Theoretical Prediction of Activation Free Energies of Various Hydride Self-Exchange Reactions in Acetonitrile at 298 K

Yang Li† and Xiao-Qing Zhu*,†‡

†The State Key Laboratory of Elemento-Organic Chemistry, College of Chemistry, and ‡Collaborative Innovation Center of Chemical Science and Engineering, Nankai University, Tianjin 300071, P. R. China

ABSTRACT: Hydride transfer reactions are very important chemical reactions in organic chemistry. It has been a chemist’s dream to predict the rate constants of hydride transfer reactions by only using the physical parameters of the reactants. To realize this dream, we have developed a kinetic equation (Zhu equation) in our previous papers to predict the activation free energies of various chemical reactions using the activation free energies of the corresponding self-exchange reactions and the related bond dissociation energies or redox potentials of the reactants. Because the activation free energy of the hydride self-exchange reaction is difficult to measure using the experimental method, in this study, the activation free energies of 159 hydride self-exchange reactions in acetonitrile at 298 K were systematically computed using an accurately benchmarked density functional theory method with a precision of 1.1 kcal mol⁻¹. The results show that the range of the activation free energies of the 159 hydride self-exchange reactions is from 16.1 to 46.6 kcal mol⁻¹. The activation free energies of 25 122 hydride transfer reactions in acetonitrile at 298 K can be estimated using the activation free energies of the 159 hydride self-exchange reactions and the corresponding heterolytic bond dissociation free energies of the reactants. The effects of the heteroatom, substituent, and aromaticity on the activation free energies of hydride self-exchange reactions were examined. The results show that heteroatoms, substituents at the reaction center, and the aromaticity of reactants, all have remarkable effects on the activation free energy of hydride self-exchange reactions. All kinetic information provided in this work on the hydride self-exchange reactions in acetonitrile at 298 K should be very useful in chemical labs and chemical industry.

1. INTRODUCTION

Hydride transfer reactions (eq 1) are very important organic chemical reactions and have been widely used for the mutual conversion between organic unsaturated and saturated compounds as well as the preparation and conversion of hydrogen gas as green energy. It is well-known that if a hydride transfer reaction can be used, there are two most fundamental scientific problems that need to be solved first: one is the thermodynamic problem, that is, how much is the thermodynamic driving force of the hydride transfer reaction, \( \Delta G^o(XH/Y^+) \)? The other is the kinetic problem, that is, how much is the activation free energy of the hydride transfer reaction, \( \Delta G^\ddagger(XH/Y^+) \)? As to the thermodynamic problem of hydride transfer reactions, as long as the molar free energy change of the hydride donor \((XH)\) to release hydride anions, \( \Delta G^o(XH) \), and the molar free energy change of the hydride acceptor \((Y^+)\) to accept hydride anions, \( \Delta G^o(Y^+) \), are available, the thermodynamic driving force of the hydride transfer reaction, \( \Delta G^o(XH/Y^+) \), can be obtained by using eq 2. Because the \( \Delta G^o(XH) \) values of many important organic hydride donors have been determined in acetonitrile at room temperature in our lab, the thermodynamic problems of many important organic hydride transfer reactions, in fact, have been well-solved in our previous work. However, unlike the thermodynamic driving force of hydride transfer reactions, \( \Delta G^o(XH/Y^+) \), the activation free energy of hydride transfer reactions, \( \Delta G^\ddagger(XH/Y^+) \), cannot be predicted using the related physical parameters of reactants up to now. The main reason is that the factors affecting the kinetics of reactions are much more complicated and diversified than those affecting the thermodynamics of reactions. In fact, it has been a chemist’s dream to predict the activation free energy of hydride transfer reactions only by using the physical parameters of reactants.

In our previous work, we reported a new kinetic equation (eq 3 and named as Zhu equation) to quantitatively estimate the activation free energy of various chemical reactions using the activation free energies of the corresponding self-exchange reactions and the related bond dissociation energies or redox potentials of the reactants. The validity of the Zhu equation has been verified by predicting the kinetic isotope effect values of 4556 hydride transfer reactions and the activation free

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energies of 5886 hydrogen atom transfer reactions in acetonitrile at 298 K.

For hydride transfer reactions, in eq 3, \( \Delta_G^{\ddagger}(XH/Y^+ \text{ or } X^+ \text{ or } YH) \) are the activation free energy and thermodynamic driving force of the hydride transfer reactions, respectively. \( \Delta_G^\circ(XH/X^+) \) and \( \Delta_G^\circ(YH/Y^+) \) are the activation free energies of the corresponding hydride self-exchange reactions for reactant \( XH \) and reactant \( Y^+ \), respectively. Because the thermodynamic driving forces of many hydride self-exchange reactions, \( \Delta_G^\circ(XH/Y^+) \), have been measured in our lab, evidently, as long as the activation free energy of the corresponding hydride self-exchange reactions is available, the activation free energies of the hydride transfer reactions can be obtained by using eq 3. Because the activation free energy value of hydride self-exchange reactions, \( \Delta_G^\ddagger(XH/X^+) \), like the molar free energy change of the hydride donor \( XH \) to release hydride anions, \( \Delta_G^\circ(XH) \), is also the characteristic parameter of the hydride donor \( XH \) or the hydride acceptor \( X^+ \), it is clear that as long as the \( \Delta_G^\ddagger(XH/X^+) \) values of the reactants \( XH \) and \( X^+ \) are available, the chemist’s dream that the activation free energy of hydride transfer reactions can be predicted only by using the characteristic physical parameters of the reactants can be realized. However, since the activation free energy values of hydride self-exchange reactions in solution have so far been scarce, there is an urgent need in chemical labs and chemical industries to determine these values in the same solvent and at the same temperature.

\[
XH + Y^+ \rightarrow X^+ + YH \quad (1)
\]

\[
\Delta_G^\circ(XH/Y^+) = \Delta_G^\circ(XH) + \Delta_G^\circ(Y^+) \quad (2)
\]

Zhu equation

\[
\Delta_G^\ddagger(XH/X^+) = \frac{1}{2} \left[ \Delta_G^\ddagger(XH/X^+) + \Delta_G^\ddagger(YH/Y^+) \right] + \frac{1}{2} \Delta_G^\circ(XH/Y^+) \quad (3)
\]

It is well-known that for electron-, proton-, and hydrogen atom- self-exchange reactions, the activation free energy values can be directly measured using dynamic electron

\[
\text{Scheme 1. Parent Structures and Marks of Hydride Donors (XH) Examined in This Work}
\]
paramagnetic resonance (EPR) or dynamic nuclear magnetic resonance (NMR) techniques because the rates of these self-exchange reactions are generally fast enough to meet the requirements of dynamic EPR or dynamic NMR techniques. However, for hydride self-exchange reactions, the reaction rates are generally too slow to be measured using dynamic NMR techniques (requiring \(k_2\) to be within \(10^{-2}\) to \(10^6\) M\(^{-1}\) s\(^{-1}\))\(^{20}\). To the best of our knowledge, except some indirect experimental methods\(^{20}\), no direct experimental methods were reported in the literature to accurately determine the activation free energy of hydride self-exchange reactions in solution.

Owing to the development of density functional theory (DFT) in recent years and the large enhancement of computational capability, the activation free energies of many organic reactions in solution can be computed by employing suitable density functionals, which means that the activation free energy values of hydride self-exchange reactions in solution could also be obtained by the DFT method. In this work, we try to use a suitable DFT method to estimate the activation free energies of hydride self-exchange reactions in acetonitrile at room temperature. Because dihydropyridine, dihydroquinoline, dihydroarcridine, and dihydroimidazole as well as their various derivatives are all well-known good hydride donors and many of them have been extensively applied as efficient reducing agents in reductions of various organic unsaturated compounds,\(^{32}-^{35}\) 159 hydride self-exchange reactions involving dihydropyridine, dihydroquinoline, dihydroarcridine, and dihydroimidazole as well as their various derivatives and analogues as hydride donors are examined in this work. The parent structures and marks of the 159 hydride donors are shown in Scheme 1.

### 2. RESULTS

Because it is the first time to systematically compute the activation free energies of various hydride self-exchange reactions in acetonitrile at room temperature by using the DFT method, it is necessary to examine the reliability of the computational method by comparing the computational results with the corresponding experimental results. In this work, six hydride cross-transfer reactions (eqs 4–9) were selected because they are all well-known hydride transfer reactions, and the activation free energies values in acetonitrile at 298 K can be directly measured using the conventional experimental methods\(^{1,20,36}\) (see Table 1).

### Table 1. Experimental and Computational Activation Free Energies (\(\Delta G^\ddagger\)) of Six Hydride Transfer Reactions in Acetonitrile at 298 K (kcal mol\(^{-1}\))

| \(\text{XH}/\text{Y}^+\) | \(\Delta G^\ddagger_{\text{exp.}}\)\(^{a}\) | \(\Delta G^\ddagger_{\text{method 1}}\) | \(\Delta G^\ddagger_{\text{method 2}}\) | \(\Delta G^\ddagger_{\text{method 3}}\) | \(\Delta G^\ddagger_{\text{method 4}}\) | \(\Delta G^\ddagger_{\text{method 5}}\) | \(\Delta G^\ddagger_{\text{method 6}}\) |
|----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| 7SH/79\(^+\)  | 23.12           | 23.2            | 23.6            | 22.8            | 24.3            | 17.9            | 16.4            |
| 3SH(Me)/72\(^+\) | 19.90           | 21.5            | 21.6            | 19.8            | 23.7            | 17.8            | 14.8            |
| 71H/35\(^+\)\((\text{Me})\) | 17.91           | 18.5            | 18.8            | 17.2            | 20.3            | 16.3            | 13.8            |
| 69H/35\(^+\)\((\text{Me})\) | 14.88           | 15.6            | 16.0            | 14.4            | 17.6            | 13.2            | 10.7            |
| 67H/35\(^+\)\((\text{Me})\) | 14.41           | 12.1            | 12.7            | 10.4            | 14.8            | 11.0            | 4.7             |
| 3SH(Me)/39\(^+\) | 11.20           | 12.2            | 12.5            | 10.4            | 14.2            | 9.6             | 4.6             |
| MAD\(^c\)     | 1.1             | 1.2             | 1.2             | 1.1             | 2.3             | 2.6             | 6.1             |
| RMSD\(^c\)    | 1.3             | 1.3             | 1.3             | 1.7             | 2.5             | 2.9             | 6.4             |

\(^{a}\)Experimental activation free energies directly derived from refs 18, 20, and 36 using Eyring equation.\(^{19,20}\) \(^{b}\)Computational activation free energies by using different methods to compute the gas-phase electronic energy (method 1: M06-2X-D3/def2-TZVPP; method 2: M06-2X-D3/def2-QZVPP; method 3: M06-2X-D3/MG3S; method 4: M06-2X/def2-TZVPP; method 5: B3LYP-D3(BJ)/def2-TZVPP; and method 6: BMK-D3(BJ)/def2-TZVPP). \(^{c}\)MAD, mean absolute deviation; RMSD, root-mean-square deviation.

Because optimization by using M06-2X/6-31+G** can give reliable geometries for organic compounds\(^{37}\) and also it has been proved that the solvation energy computation protocol M05-2X/6-31G*\(\ast\)/SMD can achieve the smallest error for general computation,\(^{38}\) we only need to evaluate the reliability of different methods to compute the gas-phase electronic energy for the six hydride cross-transfer reactions (eqs 4–9). Three different density functionals (M06-2X, B3LYP, and BMK) were compared in the evaluation with or without Grimme’s D3 dispersion correction in combination with the def2-TZVPP basis set, and the optimal density functional was further evaluated in combination with MG3S and def2-QZVPP to test the basis set effect on computational performance. The
Table 2. Activation Free Energies, Activation Enthalpies, and the Contribution of Activation Entropy to Gibbs Free Energy for 159 Hydride Self-Exchange Reactions Together with the Heterolytic Bond Dissociation Free Energies of 159 Hydride Donors in Acetonitrile at 298 K (kcal mol⁻¹)
Table 2. continued

| no. | XH  | ΔG° | ΔH° | −TΔS° | ΔG°(XH) | no. | XH  | ΔG° | ΔH° | −TΔS° | ΔG°(XH) |
|-----|-----|-----|-----|-------|---------|-----|-----|-----|-----|-------|---------|
| 54  | CN  | 20.9| 7.8 | 13.1  | 74.0    | 134 | 7H  | 19.1| 4.1 | 15.1  | 82.1    |
| 55  | NO  | 21.8| 8.2 | 13.6  | 77.1    | 135 | 75H | 26.5| 15.3| 11.2  | 79.3    |
| 56  | NO₂ | 19.4| 5.8 | 13.5  | 77.0    | 136 | 76H | 30.4| 19.2| 11.2  | 74.1    |
| 57  | Me  | 22.7| 9.4 | 13.2  | 61.5    | 137 | 77H | 35.4| 22.4| 13.0  | 81.6    |
| 58  | tBu | 24.9| 11.5| 13.4  | 61.8    | 138 | 78H | 25.5| 13.8| 11.7  | 94.4    |
| 59  | Ph  | 21.1| 7.0 | 14.1  | 65.3    | 140 | 80H | 22.0| 8.9 | 13.1  | 67.8    |
| 60  | NH₂ | 24.6| 11.6| 12.9  | 59.0    | 141 | 81H | 21.1| 8.4 | 12.7  | 87.1    |
| 61  | CHO | 20.2| 6.9 | 13.3  | 74.8    | 142 | 82H | 27.1| 13.3| 13.9  | 89.6    |
| 62  | CN  | 22.3| 9.0 | 13.3  | 75.6    | 143 | 83H | 21.4| 9.6 | 11.9  | 86.5    |
| 63  | NO  | 21.9| 8.7 | 13.2  | 83.3    | 144 | 84H | 26.4| 14.5| 11.9  | 78.3    |
| 64  | NO₂ | 20.7| 7.0 | 13.7  | 80.4    | 145 | 85H | 24.5| 11.6| 12.9  | 83.6    |
| 65  | Me  | 24.7| 11.7| 12.9  | 57.7    | 146 | 86H | 19.8| 6.9 | 12.8  | 88.5    |
| 66  | tBu | 39.1| 25.1| 14.0  | 65.5    | 147 | 87H | 22.2| 10.0| 12.2  | 81.2    |
| 67  | Ph  | 26.7| 12.8| 13.9  | 61.5    | 148 | 88H | 22.4| 8.7 | 13.7  | 83.9    |
| 68  | Me  | 22.7| 9.9 | 12.9  | 60.6    | 149 | 89H | 26.3| 15.3| 11.1  | 64.9    |
| 69  | tBu | 22.4| 8.7 | 13.7  | 60.5    | 150 | 90H | 26.7| 14.1| 12.5  | 68.4    |
| 70  | Ph  | 23.5| 9.5 | 14.1  | 62.4    | 151 | 91H | 31.0| 17.1| 13.9  | 73.0    |
| 71  | NH₂ | 25.1| 11.4| 13.8  | 55.9    | 152 | 92H | 23.4| 9.7 | 13.7  | 78.7    |
| 72  | CHO | 23.1| 9.8 | 13.3  | 65.1    | 153 | 93H | 32.0| 17.7| 14.4  | 75.7    |
| 73  | CN  | 23.3| 9.9 | 13.4  | 67.4    | 154 | 94H | 31.5| 17.0| 14.4  | 73.1    |
| 74  | NO  | 23.2| 9.8 | 13.4  | 66.6    | 155 | 95H | 40.2| 25.4| 14.8  | 73.6    |
| 75  | NO₂ | 23.5| 9.7 | 13.8  | 68.4    | 156 | 96H | 29.7| 16.0| 13.6  | 61.5    |
| 76  | 2H  | 20.7| 8.0 | 12.6  | 83.4    | 157 | 97H | 28.5| 14.8| 13.8  | 63.8    |

18H(G)

| no. | XH  | ΔG° | ΔH° | −TΔS° | ΔG°(XH) |
|-----|-----|-----|-----|-------|---------|
| 77  | Me  | 24.7| 11.7| 12.9  | 57.7    |
| 78  | tBu | 39.1| 25.1| 14.0  | 65.5    |
| 79  | Ph  | 26.7| 12.8| 13.9  | 61.5    |
| 80  | Me  | 22.7| 9.9 | 12.9  | 60.6    |
| 81  | tBu | 22.4| 8.7 | 13.7  | 60.5    |
| 82  | Ph  | 23.5| 9.5 | 14.1  | 62.4    |
| 83  | Me  | 24.7| 11.7| 12.9  | 57.7    |
| 84  | tBu | 39.1| 25.1| 14.0  | 65.5    |
| 85  | Ph  | 26.7| 12.8| 13.9  | 61.5    |

19H(R)

| no. | XH  | ΔG° | ΔH° | −TΔS° | ΔG°(XH) |
|-----|-----|-----|-----|-------|---------|
| 86  | Me  | 22.7| 9.9 | 12.9  | 60.6    |
| 87  | tBu | 22.4| 8.7 | 13.7  | 60.5    |
| 88  | Ph  | 23.5| 9.5 | 14.1  | 62.4    |
| 89  | Me  | 24.7| 11.7| 12.9  | 57.7    |
| 90  | tBu | 39.1| 25.1| 14.0  | 65.5    |
| 91  | Ph  | 26.7| 12.8| 13.9  | 61.5    |

20H(G)

| no. | XH  | ΔG° | ΔH° | −TΔS° | ΔG°(XH) |
|-----|-----|-----|-----|-------|---------|
| 92  | Me  | 22.7| 9.9 | 12.9  | 60.6    |
| 93  | tBu | 22.4| 8.7 | 13.7  | 60.5    |
| 94  | Ph  | 23.5| 9.5 | 14.1  | 62.4    |
| 95  | Me  | 24.7| 11.7| 12.9  | 57.7    |
| 96  | tBu | 39.1| 25.1| 14.0  | 65.5    |
| 97  | Ph  | 26.7| 12.8| 13.9  | 61.5    |

Figure 1. Visual comparison of ΔG°(XH/X+) for the 54 representative hydride donors in Table 2.
detailed results of different methods are listed in Table 1 (and Table S1 in the Supporting Information).

Without D3 correction, the performances of B3LYP and BMK in combination with def2-TZVPP were extremely poor with the MAD value up to 16.3 and 10.3 kcal mol$^{-1}$ (Table S1 in the Supporting Information), whereas the MAD of B3LYP-D3(BJ) and BMK-D3(BJ) were 2.6 and 6.1 kcal mol$^{-1}$ respectively. M06-2X gave a comforting result (MAD 2.3 kcal mol$^{-1}$) because of its parameterization against barrier heights and noncovalent interactions, but the deviation exceeds 2 kcal mol$^{-1}$ in four reactions. After D3 correction, M06-2X-D3/def2-TZVPP reduced the MAD to 1.1 kcal mol$^{-1}$, and its estimation error exceeded 2.0 kcal mol$^{-1}$ in one reaction, indicating the importance of including dispersion description in these reactions with rings. As for the basis set, in combination with the optimal M06-2X-D3 density functional, Ahlrichs basis set (def2-TZVPP) outperformed the Pople type basis set (MG3S) a little, and there is no improvement from def2-TZVPP to def2-QZVP in these reactions. Therefore, the method of M06-2X-D3/def2-TZVPP was chosen in this work to compute the gas-phase electronic energies for the 159 hydride self-exchange reactions (XH/X$^+$). We chose the same method as the optimal method for the computation of reaction Gibbs free energy change. To be concise, the assessment of different computational methods on the computation of reaction Gibbs free energy change are provided in the Supporting Information (Table S2). The final computed activation energies of the 159 hydride self-exchange reactions in acetonitrile at 298 K are listed in Table 2. To examine the contributions of activation enthalpy and activation entropy to the activation free energy and the effect of the heterolytic bond dissociation free energy of the hydride donors on the activation free energy, activation enthalpies and activation entropies of the 159 hydride self-exchange reactions as well as the heterolytic bond dissociation free energy of 159 hydride donors (XH) in acetonitrile at 298 K were also computed and are provided in Table 2.

3. SCALE OF $\Delta G^\ddagger$(XH/X$^+$)

From Table 2, it is clear that although the thermodynamic driving forces of the 159 hydride self-exchange reactions in acetonitrile at 298 K, $\Delta G^\ddagger$(XH/X$^+$), are all equal to zero, the activation free energy values of the 159 hydride self-exchange reactions in acetonitrile at 298 K, $\Delta G^\ddagger$(XH/X$^+$), are all quite different and range from 16.1 kcal mol$^{-1}$ for 41H/41$\ddagger$ to 46.6 kcal mol$^{-1}$ for 36H(tBu)/36$\ddagger$(tBu). Such a large range of $\Delta G^\ddagger$(XH/X$^+$) not only indicates the mistake of linear free energy relationship between $\Delta G^\ddagger$ and $\Delta G^\ddagger$ for various chemical reactions but also shows that the activation free energy of hydride self-exchange reactions is strongly dependent on the structure and composition of the reactants. To elucidate the main factors in structure and composition of the reactants that affect $\Delta G^\ddagger$(XH/X$^+$), a plot of $\Delta G^\ddagger$(XH/X$^+$) values with 53 typical hydride donors (XH) are presented in Figure 1. From Figure 1, it is clear that the magnitude of $\Delta G^\ddagger$(XH/X$^+$) depends not only on the structure but also on the composition of reactants, and no main structural factors can be easily found, which means that the factors affecting $\Delta G^\ddagger$(XH/X$^+$) are quite complex. There is no doubt that the intrinsic logic relations between $\Delta G^\ddagger$(XH/X$^+$) and the structure and composition of the reactants (XH and X$^+$) should be one of the most important issues in physical chemistry for further investigations. However, several main factors that affect $\Delta G^\ddagger$(XH/X$^+$) for some special reactants can still be examined here.

4. MAIN FACTORS AFFECTING $\Delta G^\ddagger$(XH/X$^+$)

4.1. Heteroatom Effect on the Activation Free Energy.

It is well-known that if heteroatoms, such as nitrogen, oxygen, sulfur, and so forth, are used to replace the carbon atom in a chemical compound, the heteroatom can not only change the physical property of the compound but also change the chemical property of the compound, which means that the heteroatom in the reactants should have great influence on the activation free energy of the hydride self-exchange reactions. From Table 2, it is clear that when the carbon atom at the para position to the reaction center of the reactant (9H) is replaced by nitrogen (1H), oxygen (5H), and sulfur (7H), the activation free energy values of the corresponding hydride self-exchange reactions (9H/9$\ddagger$, 1H/1$\ddagger$, 5H/5$\ddagger$, and 7H/7$\ddagger$) are altered, as shown in Figure 2. From Figure 2a, it is clear that the heteroatoms, especially the nitrogen atom (1H) and the oxygen atom (5H), can significantly increase the activation free energy of the corresponding hydride self-exchange reactions, and the increase order is that nitrogen (1H) > oxygen (5H) > sulfur (7H). It is found that the heteroatoms at the ortho position to the reaction center can also significantly increase the activation free energy of the hydride self-reactions, and the increase order is N (25.0 kcal mol$^{-1}$ for 1H/1$\ddagger$) > O atom (21.8 kcal mol$^{-1}$ for 5H/5$\ddagger$) > S atom (19.5 kcal mol$^{-1}$ for 7H/7$\ddagger$) ≥ C atom (19.5 kcal mol$^{-1}$ for 9H/9$\ddagger$). In the same way, if the carbon atom at the ortho position of the reactant (15H) is replaced by nitrogen (12H), oxygen (15H), and sulfur (14H), it is found that the heteroatoms at the ortho position to the reaction center can also significantly increase the activation free energy of the hydride self-reactions, and the increase order is N (25.0 kcal mol$^{-1}$ for 12H/12$\ddagger$) > O (24.2 kcal mol$^{-1}$ for 13H/13$\ddagger$) > S (23.1 kcal mol$^{-1}$ for 14H/14$\ddagger$) > C (18.1 kcal mol$^{-1}$ for 15H/15$\ddagger$) [Figure 2b]. Because the activation free energy changes of 14H/14$\ddagger$ (5.0 kcal mol$^{-1}$), 13H/13$\ddagger$ (6.1 kcal mol$^{-1}$), and 12H/12$\ddagger$ (6.9 kcal mol$^{-1}$) from that of 15H/15$\ddagger$ are all larger than the corresponding activation free energy changes of 7H/7$\ddagger$ (0.01 kcal mol$^{-1}$), 5H/5$\ddagger$ (2.3 kcal mol$^{-1}$), and 1H/1$\ddagger$ (4.7 kcal mol$^{-1}$) from that of 9H/9$\ddagger$, respectively, it is clear that the effect of heteroatoms at the 2-position on the activation free energy is much larger than that of the heteroatoms at the 4-position. The main reason is that the position of the heteroatom at the 2-position is closer to the

![Figure 2. Heteroatom effect on the activation parameters of 1,4-dihydrobenzene and 1,2-dihydro-isomer (energy unit: kcal mol$^{-1}$).](Image 336x355 to 535x560)
reaction center of the reactant than that of the heteroatom at the 4-position.

If the activation enthalpy and activation entropy for the hydride self-exchange reactions with 1,4-dihydro-compounds as hydride donors (9H/9\(^+\), 7H/7\(^+\), 5H/5\(^+\), and 1H/1\(^+\)) as well as 1,2-dihydro-isomers as hydride donors (15H/15\(^+\), 14H/14\(^+\), 13H/13\(^+\), and 12H/12\(^+\)) are examined together, it is found that for the hydride self-exchange reactions with 1,4-dihydro-compounds as reactants, the activation enthalpies have no significant change, but the activation enthalpies have a significant change: 12.9 kcal mol\(^{-1}\) for 1H/1\(^+\), 10.4 kcal mol\(^{-1}\) for 5H/5\(^+\), 7.9 kcal mol\(^{-1}\) for 7H/7\(^+\), and 7.7 kcal mol\(^{-1}\) for 9H/9\(^+\), which indicates that the effect of the heteroatoms at the 4-position on the activation free energy is mainly due to the activation enthalpy change. Little or no effect of the heteroatom at the 4-position on the activation entropy is found; the main reason could be that the position of the heteroatom at the 4-position in the molecule is further from the reaction center in the reactants than that at the 2-position.

Because the activation entropy change of reactions mainly depends on the conformation change of the reactant system from the initial state to the transition state (TS) and the activation entropy of reactions mainly depends on the bond energy change of the reactant system from the initial state to the TS, it is conceived that for the 1,4-dihydro-compounds as hydride donors, the conformation change of the reactant system from the initial state to the TS should be similar for each other, but for the 1,2-dihydro-isomer as hydride donors, the conformation change of the reactant system from the initial state to the TS could be a little different from each other.

In addition, from Figure 2, it is interesting to find that \(\Delta G^\circ(XH)\) values of the hydride donors decrease in the following order: 9H (90.5 kcal mol\(^{-1}\)) > 5H (76.5 kcal mol\(^{-1}\)) > 7H (75.9 kcal mol\(^{-1}\)) > 1H (52.5 kcal mol\(^{-1}\)) for the 1,4-dihydro hydride donors and 15H (89.6 kcal mol\(^{-1}\)) > 14H (77.2 kcal mol\(^{-1}\)) > 13H (74.4 kcal mol\(^{-1}\)) > 12H (49.0 kcal mol\(^{-1}\)) for the 1,2-dihydro hydride donors, but the corresponding activation free energy changes decrease in the opposite direction. The smaller the heterolytic bond dissociation free energy of the reactants, the greater the activation energy of the corresponding hydride self-exchange reactions; what is the reason for this anomaly?

In our previous paper,\(^15\) we reported a new version of Zhu equation (eq 10) from eq 3, the purpose of which is to realize chemists’ dream that the activation free energy of a chemical reaction can be directly estimated only using the corresponding characteristic physical parameter of the reactants. In eq 10, \(\Delta G^{2s}(XH)\) and \(\Delta G^{2s}(X^+)\) are called the thermo-kinetic parameters of reactants XH and X\(^+\), respectively, because both the physical parameters are made of the thermodynamic parameter of the reactants, \(\Delta G^\circ(XH)\), and the kinetic parameter of the reactants, \(\Delta G^\circ(XH/X^+)\), (see eqs 11 and 12, respectively). The physical meanings of \(\Delta G^{2s}(XH)\) and \(\Delta G^{2s}(X^+)\) are shown in Scheme 2 and Figure 3. Because \(\Delta G^\circ(XH)\) is the free energy absorbed by XH from the initial state of the reaction to the TS of the reaction and \(\Delta G^{2s}(X^+)\) is the free energy released by X\(^+\) from the initial state of the reaction to the TS of the reaction, obviously, \(\Delta G^{2s}(XH)\) is the real resistance of the reaction, and \(\Delta G^{2s}(X^+)\) is the real power of the reaction. Because the magnitudes of \(\Delta G^{2s}(XH)\) and \(\Delta G^{2s}(X^+)\) not only depend on the heterolytic bond dissociation free energy of the reactants, \(\Delta G^\circ(XH)\), but also depend on the activation free energy of the hydride self-exchange reaction, \(\Delta G^\circ(XH/X^+)\), we should not be amazed at the anomaly that the greater the heterolytic bond dissociation free energy of the reactant, the smaller the activation free energy of the hydride self-exchange reaction. To elucidate the reason for the anomaly, the thermo-kinetic parameters of 159 XH to release the hydride ion and the thermo-kinetic parameters of 159 X\(^+\) to capture the hydride ion in acetonitrile at 298 K were calculated according to eqs 11 and 12, respectively, and the results are listed in Table 3.

\[
\Delta G^\circ(XH/X^+) = \Delta G^{2s}(XH) + \Delta G^{2s}(X^+) 
\]

\[
\Delta G^{2s}(XH) = \frac{1}{2} [\Delta G^\circ(XH/X^+) + \Delta G^\circ(XH)] 
\]

\[
\Delta G^{2s}(X^+) = \frac{1}{2} [\Delta G^\circ(XH/X^+) - \Delta G^\circ(XH)] 
\]

From Table 3, we can find that the thermo-kinetic parameters of XH in acetonitrile at 298 K are 55.0, 47.7, 49.2, and 38.4 kcal mol\(^{-1}\) for 9H, 7H, 5H, and 1H, respectively, and the thermo-kinetic parameters of X\(^+\) in acetonitrile at 298 K are −35.5, −28.2, −27.4, and −14.1 kcal mol\(^{-1}\) for 9\(^+\), 7\(^+\), 5\(^+\), and 1\(^+\), respectively. Although the thermo-kinetic parameters of 9H, 5H, 7H, and 1H decrease successively as the \(\Delta G^\circ(XH)\) values of 9H (90.5 kcal mol\(^{-1}\)), 5H (76.5 kcal mol\(^{-1}\)), 7H (75.9 kcal mol\(^{-1}\)), and 1H (52.5 kcal mol\(^{-1}\)) decrease, the thermo-kinetic parameters of 9\(^+\), 7\(^+\), 5\(^+\), and 1\(^+\) increase successively as \(\Delta G^\circ(XH)\) decreases, and the values of the latter ones increase relative to that of 9\(^+\) (7.3 kcal mol\(^{-1}\)) for 7\(^+\), 8.1 kcal mol\(^{-1}\) for 5\(^+\), and 21.4 kcal mol\(^{-1}\) for 1\(^+\), respectively) are all larger than the values of the corresponding former ones that decrease relative to that of 9H (−7.3 kcal mol\(^{-1}\) for 7H, −5.8 kcal mol\(^{-1}\) for 5H, and −16.6 kcal mol\(^{-1}\) for 1H, respectively). It is this reason that leads to the anomaly that the greater the heterolytic bond dissociation free energy of reactants, the smaller the activation free energy of the hydride self-exchange reactions.

**4.2. Substituent Effect on the Activation Free Energy.** It is well-known that the substituent effect is the thermody-
Table 3. Thermo-kinetic Parameter Values of 159 Hydride Donors and 159 Hydride Acceptors in Acetonitrile at 298 K (kcal mol\(^{-1}\))

| no. | XH | \(\Delta G^{\text{ref}}(\text{XH})\) | \(\Delta G^\circ(\text{X}^-)\) | no. | XH | \(\Delta G^\circ(\text{XH})\) | \(\Delta G^\circ(\text{X}^-)\) |
|-----|----|-----------------|-----------------|-----|----|-----------------|-----------------|
| 1H(G) |    |                  |                  | 2H(G) |    |                  |                  |
| 1   | H  | 38.4            | −14.1           | 77   | 22H| 52.5            | −28.0           |
| 2   | Me | 37.2            | −12.9           | 78   | 23H| 50.7            | −32.2           |
| 3   | tBu| 38.1            | −11.0           | 79   | 24H| 52.5            | −28.8           |
| 4   | Ph | 40.3            | −16.5           | 80   | 25H| 55.6            | −37.8           |
| 5   | NH\(_2\)| 38.4          | −13.3           | 81   | 26H| 56.4            | −33.6           |
| 6   | CHO| 48.6            | −23.2           | 82   | 27H| 41.3            | −17.7           |
| 7   | CN | 51.6            | −26.6           | 83   | 28H| 53.0            | −29.4           |
| 8   | NO | 52.9            | −25.1           | 84   | 29H| 53.3            | −31.2           |
| 9   | NO\(_2\)| 53.7          | −26.5           | 85   | 30H| 56.4            | −39.1           |
|     |    |                  |                  | 31H |    | 42.3            | −18.6           |
| 10  | Me | 37.1            | −13.6           | 86   | 32H| 54.7            | −30.2           |
| 11  | tBu| 37.2            | −13.4           | 87   | 33H| 54.6            | −32.1           |
| 12  | Ph | 38.6            | −14.3           | 88   | 34H| 58.2            | −40.5           |
| 13  | NH\(_2\)| 35.6          | −8.6            | 90   | H | 47.6            | −26.5           |
| 14  | CHO| 42.2            | −18.6           | 91   | Me| 48.5            | −27.7           |
| 15  | CN | 44.2            | −20.1           | 92   | tBu| 57.7            | −26.8           |
| 16  | NO | 45.5            | −21.4           | 93   | Ph| 48.7            | −26.8           |
| 17  | NO\(_2\)| 45.9          | −21.5           | 94   |    |                  | 35H(R)          |
|     |    |                  |                  |      |    |                  |                  |
| 3H(G) |    |                  |                  | 36H(G) |    |                  |                  |
| 18  | Me | 37.6            | −14.1           | 95   |    |                  |                  |
| 19  | tBu| 37.6            | −13.6           | 96   |    |                  |                  |
| 20  | Ph | 39.5            | −15.8           | 97   |    |                  |                  |
| 21  | NH\(_2\)| 36.5          | −11.9           | 98   |    |                  |                  |
| 22  | CHO| 44.2            | −21.7           | 99   |    |                  |                  |
| 23  | CN | 45.9            | −21.6           | 100  |    |                  |                  |
| 24  | NO | 49.1            | −25.9           | 101  |    |                  |                  |
| 25  | NO\(_2\)| 48.0          | −24.6           | 102  |    |                  |                  |
|     |    |                  |                  | 103  |    |                  |                  |
| 4H(G) |    |                  |                  | 5H  |    |                  |                  |
| 26  | Me | 37.3            | −11.0           | 104  |    |                  |                  |
| 27  | tBu| 42.4            | −9.0            | 105  |    |                  |                  |
| 28  | Ph | 38.4            | −11.7           | 106  |    |                  |                  |
| 29  | NH\(_2\)| 35.8          | −0.7            | 107  |    |                  |                  |
| 30  | CHO| 39.1            | −17.2           | 108  |    |                  |                  |
| 31  | CN | 44.9            | −17.2           | 109  |    |                  |                  |
| 32  | NO | 44.5            | −19.5           | 110  |    |                  |                  |
| 33  | NO\(_2\)| 52.1          | −20.2           | 111  |    |                  |                  |
| 34  | 5H | 49.2            | −27.4           | 112  |    |                  |                  |
| 35  | 6H | 48.1            | −23.6           | 113  |    |                  |                  |
| 36  | 7H | 47.7            | −28.2           | 114  |    |                  |                  |
| 37  | 8H | 47.0            | −24.5           | 115  |    |                  |                  |
| 38  | 9H | 55.0            | −35.5           | 116  |    |                  |                  |
| 39  | 10H| 52.5            | −30.8           | 117  |    |                  |                  |
| 40  | 11H| 43.3            | −16.0           | 118  |    |                  |                  |
| 41  | 12H| 37.0            | −12.0           | 119  |    |                  |                  |
| 42  | 13H| 49.3            | −25.1           | 120  |    |                  |                  |
| 43  | 14H| 50.1            | −27.1           | 121  |    |                  |                  |
| 44  | 15H| 53.8            | −35.8           | 122  |    |                  |                  |
| 16H(G) |    |                  |                  | 17H(G) |    |                  |                  |
| 45  | H  | 42.3            | −19.9           | 123  |    |                  |                  |
| 46  | Me | 41.6            | −18.9           | 124  |    |                  |                  |
| 47  | tBu| 45.3            | −16.1           | 125  |    |                  |                  |
| 48  | Ph | 44.4            | −20.1           | 126  |    |                  |                  |

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The cancelation leads to the fact that the electronic enhancement of the hydride acceptor.

The reason is that although CN reduces the hydride-donating ability of the hydride donor, at the same time, CN can also does not make the hydride self-exchange reaction much slower.

when the activation enthalpy and activation entropy change is enthalpy rather than entropy.

Although CN is a strong electron-withdrawing group, its effect on the reaction rate can be used to rationalize the reaction mechanism. However, for a hydride self-exchange reaction, as both the reactants carry the same substituent, the substituent effect on the reaction rate could become more complex. To elucidate the effect of the substituent nature, position, and size on the rate of hydride self-exchange reactions, the activation free energies of hydride self-exchange reactions, with 4H(Me) as hydride donors [Figure 4a], and the activation free energies of hydride self-exchange reactions, with 2H(CN), 3H(CN), 1H(H), 1H(Me), and 4H(Me) as hydride donors [Figure 4b], as well as the activation free energies of hydride self-exchange reactions with 1H(H), 4H(Me), and 4H(iBu) as hydride donors [Figure 4c] are compared together.

From Figure 4a, it is clear that the effects of the substituent at 1-, 2-, and 3-positions are all quite small, but the effect of the substituent at the 4-position is prominent; the reason is that the substituent at the 4-position is closest to the reaction center. However, when the activation enthalpy and activation entropy of the hydride self-exchange reactions for the 4-substituted reactants are compared, an unexpected finding is that the main change is enthalpy rather than entropy.

When Figure 4a and 4b are compared, it is found that although CN is a strong electron-withdrawing group, its effect does not make the hydride self-exchange reaction much slower. The reason is that although CN reduces the hydride-donating ability of the hydride donor, at the same time, CN can also enhance the hydride-accepting ability of the hydride acceptor. The cancelation leads to the fact that the electronic effects of the substituent is not a major factor to affect hydride self-exchange reactions (eq 13).

```
| no. | XH | ΔG°(XH) | ΔG°(X+) | no. | XH | ΔG°(XH) | ΔG°(X+) |
|-----|----|---------|---------|-----|----|---------|---------|
| 55  | NO | 49.4    | -27.7   | 135 | 75H| 52.9    | -26.4   |
| 56  | NO₂| 48.2    | -28.8   | 136 | 76H| 52.2    | -21.9   |
| 57  | Me | 42.1    | -19.4   | 137 | 77H| 58.5    | -23.1   |
| 58  | iBu| 43.4    | -18.4   | 138 | 78H| 60.0    | -34.4   |
| 59  | Ph | 43.2    | -22.1   | 139 | 79H| 61.3    | -29.7   |
| 60  | NH₂| 41.8    | -17.2   | 140 | 80H| 44.9    | -22.9   |
| 61  | CHO| 47.5    | -27.3   | 141 | 81H| 54.1    | -33.0   |
| 62  | CN | 49.0    | -26.7   | 142 | 82H| 58.4    | -31.2   |
| 63  | NO | 52.6    | -30.7   | 143 | 83H| 54.0    | -32.5   |
| 64  | NO₂| 50.6    | -29.8   | 144 | 84H| 52.3    | -26.0   |
| 65  | Me | 41.2    | -16.5   | 145 | 85H| 54.1    | -29.6   |
| 66  | iBu| 52.3    | -15.2   | 146 | 86H| 54.2    | -34.4   |
| 67  | Ph | 44.1    | -17.4   | 147 | 87H| 51.7    | -29.5   |
| 68  | Me | 41.7    | -19.0   | 148 | 88H| 53.2    | -30.8   |
| 69  | iBu| 41.5    | -19.1   | 149 | 89H| 45.6    | -19.3   |
| 70  | Ph | 42.9    | -19.4   | 150 | 90H| 47.5    | -20.9   |
| 71  | NH₂| 40.5    | -15.4   | 151 | 91H| 52.0    | -21.0   |
| 72  | CHO| 44.1    | -21.0   | 152 | 92H| 51.1    | -27.7   |
| 73  | CN | 45.4    | -22.0   | 153 | 93H| 53.9    | -21.9   |
| 74  | NO | 44.9    | -21.7   | 154 | 94H| 52.3    | -20.8   |
| 75  | NO₂| 45.9    | -22.4   | 155 | 95H| 56.9    | -16.7   |
| 76  | Me | 52.1    | -31.4   | 156 | 96H| 45.6    | -15.9   |
|     |    |         |         | 157 | 97H| 46.2    | -17.7   |
|     |    |         |         | 158 | 98H| 52.8    | -13.7   |
|     |    |         |         | 159 | 99H| 57.4    | -30.8   |
```

Figure 4. Effects of nature, position, and size of the substituent groups on the activation free energy (energy unit: kcal mol⁻¹).
From Figure 4c, it is clear that when the hydrogen atom at the 4-position in 1,4-dihydropyridine is replaced by different bulky substituents (Me and tBu), the activation free energy increases significantly as the size of the substituent increases. If the activation enthalpy change and the activation entropy change are compared, it is surprising to find that the main cause of the bulky effect of the substituent is the activation enthalpy change rather than the activation entropy change.

4.3. Aromatization Effect of the Reactant on the Activation Free Energy. From the structure of the hydride donors examined in this work (Scheme 1), it is clear that the 159 organic compounds are mostly heterocyclic compounds. Because the aromaticity of the heterocyclic compounds is an important component of the thermodynamic driving force for the heterocyclic compounds to release hydride ions, obviously, the aromatization of heterocyclic compounds should be an important factor to affect the activation free energy values of the corresponding hydride self-exchange reactions. To elucidate the dependence of the activation free energy of hydride self-exchange reactions on the aromatization of heterocyclic compounds, some related physical parameters of 1H, 16H, and 35H for their corresponding hydride self-exchange reactions are compared together in Figure 5. From Figure 5, it is interesting to find that the greater the aromaticity of the hydride acceptor, the smaller the activation free energy of the corresponding hydride self-exchange reaction.

5. APPLICATION OF $\Delta G^\ddagger(XH/X^\ddagger)$

5.1. Prediction of the Activation Free Energy of Various Hydride Transfer Reactions. Because the thermo-kinetic parameters of the 159 hydride donors ($\Delta G^\ddagger(XH)$) and 159 hydride acceptors ($\Delta G^\ddagger(X^\ddagger)$) in acetonitrile at 298 K can be obtained from the activation free energy of the corresponding 159 hydride self-exchange reactions and the molar free energy change of the 159 hydride donors to release hydride ions in acetonitrile at 298 K (Table 3), the activation free energy values of 25 122 (A159 = 25 122) hydride transfer reactions in acetonitrile at 298 K can be estimated from these thermo-kinetic parameters of hydride donors (XH) and acceptors ($X^\ddagger$), according to the new version of Zhu equation (eq 10). Because of the limitation of the paper space, the detailed results of the 25 122 activation free energy values are not provided in this paper. However, to verify the 25 122 predictions, the activation free energies of 41 representative cross-reactions among them were examined by DFT computation, and the results are provided in Table 4. As we can see, the activation free energies derived from Zhu equation (eq 10) are all quite close to those directly computed by the benchmarked DFT method.

Because compounds XH or corresponding compounds X$^\ddagger$ in Scheme 1 can all be extensively used as hydride donors or acceptors, it is clear that the activation free energy values of the 25 122 hydride transfer reactions in acetonitrile at 298 K should be very useful in chemical labs and in chemical industry.

5.2. Quest for the Oxidation–Reduction Center Structure of Nicotinamide Coenzyme. It is well-known that nicotinamide-adenine dinucleotide coenzyme (NADH and NAD$^+$) plays a vital role in bioreductions in living bodies by cycle transfer of an apparent hydride ion (eq 14). In the past decade, studies on the oxidation–reduction center structure of NADH have generally been believed to be 1,2-dihydropyridine. This is because the center structure of NADH was generally identified to be 1,4-dihydropyridine rather than 1,2-dihydropyridine. This naturally introduces an interesting question: why NADH coenzyme chooses 1,4-dihydropyridine rather than 1,2-dihydropyridine? This is because compounds XH or corresponding compounds X$^\ddagger$ in Scheme 1 can all be extensively used as hydride donors or acceptors, it is clear that the activation free energy values of the 25 122 hydride transfer reactions in acetonitrile at 298 K should be very useful in chemical labs and in chemical industry.

![Figure 5. Aromatization effect of the reactants on the hydride self-exchange reaction activation free energy.](image)
Table 4. Activation Free Energies of 41 Hydride Transfer Reactions Predicted by Zhu Equation (eq 10) and the Benchmarked DFT Method Together with the Thermo-kinetic Parameters of Hydride Donors and Acceptors (kcal mol⁻¹)

| entry | XH   | Y⁺   | ΔG⁺\text{DFT} | ΔG⁺\text{Diss} | d   | ΔG⁺(XH) | ΔG⁺(Y⁺) |
|-------|------|------|---------------|----------------|-----|---------|---------|
| 1     | 1H   | 2’(Me) | 24.9           | 24.7           | −0.1| 38.4    | −13.6   |
| 2     | 1H   | 2’(Bu) | 24.9           | 24.9           | 0.1 | 38.4    | −13.4   |
| 3     | 1H   | 2’(NH₂) | 30.0           | 29.7           | −0.2| 38.4    | −8.6    |
| 4     | 1H   | 2’(CHO) | 19.7           | 19.8           | 0.1 | 38.4    | −18.6   |
| 5     | 1H   | 2’(CN)  | 18.0           | 18.3           | 0.3 | 38.4    | −20.1   |
| 6     | 1H   | 2’(NO)  | 16.3           | 17.0           | 0.7 | 38.4    | −21.4   |
| 7     | 1H   | 2’(NO₂) | 16.5           | 16.9           | 0.4 | 38.4    | −21.5   |
| 8     | 1H   | 3’(Me)  | 24.4           | 24.3           | 0.0 | 38.4    | −14.1   |
| 9     | 1H   | 3’(Bu)  | 24.9           | 24.8           | −0.1| 38.4    | −13.6   |
| 10    | 1H   | 3’(NH₂) | 26.4           | 26.5           | 0.1 | 38.4    | −11.9   |
| 11    | 1H   | 3’(CHO) | 16.7           | 16.6           | 0.0 | 38.4    | −21.7   |
| 12    | 1H   | 3’(CN)  | 16.8           | 16.8           | −0.1| 38.4    | −21.6   |
| 13    | 1H   | 3’(NO)  | 12.8           | 12.5           | −0.3| 38.4    | −25.9   |
| 14    | 1H   | 3’(NO₂) | 13.8           | 13.8           | 0.0 | 38.4    | −24.6   |
| 15    | 1H   | 18’(Me) | 22.8           | 22.9           | 0.1 | 42.3    | −19.4   |
| 16    | 1H   | 18’(Bu) | 23.8           | 23.9           | 0.1 | 42.3    | −18.4   |
| 17    | 1H   | 18’(NH₂) | 25.2          | 25.1           | −0.1| 42.3    | −17.2   |
| 18    | 1H   | 18’(CHO) | 15.0           | 15.0           | 0.0 | 42.3    | −27.3   |
| 19    | 1H   | 18’(CN) | 15.5           | 15.6           | 0.1 | 42.3    | −26.7   |
| 20    | 1H   | 18’(NO) | 11.9           | 11.6           | −0.3| 42.3    | −30.7   |
| 21    | 1H   | 18’(NO₂) | 12.6           | 12.5           | −0.1| 42.3    | −29.8   |
| 22    | 1H   | 16’    | 18.4           | 18.5           | 0.1 | 38.4    | −19.9   |
| 23    | 1H   | 35’    | 12.3           | 11.8           | −0.5| 38.4    | −26.5   |
| 24    | 1H   | 35’    | 15.9           | 15.8           | −0.2| 42.3    | −26.5   |
| 25    | 1H   | 5’     | 11.7           | 11.0           | −0.7| 38.4    | −27.4   |
| 26    | 1H   | 7’     | 10.6           | 10.2           | −0.4| 38.4    | −28.2   |
| 27    | 1H   | 21’    | 11.6           | 10.9           | −0.7| 42.3    | −31.4   |
| 28    | 1H   | 23’    | 10.8           | 10.1           | −0.6| 42.3    | −32.2   |
| 29    | 1H   | 37’    | 12.2           | 11.7           | −0.5| 47.6    | −35.9   |
| 30    | 1H   | 39’    | 11.6           | 11.2           | −0.4| 47.6    | −36.4   |
| 31    | 1H   | 39’    | 18.2           | 17.7           | −0.5| 54.1    | −36.4   |
| 32    | 1H   | 75’    | 18.6           | 18.4           | −0.2| 52.9    | −34.4   |
| 33    | 1H   | 75’    | 23.2           | 23.2           | 0.0 | 52.9    | −29.7   |
| 34    | 1H   | 99’    | 11.0           | 11.3           | 0.3 | 42.1    | −30.8   |
| 35    | 1H   | 90’    | 21.4           | 21.2           | −0.2| 42.1    | −20.9   |
| 36    | 1H   | 91’    | 21.8           | 21.1           | −0.7| 42.1    | −21.0   |
| 37    | 1H   | 93’    | 19.6           | 20.3           | 0.7 | 42.1    | −21.9   |
| 38    | 1H   | 94’    | 20.7           | 21.3           | 0.7 | 42.1    | −20.8   |
| 39    | 1H   | 91’    | 24.2           | 23.4           | −0.9| 44.4    | −21.0   |
| 40    | 1H   | 94’    | 24.1           | 23.6           | −0.6| 44.4    | −20.8   |
| 41    | 1H   | 91’    | 26.5           | 25.6           | −0.9| 46.6    | −21.0   |

MAD: 0.4

6. CONCLUSIONS

In this work, the activation free energies, activation enthalpies, and activation entropies of 159 hydride self-exchange reactions as well as the heterolytic bond dissociation free energies of the corresponding 159 hydride donors in acetonitrile at 298 K were systematically computed by the DFT method: M06-2X-D3/def2-TZVPP/M06-2X-D3/6-31+G**/SMD with solvation energy computed at M05-2X/6-31G*/SMD level of theory. After analysis of the activation free energies scale of the 159 hydride self-exchange reactions in acetonitrile at 298 K and examination of the effects of the heteroatom, substituent, and aromatic property of reagents on the activation free energies of the hydride self-exchange reactions, the following conclusions can be made: (i) The activation free energy values of the 159 hydride self-exchange reactions range from 16.1 to 46.6 kcal mol⁻¹, which strongly indicates the incorrectness of the linear
free energy relationship between the activation free energies ($\Delta G^\text{⧧}$) and the corresponding thermodynamic driving forces of reactions ($\Delta G^\circ$) for chemical reactions. (ii) For the 159 hydride self-exchange reactions, the activation free energy differences among them are mainly due to the differences in the activation enthalpies. (iii) Heteroatoms (N, O, and S) in the reactants can effectively change the activation free energies of hydride self-exchange reactions. In general, the order of decrease of the activation energy as heteroatoms change is N > O > S > C. (iv) The effects of substituents on the activation free energies of hydride self-exchange reactions are generally quite small (smaller than 1 kcal mol$^{-1}$), except the substituent at the position of the reaction center where both electron-withdrawing and electron-donating substituents significantly increase the activation free energies of hydride self-exchange reactions. The steric substituent at the reaction center can also effectively increase the activation free energies of hydride self-exchange reactions. In general, the larger the substituent size, the larger the activation free energy. (v) The activation free energy of a hydride self-exchange reaction, $\Delta G^\text{⧧}(XH/X^+)$, is defined as the Gibbs free energy difference between TS and isolated reactants ($XH$ and $X^+$) by eq 15. The Gibbs free energy of each species ($XH$, $X^+$, and TS) in solution is calculated by eq 16, where $E_{\text{gas}}$ is the gas phase electronic energy, $\Delta G^\text{sol}$ is the solvation energy, $\Delta G^\text{corr}$ is the thermal correction to Gibbs free energy, and the last term 1.9 kcal mol$^{-1}$ accounts for the change of reference state from 1 atm to 1 M.

7. COMPUTATIONAL METHOD

All structures were optimized by using M06-2X/43-D3/6-31+G**45,46 in acetonitrile with the SMD solvation model38 accounting for solvent effects. Each optimized structure was confirmed to be a real minimum for a reactant or a first order saddle point with only one imaginary frequency corresponding to the hydride transfer process for the TS by frequency analysis at the same level of theory as optimization. Electronic energies were computed in the gas phase at M06-2X/def2-TZVPP, M06-2X-D3/def2-TZVPP, M06-2X-D3/MG3S, M06-2X-D3/def2-QZVP, B3LYP/def2-TZVPP, B3LYP-D3(BJ)/def2-TZVPP, and BMK-D3(BJ)/def2-TZVPP levels. Solvation energies were computed on the optimized structures in acetonitrile at M05-2X/6-31G* level with the SMD solvation model. The thermal corrections to the Gibbs free energy were obtained at 298.15 K with a vibrational frequency scale factor of 0.967 whereas entropic contributions to the free energy were calculated using Truhlar’s quasi-harmonic correction by setting all vibrational frequencies less than 100 cm$^{-1}$ to reduce errors arising from treating low frequency vibrations as harmonic oscillators. The reference state for gas-phase computation is 1 atm, whereas for solution phase, it is 1 M. The ultrafine integral grid was used throughout the study. All computations were performed by using Gaussian 09 program package.55

The activation free energy of a hydride self-exchange reaction, $\Delta G^\text{⧧}(XH/X^+)$, is defined as the Gibbs free energy difference between TS and isolated reactants (XH and X') by eq 15. The Gibbs free energy of each species (XH, X', and TS) in solution is calculated by eq 16, where $E_{\text{gas}}$ is the gas phase electronic energy, $\Delta G^\text{sol}$ is the solvation energy, $\Delta G^\text{corr}$ is the thermal correction to Gibbs free energy, and the last term 1.9 kcal mol$^{-1}$ accounts for the change of reference state from 1 atm to 1 M.
\[ \Delta G^\circ(XH/X^+) = G_{\text{sol}}(\text{TS}) - [G_{\text{sol}}(XH) + G_{\text{sol}}(X^+)] \]  
(15)

\[ G_{\text{sol}} = E_{\text{gas}} + \Delta G_{\text{sol}} + \Delta G_{\text{corr}} + 1.9 \text{ kcal mol}^{-1} \]  
(16)

The heterolytic bond dissociation free energy of hydride compound (XH), \( \Delta G^\circ(XH) \), is defined in this work as the molar Gibbs free energy change of XH releasing the hydride ion (H\(^-\)) in acetonitrile at 298 K. The isodesmic reaction (eq 17) is constructed to compute \( \Delta G^\circ(XH) \) to avoid the inaccuracy in directly computing the energy of a hydride ion in acetonitrile. A reliable experimental \( \Delta G^\circ(XH) \) value (76.2 kcal mol\(^{-1}\)) of 10-methyl-9,10-dihydroacridine (AcrH\(_2\)) in acetonitrile was used in the computation. \( \Delta G^\circ(XH) \) of XH in acetonitrile is computed by eq 18.

\[ \text{XH} + \text{AcrH}^+ \rightarrow X^+ + \text{AcrH}_2 \]  
(17)

\[ \Delta G^\circ(XH) = G_{\text{sol}}(X^+) + G_{\text{sol}}(\text{AcrH}_2) - G_{\text{sol}}(XH) - G_{\text{sol}}(\text{AcrH}^+) + 76.2 \text{ kcal mol}^{-1} \]  
(18)

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