{\text{H-d}}(\text{XH}), \Delta H_{\text{H-d}}(\text{XH}^+), \) and \( \Delta H_{\text{PD}}(\text{XH}^+) \) of the 3,5-disubstituted 1,4-dihydropyridines in acetonitrile and they are readily summarized in Table 2.

## DISCUSSION

Thermodynamic Driving Forces of 3,5-Disubstituted 1,4-Dihydropyridines (XH) To Release Hydride Ions in Acetonitrile. \( \Delta H_{\text{H-d}}(\text{XH}) \) is an intrinsic thermodynamic parameter to evaluate the hydride-donating abilities of 3,5-disubstituted 1,4-dihydropyridines. Overall, the enthalpy changes range from 66.5 kcal mol\(^{-1}\) for 6H \((R^2 = \text{CH}_3)\) to 79.5 kcal mol\(^{-1}\) for 7H \((R^2 = p-\text{H})\) (Table 2). The relative large span (13 kcal mol\(^{-1}\)) constituted a diverse organic hydrides library, which could be further adjusted via structural modification. The energy gap between 25 XH was extremely related to the substituent effect at N1 position and structural variants at C3/C5 positions. The substituents attached to the benzyl group exhibited a minor effect for the hydride-donating abilities of 3,5-disubstituted 1,4-dihydropyridine derivatives. Strong electron-donating group \((p-\text{OCH}_3)\) can slightly improve the hydride-donating ability as compared with the remarkable electron-withdrawing group \((p-\text{CN})\) (Table 2). Replacement of methyl group by benzyl group at N1 position decreased hydride-donating abilities by 3.7 kcal mol\(^{-1}\) \(6H \ (R^2 = \text{CH}_3)\) vs \( (R^2 = \text{CH}_2\text{Ph})\) Table 2]. It is not unexpected because the benzyl group possessed stronger electron-withdrawing ability than the methyl group. Importantly, the hydride-donating abilities for the nonbridged and bridged XH did not display obvious differences, which meant that the ring structure did not affect the thermodynamic driving forces of releasing hydride anions \([1H−3H (R^2 = p-H) vs 6H \ (R^2 = \text{CH}_2\text{Ph}) \text{vs } 4H, \ 	ext{Table } 2\]. In this context, these results provided some implications for chemists that introducing chiral groups on the bridged ring would not interfere with the hydride-donating ability of XH, thus enabling us to design more elegant chiral groups on the bridged ring structure of XH in order to further improve the enantioselectivity, but did not worry about exerting influence on the reductive capability. Additionally, the variants of C3/C5 functional groups allowed us to closely investigate the structure-reactivity relationship of these organic hydrides. The electron-withdrawing abilities of 3,5-disubstituted functional groups are undoubtedly in the sequence of −CN > −CO\(_2\text{C}_2\text{H}_5\) > −CO\(_2\text{C}_2\text{H}_3\) > −CONH\(_2\). Because the stronger electron-withdrawing groups would decrease the stability of the corresponding pyridine-type cations after releasing hydride anions; therefore, the abilities of the 3,5-disubstituted 1,4-dihydropyridines to donate hydride anions are extremely reserved with this trend and resulted in the order of \(7H < 8H < 4H < 1H\).

It is important to mention here that the thermodynamic scale was established to provide a straight-forward pathway to compare the hydride-donating abilities between 3,5-disubstituted 1,4-dihydropyridines and other common NADH analogues (BNAH, HEH, and AcrH\(_2\)) in acetonitrile. The 3,5-disubstituted 1,4-dihydropyridines in our system were selected the N1 positions with methyl and benzyl groups in order to make consistent with BNAH, HEH, and AcrH\(_2\).

As shown in Figure 3, the enthalpy changes of the 3,5-disubstituted 1,4-dihydropyridines (XH) are located at the middle of the scale. The abilities of all 3,5-disubstituted 1,4-dihydropyridines to release hydrides were inferior to the BNAH (64.2 kcal mol\(^{-1}\)),46 but stronger than the AcrH\(_2\) (81.1 kcal mol\(^{-1}\)).46 However, all of 3,5-disubstituted 1,4-dihydropyridine organic hydrides are weaker than the widely used inorganic hydrides, such as LiAlH\(_4\) (48 kcal mol\(^{-1}\))55,56 and NaBH\(_4\) (55 kcal mol\(^{-1}\)).55,56 Among them, the enthalpy changes of 6H \((R^2 = \text{CH}_3)\) are close with that of BNAH, indicating that it is a strong organic hydride reductant. Meanwhile, most of the 3,5-disubstituted 1,4-dihydropyridine organic hydrides \([1H−5H, 6H \ (R^2 = \text{CH}_2\text{Ph})]\) are concentrated on the enthalpy changes from 68.5 to 71.6 kcal mol\(^{-1}\), which are similar to that of HEH (69.3 kcal mol\(^{-1}\)).46 and could also be referred to as strong organic hydrides. In theory, these organic hydrides have the potential to replace HEH as ideal reductants in organic catalysis and synthesis, especially for 5H, which could be employed as an effective reductant in the asymmetric reaction if some chiral groups are introduced on the bridged ring.46 In contrast, the stronger electron-withdrawing groups at the C3/C5 positions (\(7H, 8H\)) lead to a significant decrease of the hydride-donating abilities,
which are close to AcrH₂, classified as the moderate organic hydrides. More interestingly, although the reductive abilities for 3,5-disubstituted 1,4-dihydropyridines were weaker than the BNAH, they were not encountered with side reactions, such as hydrated and addition to the carbonyl group in terms of ketone reduction. Hence, these 3,5-disubstituted 1,4-dihydropyridines perform a good balance between their stabilities and reactivities and serve as suitable reducing agents.

**Thermodynamic Driving Forces of the 3,5-Disubstituted 1,4-Dihydropyridines (XH) To Release Hydrogen Atoms in Acetonitrile.**

As shown in Table 2, the enthalpy changes $\Delta H_{\text{HD}}(XH)$ of 3,5-disubstituted 1,4-dihydropyridines were calculated from eq 4 by using $\Delta H_{\text{H}^+-(\text{PhXn}^+)} = -96.8$ kcal mol$^{-1}$ in acetonitrile. The values of $5H$ and $7H$ were obtained from eq 4 by using $\Delta H_{\text{H}^+-(\text{TEMPO}^+)} = -105.6$ kcal mol$^{-1}$ in acetonitrile.

According to eqs 5–7, $\Delta H_{\text{H}^+}(XH)$, $\Delta H_{\text{H}^+}(XH^+)$, and $\Delta H_{\text{PD}}(XH^+)$ were obtained.

![Figure 3. Hydride-donating abilities scale for 3,5-disubstituted 1,4-dihydropyridines and other common organic hydrides in acetonitrile.](image)

**Table 2. Enthalpy Changes of XH To Release Hydride Anions and Hydrogen Atoms As Well As Enthalpy Changes of XH$^{+}$ To Release Hydrogen Atoms and Protons in Acetonitrile (kcal mol$^{-1}$).**

| XH   | $R^1/R^2$ | $\Delta H_{\text{H}^+}(XH)^a$ | $\Delta H_{\text{H}}(XH)^b$ | $\Delta H_{\text{H}^+}(XH^+)^b$ | $\Delta H_{\text{PD}}(XH^+)^b$ |
|------|-----------|-------------------------------|-----------------------------|---------------------------------|-------------------------------|
| 1H   | $(R^1=)$  |                               |                             |                                 |                               |
| $p$-OCH$_3$ | 68.4     | 72.1                          | 33.6                        | 10.3                            |                               |
| $p$-CH$_3$  | 68.9     | 72.4                          | 33.9                        | 10.3                            |                               |
| $p$-H       | 69.5     | 72.8                          | 34.3                        | 10.6                            |                               |
| $p$-Br      | 70.1     | 73.0                          | 34.7                        | 10.6                            |                               |
| $p$-CN      | 71.3     | 73.6                          | 35.2                        | 10.4                            |                               |
| 2H   | $(R^1=)$  |                               |                             |                                 |                               |
| $p$-OCH$_3$ | 68.2     | 72.1                          | 33.8                        | 10.6                            |                               |
| $p$-CH$_3$  | 68.6     | 72.3                          | 34.0                        | 10.7                            |                               |
| $p$-H       | 69.1     | 72.6                          | 34.3                        | 10.8                            |                               |
| $p$-Br      | 69.8     | 73.1                          | 34.8                        | 11.1                            |                               |
| $p$-CN      | 71.0     | 73.8                          | 35.3                        | 11.1                            |                               |
| 3H   | $(R^1=)$  |                               |                             |                                 |                               |
| $p$-OCH$_3$ | 67.5     | 71.5                          | 33.4                        | 10.5                            |                               |
| $p$-CH$_3$  | 67.9     | 71.7                          | 33.7                        | 10.5                            |                               |
| $p$-H       | 68.5     | 72.1                          | 34.1                        | 10.7                            |                               |
| $p$-Br      | 69.1     | 72.5                          | 34.4                        | 10.8                            |                               |
| $p$-CN      | 70.4     | 73.3                          | 34.9                        | 10.7                            |                               |
| 4H   | $(R^1=)$  |                               |                             |                                 |                               |
| $p$-OCH$_3$ | 70.8     | 71.2                          | 30.7                        | 4.1                             |                               |
| $p$-CH$_3$  | 71.3     | 71.5                          | 31.0                        | 4.2                             |                               |
| $p$-H       | 71.6     | 71.5                          | 31.1                        | 4.0                             |                               |
| $p$-Br      | 72.1     | 71.6                          | 31.3                        | 3.8                             |                               |
| $p$-CN      | 72.9     | 71.7                          | 31.6                        | 3.4                             |                               |
| 5H   | $(R^1=)$  |                               |                             |                                 |                               |
| 6H   | $(R^2=)$  |                               |                             |                                 |                               |
| CH$_2$Ph   | 70.2     | 72.7                          | 34.0                        | 9.6                             |                               |
| CH$_3$     | 66.5     | 70.7                          | 31.6                        | 8.8                             |                               |
| 7H   | $(R^1=)$  |                               |                             |                                 |                               |
| 8H   | $(R^1=)$  |                               |                             |                                 |                               |

$a$ The $\Delta H_{\text{H}^+}(XH)$ values of 1H–4H, 6H, and 8H were calculated from eq 4 by using $\Delta H_{\text{H}^+-(\text{PhXn}^+)} = -96.8$ kcal mol$^{-1}$ in acetonitrile. The values of 5H and 7H were obtained from eq 4 by using $\Delta H_{\text{H}^+-(\text{TEMPO}^+)} = -105.6$ kcal mol$^{-1}$ in acetonitrile.54

$^b$ According to eqs 5–7, $\Delta H_{\text{H}^+}(XH)$, $\Delta H_{\text{H}^+}(XH^+)$, and $\Delta H_{\text{PD}}(XH^+)$ were obtained.
to release hydrogen atoms in acetonitrile range from the strongest 70.7 kcal mol\(^{-1}\) for \(6H (R^1 = CH_3)\) to weakest 74.0 kcal mol\(^{-1}\) for \(8H\). The relative narrow span indicated that the hydrogen-donating ability is not sensitive to the structural changes both at N1 and C3/C5 positions. The enthalpy changes of 3,5-disubstituted 1,4-dihydropyridines for delivering hydrogen atoms were similar to those of BNAH (70.7 kcal mol\(^{-1}\)),\(^{46}\) TEMPOH (71.2 kcal mol\(^{-1}\)),\(^7\) and AcrH\(_2\) (73.0 kcal mol\(^{-1}\)),\(^6\) but remarkably lower than those of common hydrogen atom donors, such as vitamin E (80.9 kcal mol\(^{-1}\))\(^{16}\) and BHT (81.6 kcal mol\(^{-1}\))\(^{17}\), illustrating that they are good to excellent hydrogen atom donors. It is further proved by the facts that they have the potential abilities to quench some typical radicals, such as (CN)\(_2\)C\(^\cdot\) (isobutyronitrile radical generated by AIBN, 91.9 kcal mol\(^{-1}\))\(^{15}\) and PhC(O)OO\(^\cdot\) (benzoyl radical generated by BPO, 111 kcal mol\(^{-1}\))\(^{16}\), \(i\)-C\(_3\)H\(_7\)OO\(^\cdot\) (85.1 kcal mol\(^{-1}\))\(^{17}\) and PhS\(^\cdot\) (83.5 kcal mol\(^{-1}\))\(^{6}\), which could be used as the antioxidants. Evidently, it may be concluded that these 3,5-disubstituted 1,4-dihydropyridines exhibited the strong abilities to donate hydrogen anions and hydrogen atoms in acetonitrile. However, for the real transfer process, it should be analyzed by consideration of both hydride donors and hydride acceptors.

**Thermodynamic Driving Forces of the 3,5-Disubstituted 1,4-Dihydropyridine Radical Cations (XH\(^{**}\)) To Release Hydrogen Atoms in Acetonitrile.** Hydride transfer initiated by electron transfer would generate radical cations (XH\(^{**}\)), which are the most important intermediates for organic hydrides. However, research based on capturing and analyzing the intermediates is not easy because of the short life time and considerably reactive features of these intermediates, even by the aid of advanced instruments and techniques. Through our thermodynamic cycles (Scheme 4), the thermodynamic driving forces of the radical cations to release hydrogen atoms \(\Delta H_{\text{rd}}(\text{XH}^{**})\) could be obtained, which was very useful to understand their chemical properties and help to diagnose the hydride transfer mechanisms. The enthalpy changes \(\Delta H_{\text{rd}}(\text{XH}^{**})\) span from 30.7 kcal mol\(^{-1}\) for \(4H (R^1 = p-OCH}_3)\) to 36.8 kcal mol\(^{-1}\) for \(7H\) (Table 2). The relatively narrow energy gap (6.1 kcal mol\(^{-1}\)) implied that the hydrogen-donating abilities of 3,5-disubstituted 1,4-dihydropyridine radical cations are less sensitive to the remote substituent effect at N1 positions and structural variants at C3/C5 positions. The radical cations of XH\(^{**}\) are unstable in the air and prefer to deliver hydrogen atoms to other active radical species as a result of comparison with HOO\(^\cdot\) (48.3 kcal mol\(^{-1}\)) in acetonitrile.\(^6\)

**Thermodynamic Driving Forces of the 3,5-Disubstituted 1,4-Dihydropyridine Radical Cations (XH\(^{**}\)) To Release Protons in Acetonitrile.** The enthalpy changes \(\Delta H_{\text{pd}}(\text{XH}^{**})\) for the radical cations to release protons range from \(-0.2\) kcal mol\(^{-1}\) for \(7H\) to 11.1 kcal mol\(^{-1}\) for \(2H (R^1 = \text{p-CN})\) (Table 2). The outcomes showed that the values are more sensitive to the variation at C3/C5 positions, but small effect imposed by the remote substituents on the benzyl group. For examples, \(1H (R^1 = \text{p-H})\) and \(R^1 = \text{p-Br}\) as well as \(2H (R^1 = \text{p-Br})\) and \(R^1 = \text{p-CN}\) gave the same enthalpy changes. All the enthalpy changes for XH\(^{**}\) to release protons are smaller than BNAH\(^{**}\) (12.4 kcal mol\(^{-1}\))\(^{6}\), indicating that other electron-withdrawing groups at CS positions increased their acidities. Moreover, the acidities of these radical cations are extremely stronger than acetic acid (30.4 kcal mol\(^{-1}\))\(^{20}\) and trifluoroacetic acid (22.4 kcal mol\(^{-1}\)) in acetonitrile,\(^{57}\) and \(4H^{**}, 5H^{**}, 7H^{**}, 8H^{**}\) are even greater than hydromorphic acid (7.5 kcal mol\(^{-1}\)) in acetonitrile.\(^{60}\) Therefore, the 3,5-disubstituted 1,4-dihydropyridine radical cations (XH\(^{**}\)) are identified as strong acids. Because the intermediates (XH\(^{**}\)) are preferred to deliver protons instead of hydrogen atoms (smaller enthalpy changes for proton transfer), if hydride transfer is triggered by the electron transfer, the intermediates (XH\(^{**}\)) could rapidly undergo degradation process via proton transfer (\(e^- + \text{H}^+ \rightarrow \text{H}_2\)) instead of hydrogen transfer. Particularly interesting example is the intermediate \(7H^{**}\); the spontaneous proton transfer process was proposed to take place as proof by the negative value of enthalpy change (\(-0.2\) kcal mol\(^{-1}\)). These findings suggested that 3,5-disubstituted 1,4-dihydropyridines could be used as the proton and electron sources in the proton-coupled electron transfer reaction upon initiation by photocatalysis, which is the hot research area in organic synthesis.\(^{69}\)

**Thermodynamic Driving Forces of the 3,5-Disubstituted 1,4-Dihydropyridines (XH) To Release Electrons in Acetonitrile.** The standard oxidation potential \(E_{\text{ox}}(\text{XH})\) of the 3,5-disubstituted 1,4-dihydropyridines (XH) is an essential and crucial electrochemical parameter to evaluate the single-electron oxidation behavior in acetonitrile. The indicators of

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**Figure 4.** Comparison of the electron-donating abilities between 3,5-disubstituted 1,4-dihydropyridines (XH) and other common organic hydrides in acetonitrile.
the electron-donating abilities were determined by OSWV method because of their irreversible oxidation process, suggesting that the intermediates after donating a single electron were unstable and rapid degradation to other species. All the hydride donors exhibited the oxidation potentials in the scope from 0.338 (V vs Fc+/0) for 3H (R1 = p-OCH3) to 0.861 (V vs Fc+/0) for 7H as shown in Table 1. The values are positive than ferrocene, indicating that the 3,5-disubstituted 1,4-dihydropyridines are remarkably reluctant one-electron donors. The electron-withdrawing groups at the C3/C5 positions are tightly related to their oxidation potentials. The increased electron-withdrawing abilities of −CN > −COCH3 > −CO2C2H5 > −CONH2 > −CONHMe > −CONHC4H9 resulted in the decreased abilities of XH to release electrons (Table 1). The substrates with electron-donating substituent on the benzyl group (p-OCH3) presented stronger electron-donating abilities than the electron-withdrawing substituent (p-CN). Similarly, the nonbridged or bridged structures do not alter the electron-donating abilities [1H−3H (R1 = p-H) vs 6H (R2 = CH2Ph) and 4H (R1 = p-H) vs 5H, Table 1].

In Figure 4, the electron-donating abilities of the 3,5-disubstituted 1,4-dihydropyridines and other common hydride donors were intuitively compared. The single electron-donating abilities for 1H−3H and 6H are situated between BNAH (0.219 V vs Fe+/0) and HEH (0.479 V vs Fe+/0),46 which are classified as moderate-to-weak single-electron reductants, but 4H−5H and 7H−8H are remarkably larger than HEH, indicating that they are extremely weak single-electron reductants. Although the presence of the second electron-withdrawing groups at C5 position decreased their single-electron transfer abilities, it led to improve their stabilities toward hydration and oxidation.70

**Thermodynamic Driving Forces of the 3,5-Disubstituted Pyridine-Type Radicals (X*) To Release Electrons in Acetonitrile.** Because the highly reactive radicals X* could not be obtained, the determination of their oxidation potentials Eox(X*) was realized by detection of the reduction potentials of X+, which were also available from the OSWV method because of their irreversibilities. The reduction potentials for cations (X+) distributed between −1.318 (V vs Fe+/0) for 6+ (R2 = CH3) and −0.707 (V vs Fe+/0) for 7+ (Table 1), which means that they are relatively difficult to be reduced. In other words, the neutral radicals (X*) are preferred to release one electron and assigned as strong single-electron reducing agents. All the
electron-withdrawing substituents (–CN, –Br) on the benzyl group could partially stabilize the X⁺, suggesting that the radicals (X*) are relatively electron-rich and electron-donating substituents could easily cause oxidation. This rule was significantly reflected by the functional groups at C3/C5 positions. The strongest electron-withdrawing group (cyano) decreased the electron-donating ability of 7 as compared with the contributions of other functional groups (ester, ketone, and amide). The comparative results reflected that our data were reliable and consistent with the solely reported example 1⁺ (R¹ = p-H). The reduction potential for the 1⁺ (R¹ = p-H) was measured as −1.31 (V vs Fe⁶⁺/⁵⁺) in this work, according to the CV value with platinum electrolyte in acetonitrile, while a similar result was found for 1⁺ (R¹ = p-H) as −1.35 (V vs SCE) according to the CV value with mercury electrolyte in pH = 9 aqueous medium.⁷¹ Interestingly, for the series of 1⁺−6⁺, the reduction potentials are close to or even more negative than molecular oxygen (−1.050 V vs Fe⁶⁺/⁵⁺).⁷² Hence, it could be concluded that the neutral radicals (X*) could not survive under oxygen saturated solution. Thus, if the neutral radicals (X*) are in need of detection during the reaction process, oxygen should be strictly excluded from the reaction system.

Diagnoses of Hydride Transfer Mechanisms from 3,5-Disubstituted 1,4-Dihydropyridines (XH) to Hydride Acceptors. The observed hydride transfer from donor to acceptor should include three possible reaction mechanisms, namely initiated by hydride transfer, hydrogen transfer, and electron transfer. Because thermodynamics could provide reliable evidence to judge the possibilities of hydride transfer reactions, the thermodynamic analysis platform was constructed with the thermodynamic parameters of the 6 elementary steps of hydride donors and acceptors.⁷³ In order to deeply understand the reduction mechanisms between organic hydrides and carbonyl groups, we chose chiral organic hydride 6H (R² = CH₃) as the hydride donor and ethyl benzoylformate as the hydride acceptor to elucidate the detailed reaction mechanisms according to the thermodynamic analysis platform, which so far has remained unclear in Kellogg’s work.⁷⁹⁻⁸⁰

Among them, the thermodynamic driving forces for 6 elementary steps of 6H (R² = CH₃) have been already established; the hydride affinity, hydrogen affinity, and electron affinity of ethyl benzoylformate, as well as their corresponding intermediates could be measured by using previous method.⁸¹ The hydride affinity of ethyl benzoylformate ΔH₆H−A(A) was emerged as −77.6 kcal mol⁻¹ in acetonitrile according to the hydride transfer reaction heat (ΔHᵣₑ₄) from ITC by treating ethyl mandelate anion (ethyl mandelate anion was generated by deprotonation of ethyl mandelate with KH) with TEMPO-OCl⁻ [ΔH₆H−A(A) = ΔH₆H−A(TEMPOT) + ΔHₑ₄], eqs S1–S4, SI-5]. The reduction potential for ethyl benzoylformate was reversible and recorded as Eₑ₄(A) = −1.731 (V vs Fe⁶⁺/⁵⁺) according to the CV value. The oxidation potential for the ethyl mandelate anion adopted the OSWV value as Eₑ₄(AH⁺) = 0.791 (V vs Fe⁶⁺/⁵⁺) because of its irreversibility. According to the Hess’s law and eqs 5–7, the hydrogen affinity ΔH₆H(A) of ethyl benzoylformate and the hydrogen affinity ΔH₆H(A*) and proton affinity ΔH₆H(A*) of ethyl benzoylformate radical were calculated as −34.8, −91.3, and −21.4 kcal mol⁻¹, respectively. All the values for the 6 thermodynamic parameters of 6H (R² = CH₃) and ethyl benzoylformate were readily available and the reaction mechanism could be comprehensively elucidated via the thermodynamic analysis platform (eqs S5–S10, SI-5; Scheme 5).

The reduction initiated by electron transfer (step a) and hydrogen transfer (step b) from 6H (R² = CH₃) to ethyl benzoylformate is highly impossible because of the thermodynamic inhibition over 35.9 kcal mol⁻¹. In contrast, a concerted hydride transfer manner (step c) is preferred to take place spontaneously, even though the thermodynamic driving force is limited to 11.1 kcal mol⁻¹. The small thermodynamic value suggested that the hydride transfer process could be slowly in acetonitrile at 298 K. In fact, the experiment process showed that the asymmetric reduction of carbonyl group by 6H (R² = CH₃) in the presence of MgClO₄·1.5H₂O as Lewis acid was very slow and required 3–5 days for completing the conversion. These results clearly proved that the hydride transfer (step c) governed the reaction conversion and was assumed as the rate determining step. However, the 6H (R² = CH₃) could not reduce other inactivated ketones (normal ketones, such as acetone, acetophenone, and so on) via the hydride transfer process because the thermodynamic driving force was not permitted as shown in Table S1 (SI-5). If it worked, other additives, such as strong Lewis acids or phosphoric acids, are demanded to activate the carbonyl group (C=O). In this regard, these findings allow us to deeply understand the properties of C=O π bonds for different carbonyl compounds.

CONCLUSIONS

In this work, a series of 3,5-disubstituted 1,4-dihydropyridines have been successfully synthesized and they are constituted as a broad scope of organic hydride donors. The thermodynamic driving forces of each elementary-step for the hydride donors in acetonitrile were realized by experimental techniques and thermodynamic cycles, which allowed us to understand their reductive abilities qualitatively and learn about the properties of related intermediates. Thermodynamic values suggested that the 3,5-disubstituted 1,4-dihydropyridines belong to moderate to strong hydride donors and moderate to weak single-electron donors as compared with the conventional biomimic hydride donors (BNAH, HEH, and AcrH₂). The para-substituents on the benzene ring bearing at the N1 positions have relatively minor influence on the reducing capabilities. In contrast, the functional groups attached on the C3/C5 positions exhibited visible effect for the hydride-donating as well as single-electron-donating abilities. The mechanism between the chiral organic hydride 6H (R² = CH₃) and activated ketone (ethyl benzoylformate) has been first verified as the concerted hydride transfer pathway depended on the thermodynamic analysis platform. All the valuable thermodynamic parameters are essential and crucial to understand the reducing capabilities of the 3,5-disubstituted 1,4-dihydropyridines, offering guidance for chemists to design other novel chiral and nonchiral 3,5-disubstituted 1,4-dihydropyridine derivatives.

EXPERIMENTAL SECTION

Materials. The target 3,5-disubstituted 1,4-dihydropyridine compounds (XH, X = 1–8) were synthesized and identified by ¹H NMR. The detailed synthetic procedures and related references are provided in the Supporting Information (SI-1, 2). Reagent-grade acetonitrile and tetrabutylammonium hexafluorophosphate were purchased from Aldrich. Acetonitrile was treated with potassium permanganate and potassium...
carbonate and refluxed for several hours. Then, it was redistilled over phosphoric anhydride under an argon atmosphere before use. Tetrabutylammonium hexafluorophosphate was recrystallized from dichloromethane and dried under vacuum at 383 K for overnight.46

**Electrochemical Experiment.** The electrochemical experiments were carried out using an electrochemical apparatus (BAS-100B) with a standard three-electrode cell. All the compounds were measured in acetonitrile under an argon atmosphere at 298 K with ferrocenium/ferrocene as the internal standard, a glassy carbon disk as the working electrode, a platinum wire as the counter electrode, and 0.1 M silver nitrate/silver (containing 0.1 M tetrabutylammonium hexafluorophosphate in acetonitrile) as the reference electrode.50

The sweep rate was 100 mV s\(^{-1}\) in this work.

**Isothermal Titration Calorimetry.** The titration experiments were conducted on an isothermal titration calorimeter (CSC4200) in acetonitrile at 298 K. The hydride donor and acceptor were dissolved in the acetonitrile with certain concentration. Injection of hydride donor (10 µL) into acceptor was delivered in 0.5 s. The time interval between two injections was 400 s, and the injection was repeated over 10 times for each spectrum. The reaction heat was calculated by integration of each peak except for the first one, which was lower than the normal due to the diffusion during the pre-equilibrium time of the instrument.59

**ASSOCIATED CONTENT**

- **Supporting Information**
  The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b01815.

- **Detailed experimental procedures, NMR data, electrochemical and ITC spectra of 3,5-disubstituted 1,4-dihydropyridines, and the equations and calculations for each elementary steps of the thermodynamic driving forces (PDF)**

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**Notes**

The authors declare no competing financial interest.

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