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Conversion and Origin of Normal and Abnormal Temperature Dependences of Kinetic Isotope Effect in Hydride Transfer Reactions

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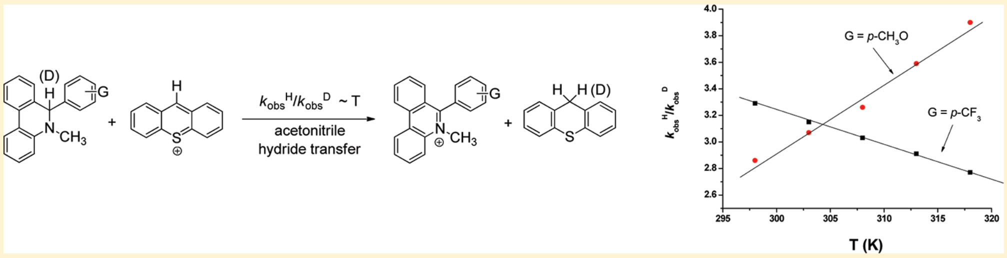
Ⓢ *Supporting Information*



ABSTRACT: The effects of substituents on the temperature dependences of kinetic isotope effect (KIE) for the reactions of the hydride transfer from the substituted 5-methyl-6-phenyl-5,6-dihydrophenanthridine (G-PDH) to thioxanthylium (TX^+) in acetonitrile were examined, and the results show that the temperature dependences of KIE for the hydride transfer reactions can be converted by adjusting the nature of the substituents in the molecule of the hydride donor. In general, electron-withdrawing groups can make the KIE to have normal temperature dependence, but electron-donating groups can make the KIE to have abnormal temperature dependence. Thermodynamic analysis on the possible pathways of the hydride transfer from G-PDH to TX^+ in acetonitrile suggests that the transfers of the hydride anion in the reactions are all carried out by the concerted one-step mechanism whether the substituent is an electron-withdrawing group or an electron-donating group. But the examination of Hammett-type free energy analysis on the hydride transfer reactions supports that the concerted one-step hydride transfer is not due to an elementary chemical reaction. The experimental values of KIE at different temperatures for the hydride transfer reactions were modeled by using a kinetic equation formed according to a multistage mechanism of the hydride transfer including a returnable charge-transfer complex as the reaction intermediate; the real mechanism of the hydride transfer and the root that why the temperature dependences of KIE can be converted as the nature of the substituents are changed were discovered.

■ INTRODUCTION

Kinetic isotope effect (KIE) is a change of reaction rates when an isotopic atom is substituted by another isotopic atom in reaction molecules and is conventionally expressed by the ratio of reaction rates of two different isotopically labeled molecules in a chemical reaction.[1] KIE is a very common chemical kinetic phenomenon, and the magnitude of KIE not only depends on the nature of isotopic atom, but also depends on the reaction mechanism as well as many other factors, such as temperature, solvent, pressure, and so on. So, KIE is very useful in chemical research, especially in mechanistic studies of reactions, which can provide insight into the transition state of the reactions examined.[2] In recent years, the relationship between KIE and the temperature has drawn more and more attention from biochemists, and the reason is that the dependence of KIE on the temperature can be used as an indicator for the physical nature of enzyme-catalyzed H-transfer reactions.[3] In fact, for the most chemical reactions, the investigations show that the relationship between KIE and the temperature is more or less in an inverse proportion; i.e., KIE decreases with a temperature increase, or KIE increases with a temperature decrease. Since the inverse proportion relationship between KIE and the temperature can be well rationalized by semiclassical models based on transition state theory and was supported by lots of experiment results,[4−6] it has been widely accepted as a well-known conception and called as a normal temperature dependence of KIE ("normal KIE" for short in this work).[4,5] However, there are also a quite lot of examples in which the dependence of KIE on the temperature has a character of the direct proportion; that is, KIE increases with a temperature increase, or KIE decreases with a temperature decrease.[7−13] Since this relationship between KIE and the temperature with the direct proportion cannot be explained by the orthodox kinetic theory, chemists generally call this kinetic phenomenon as an abnormal temperature dependence of KIE ("abnormal KIE" for short in this work). By examining the past publications on the relationship between KIE and the temperature, it is found that although the "normal KIE" phenomenon and the "abnormal KIE" phenomenon have received a lot of examination, most of the chemists' attention focused on the isolated cases, no or very little attention has been focused on

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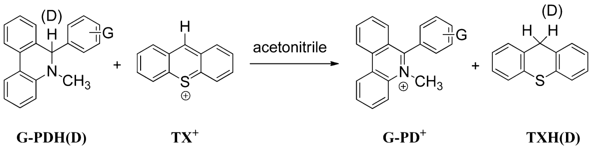
the intrinsic relationship between the different kinetic KIE phenomena. In fact, it is quite difficult until now to safely answer the following questions: (1) Why do some reactions have "normal KIE", but some other reactions have "abnormal KIE"? (2) Can or cannot the conversion between the "normal KIE" and the "abnormal KIE" take place in a chemical reaction? (3) What is the real reason that results in the "abnormal KIE"? It is clear that these scientific questions on the temperature dependence of KIE should be not only fundamental but also very interesting and important, which, of course, has attracted our high attention for a long time. In order to answer the questions mentioned above and dig up the root resulting in the abnormal temperature dependence of KIE in a chemical reaction, it is conceived that the key work is to thoroughly elucidate the intrinsic relationship between the "normal KIE" phenomenon and the "abnormal KIE" phenomenon. Since the nature of the substituent groups in molecules generally have significant effects on the temperature dependence of KIE, the hydride transfer reaction is one type of very important fundamental chemical processes, and the mechanistic detail for many hydride transfer reactions is still a conflicting issue and has been the focus of interest for many chemists and biochemists,[14−19] in this work, a series of substituted 5-methyl-6-phenyl-5,6-dihydrophenanthridine (G-PDH) were synthesized as the hydride donors, and thioxanthylium (TX^+) was chosen as the hydride acceptor. The mechanistic details of the hydride transfer from G-PDH to TX^+ and the effects of the substituent groups on the temperature dependences of KIE for the hydride transfer process from G-PDH to TX^+ in acetonitrile were all examined in detail. The experiment results show that the temperature dependence of KIE for the hydride transfer reaction in eq 1 can be altered from the "normal KIE" to the "abnormal KIE", as the substituents changed from electron-withdrawing groups to electron-donating groups.



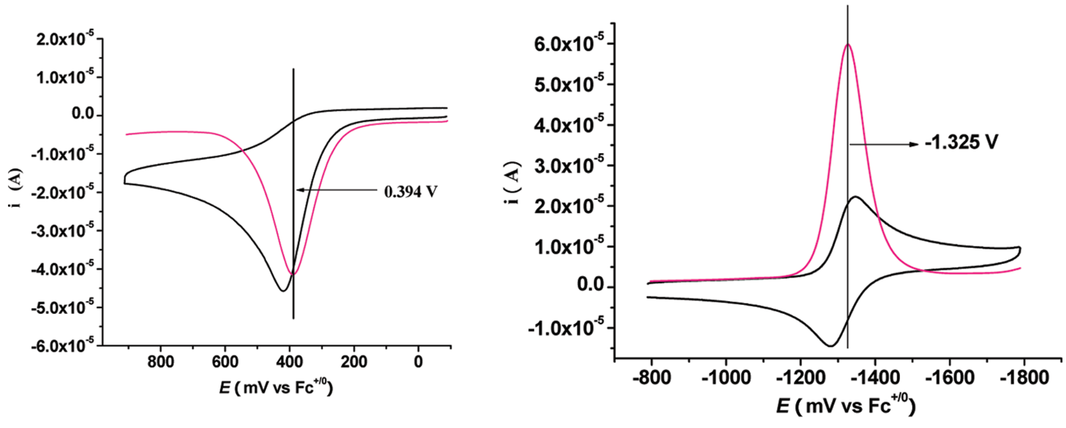
(1)

G = *p*-CF_3, *p*-Cl, *m*-CH_3O, *p*-H, *p*-CH_3 and *p*-CH_3O

■ RESULTS

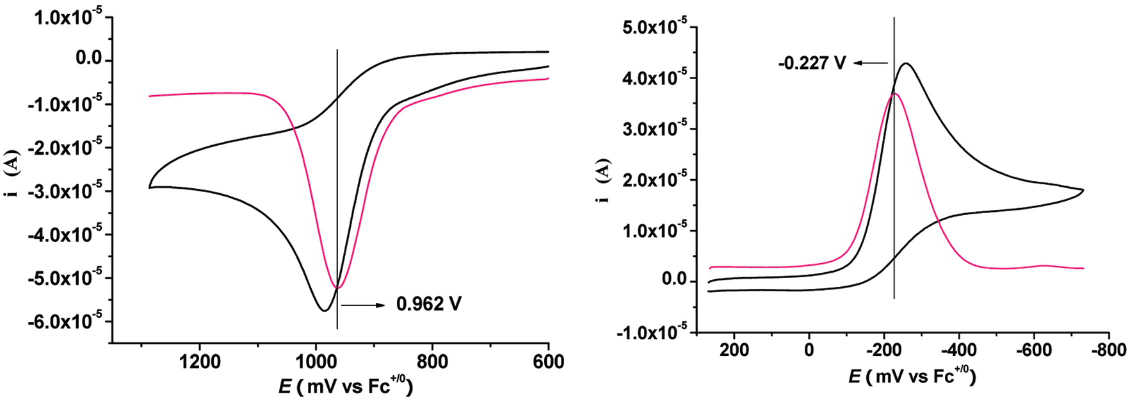
The substituted 5-methyl-6-phenyl-5,6-dihydrophenanthridine (G-PDH) and the corresponding deuterated compounds (G-PDD) as well as thioxanthylium perchlorate ($TX^+ClO_4^-$) were synthesized in this work according to conventional synthetic strategies, and the target products were identified by ^1H NMR and MS; the detailed synthetic routes were provided in the Supporting Information. The standard one-electron oxidation potentials of G-PDH and TXH and the standard one-electron reduction potentials of their corresponding salts (G-PD^+ and TX^+) in acetonitrile were determined by using two electrochemical methods CV and OSWV (Figures 1 and 2); the detailed experimental results are summarized in Table 1. When G-PDH were treated by TX^+ in acetonitrile at room temperature, the final products are identified to be G-PD^+ and TXH, and the reaction stoichiometric relationship between the hydride donors and the hydride acceptor is 1 mol per 1 mol, which means that these reactions were completed by one hydride anion transfer. The molar enthalpy change (ΔH_{rxn}) of the hydride transfer from G-PDH to TX^+ in acetonitrile at 298 K was determined by titration calorimeter on a CSC 4200 isothermal titration calorimeter (Figure 3). The detailed results are also listed in Table 1.

The pseudofirst-order rate constants of the hydride transfer from the substituted 5-methyl-6-phenyl-5,6-dihydrophenanthridine (G-PDH) to thioxanthylium (TX^+) (eq 1) in acetonitrile were determined using an Applied Photophysics SX.18MV-R stopped-flow spectrometer by monitoring the spectra change of thioxanthylium (TX^+) at $\lambda = 500$ nm with the concentration of G-PDH at more than 20-fold excess of TX^+ (Figure 4). The second order observed rate constants (k_{obs}) for the reactions at different temperatures between 298 and 318 K were derived from the corresponding pseudofirst-order rate constants by the linear correlation against the concentration of the hydride donors and listed in Table 2. The Arrhenius parameters, E_a and *A*, were calculated from the slope and the intercept of the Arrhenius plots of $\ln(k_{obs})$ versus the reciprocal of the absolute temperature ($1/T$), which were also listed in Table 2. The kinetic isotope effects ($k_{obs}{}^H/k_{obs}{}^D$) of the reactions at different temperatures between 298 and 319 K were listed in Table 3.



(a) (b)

Figure 1. Cyclic voltammogram (CV), Osteryong square wave voltammogram (OSWV) of H-PDH (a) and H-PD^+ (b) in anhydrous deaerated acetonitrile solution containing 0.1 M (n-Bu)$_4NPF_6$ as supporting electrolyte: CV graph (black line), OSWV graph (red line). The sweep rate is 100 mV/s.



(a) (b)

Figure 2. Cyclic voltammogram (CV), Osteryong square wave voltammogram (OSWV) of TXH (a) and TX^+ (b) in anhydrous deaerated acetonitrile solution containing 0.1 M $(n\text{-}Bu)_4NPF_6$ as supporting electrolyte: CV graph (black line), OSWV graph (red line). The sweep rate is 100 mV/s.

Table 1. Enthalpy Changes of the Hydride Transfer from G-PDH with $TX^+ClO_4^-$ in Acetonitrile at 298 K Together with Redox Potentials of the Related Species in Acetonitrile at Room Temperature

		$E_{ox}(XH)^b$		$E_{red}(X^+)^b$	
species (XH)	ΔH_{rxn}[a]	CV	OSWV	CV	OSWV
G-PDH					
p-CF_3	−24.7	0.459	0.435	−1.241	−1.256
p-Cl	−26.4	0.436	0.411	−1.271	−1.294
m-CH_3O	−26.6	0.415	0.398	−1.307	−1.312
p-H	−27.5	0.420	0.394	−1.313	−1.325
p-CH_3	−28.1	0.410	0.383	−1.322	−1.346
p-CH_3O	−29.2	0.398	0.372	−1.329	−1.356
TXH		0.983	0.962	−0.258	−0.227

[a] ΔH_{rxn} was obtained from the reaction heats of G-PDH with $TX^+ClO_4^-$ in acetonitrile by switching the sign; the latter were measured by titration calorimetry in acetonitrile at 298 K. The data, given in kcal/mol, were average values of at least three independent runs. The reproducibility is ≤0.5 kcal/mol. [b] Measured by CV and OSWV methods in acetonitrile at room temperature, the unit in volts vs Fc^+/Fc^0 and reproducible to 5 mV or better.

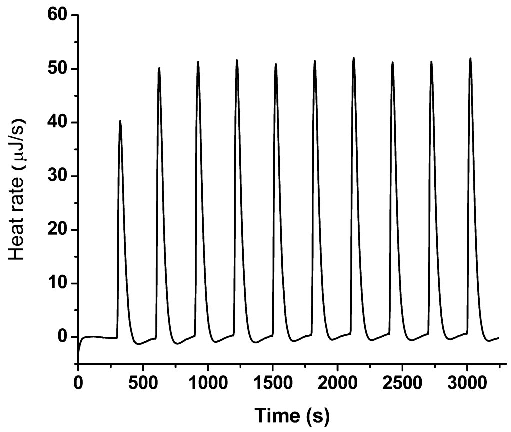


Figure 3. Isothermal titration calorimetry (ITC) for the reaction heat of p-CH_3–PDH with $TX^+ClO_4^-$ in acetonitrile at 298 K. Titration was conducted by adding 10 μL of p-CH_3–PDH (2.34 mM) every 300s into the acetonitrile containing $TX^+ClO_4^-$ (ca. 10 mM).

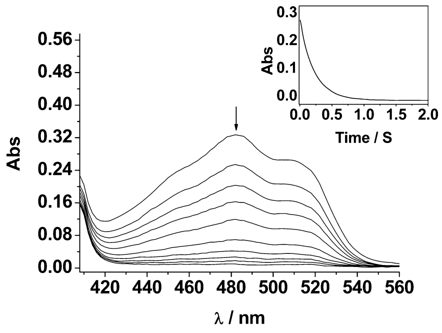


Figure 4. UV–vis spectra change obtained from the reaction of H-PDH (5.5×10^{-3} mol/L) with $TX^+ClO_4^-$ (ca. 2.0×10^{-4} mol/L) in dry acetonitrile at 298 K at 1 s intervals. Inset: the time-resolved spectrum at 500 nm.

■ DISCUSSION

From Table 3 it is clear that when the substituent group (G) in the molecule of the hydride donor G-PDH is p-CF_3, the KIE value of the hydride transfer from G-PDH to TX^+ decreases from 3.29 to 2.77 as the temperature increases from 298 to 318 K. But when the substituent group in G-PDH is p-CH_3O, the relationship between KIE and the temperature is as reverse as in the case that G is p-CF_3; i.e., when the temperature increases from 298 to 318 K, the KIE value does not decrease, but increases from 2.86 to 3.90. This result indicates that for the reaction of the hydride transfer from G-PDH to TXH^+ in acetonitrile, the KIE has two different temperature dependences: a normal temperature dependence ("normal KIE") for G = p-CF_3 and an abnormal temperature dependence ("abnormal KIE") for G = p-CH_3O. As we know, this should be the first example of the hydride transfer reactions that the KIE has two different temperature dependences in the same reaction. If the effect of each substituent among the six substituents on the temperature dependence of KIE all was examined, respectively (Figure 5), it is found that the KIE values for the six substituted groups all have good linear dependences on the temperature when the temperature increases from 298 to 318 K. In general, when the substituent is an electron-withdrawing group, the temperature dependence of KIE is "normal", but when the substituent is an electron-donating group, the temperature dependence of KIE is "abnormal". In addition, from the line slopes in Figure 5, it is clear that the stronger the electron-

Table 2. Rate Constants of the Hydride Transfer from G-PDH and G-PDD to $TX^+ClO_4^-$ in Acetonitrile at Different Temperatures between 298 and 318 K Together with the Corresponding Arrhenious Parameters

	$k_{obs} \times 10^{-2}$ $(M^{-1}\ s^{-1})^a$						
hydrides	298 K	303 K	308 K	313 K	318 K	A^b	$E_a{}^c$
G-PDH							
p-CF_3	2.86	3.28	3.77	4.36	4.86	1.46×10^6	5.06
p-Cl	9.11	10.61	11.77	13.90	14.91	2.71×10^6	4.73
m-CH_3O	13.27	14.99	17.98	20.99	23.68	1.78×10^7	5.63
p-H	17.26	19.90	22.87	27.28	32.28	3.57×10^7	5.89
p-CH_3	23.09	27.74	32.88	38.55	45.80	1.14×10^8	6.40
p-CH_3O	25.57	30.50	36.61	43.62	51.56	1.86×10^8	6.63
G-PDD							
p-CF_3	0.87	1.04	1.25	1.50	1.76	6.78×10^6	6.67
p-Cl	2.90	3.52	4.00	4.82	5.38	5.64×10^6	5.84
m-CH_3O	4.16	4.67	5.75	6.48	7.36	4.75×10^6	5.54
p-H	5.35	6.13	6.87	8.09	9.42	4.10×10^6	5.30
p-CH_3	7.13	8.21	9.39	10.70	12.23	3.70×10^6	5.07
p-CH_3O	8.93	9.94	11.22	12.14	13.23	4.83×10^5	3.72

[a] Second-order observed rate constants k_{obs} for the hydride transfer reactions were obtained from the corresponding pseudofirst-order rate constants by the linear correlation against the concentration of the hydride donors; the experimental error is within 5%. [b] From the intercepts of the Arrhenius plots. [c] From the slopes of the Arrhenius plots, the unit is kcal/mol, and the uncertainty is smaller than 0.05 kcal/mol.

Table 3. Dependence of Kinetic Isotope Effect ($k_{obs}{}^H/k_{obs}{}^D$) for the Reactions of G-PDH(D) with TX^+ in Acetonitrile on the Reaction Temperature

		$k_{obs}{}^H/k_{obs}{}^D$				
groups	σ	298 K	303 K	308 K	313 K	318 K
p-CF_3	0.54	3.29	3.15	3.03	2.91	2.77
p-Cl	0.23	3.14	3.02	2.94	2.88	2.77
m-CH_3O	0.12	3.19	3.21	3.13	3.24	3.22
p-H	0.00	3.23	3.25	3.33	3.37	3.42
p-CH_3	−0.17	3.24	3.38	3.50	3.60	3.75
p-CH_3O	−0.27	2.86	3.07	3.26	3.59	3.90

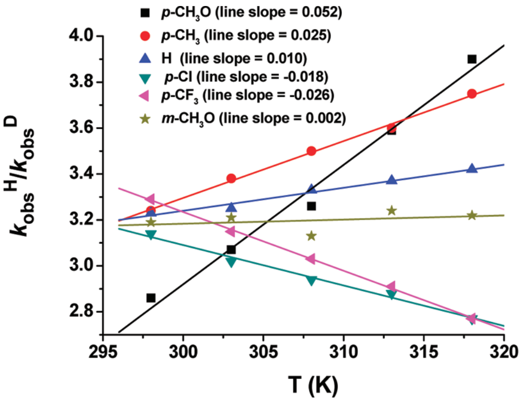


Figure 5. Plot of kinetic isotope effect $k_{obs}{}^H/k_{obs}{}^D$ against temperature for the hydride transfer from G-PDH(D) to $TX^+ClO_4^-$ in acetonitrile.

withdrawing ability or electron-donating ability of the substituent group is, the greater the effect of the substituent on the temperature dependence of KIE is, which indicates that whether "normal" or "abnormal" temperature dependence of KIE in the hydride transfer reactions directly depends on the nature of the substituent groups.

In order to determine the substituent group that can make the temperature dependences of KIE to convert from "normal" to "abnormal", plots of the KIEs for the reactions of the hydride transfer from G-PDH(D) to $TX^+ClO_4^-$ in acetonitrile at the temperatures of 298, 303, 308, 313, and 318 K against the Hammett substituent parameters σ were made (Figure 6).

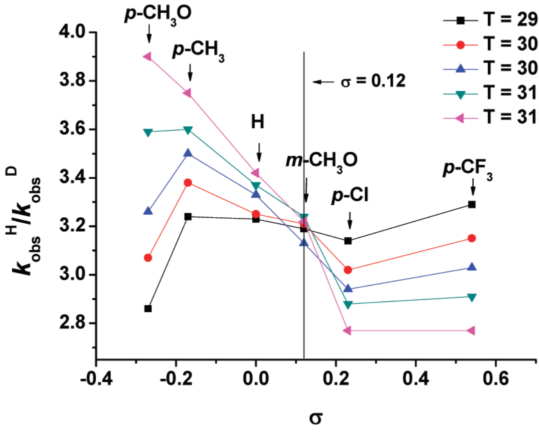


Figure 6. Plots of kinetic isotope effect $k_{obs}{}^H/k_{obs}{}^D$ against the Hammett substituent parameters σ for the hydride transfer reactions from G-PDH(D) to $TX^+ClO_4^-$ in acetonitrile at the various temperatures.

From Figure 6, it is clear that the substituent group that the Hammett parameter σ value is about 0.12, such as *m*-MeO, which could make the temperature dependences of KIE to convert.

From the statements described above, it is evident that the reaction of the hydride transfer from G-PDH to TX^+ in acetonitrile has two reversed temperature dependences of KIE; i.e., when the σ-value of the substituent is larger than 0.12, the reaction has "normal" KIE, but when the σ-value of the substituent is smaller than 0.12, the reaction has "abnormal" KIE. Why can the nature of the substituents cause the conversion of the relationship between KIE and the temperature? What is the reason that the substituents with the σ-values smaller than 0.12 can result in "abnormal" KIE for the hydride transfer reaction?

In order to dig out the origin that results in the questions mentioned above, KIEs of the six hydride transfer reactions with different substituents were examined. Table 3 shows that the KIE values of the six hydride transfer reactions with different substituents range from 3.29 for G = p-CF_3 to 2.86 for p-CH_3O at 298 K. Since the KIE values of the six hydride transfer reactions with different substituents are all quite large, generally greater than 3.0, the six hydride transfer reactions with different substituents all have primary KIE, which means that the dissociation of C−H(D) bond in G-PDH(D) should take place in the rate-determining step for each of the six hydride transfer reactions. When the logarithmic values of k_{obs} against Hammett substituent parameters σ were plotted in Figure 7, it is found that the linearity of the six points is not good. But when the effects of the electron-donating groups and of the electron-withdrawing groups on the logarithmic values of k_{obs} were examined, respectively, two quite straight lines (black lines in Figure 7) were obtained with the line slopes of −1.69 and −3.67 for electron-donating groups and for electron-withdrawing groups, respectively, which means that it is impossible that the reactions of the hydride transfer from G-PDH to TX^+ in acetonitrile take place by one step mechanism as an elementary chemical reaction. Since the hydride transfer may proceed by multistep sequence (e^-−H^+−e^-, e^-−$H^\bullet$, and $H^\bullet$−e^-) in addition to by one-step (Scheme 1), and the chemical processes of the hydrogen atom transfer (steps *c* and *e*) and proton transfer (step *d*) like hydride transfer (step *a*) all involve the C−H(D) bond dissociations (i.e., the reaction steps *a*, *c*, *e*, and *d* all have primary KIE), evidently, it is necessary to elucidate the mechanistic details of the six hydride transfer reactions with different substituents in acetonitrile.

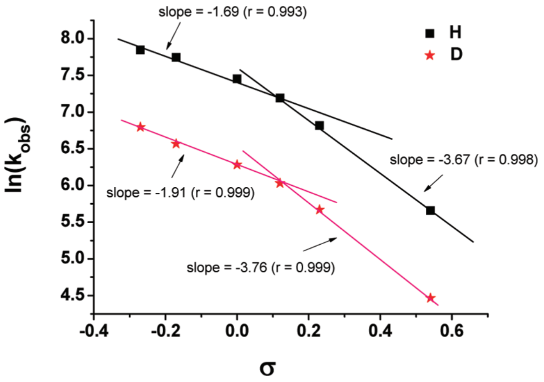


Figure 7. Plot of ln(k_{obs}) against the Hammett substituent parameters σ for the reactions of G-PDH and G-PDD with TX^+ in acetonitrile at 298 K.

To elucidate the most likely mechanisms of the hydride transfer from G-PDH to TX^+ in acetonitrile, the *thermodynamic analysis platform*[20] on the possible mechanism of the hydride transfer from G-PDH to TX^+ in acetonitrile was constructed (Scheme 1), and the change of the standard state energy of each reaction step for the hydride transfer can be estimated according to eqs 2−7, of which eqs 4−6 were derived from three suitable thermodynamic cycles according to Hess' law (in the Supporting Information).[21] The detailed results for the change of the standard state energy of each reaction step are summarized in Table 4.

$$\Delta H(\text{step } a) = \Delta H_{rxn} \tag{2}$$

$$\Delta G(\text{step } b) = -\mathrm{F}[E_{red}(\mathrm{TX}^+) - E_{ox}(\text{G-PDH})] \tag{3}$$

$$\Delta H(\text{step } c) = \Delta H_{rxn} - \mathrm{F}[E_{red}(\text{G-PD}^+) - E_{ox}(\mathrm{TXH})] \tag{4}$$

$$\Delta H(\text{step } d) = \Delta H_{rxn} - \mathrm{F}[E_{red}(\text{G-PD}^+) - E_{ox}(\mathrm{TXH})] + \mathrm{F}[E_{red}(\mathrm{TX}^+) - E_{ox}(\text{G-PDH})] \tag{5}$$

$$\Delta H(\text{step } e) = \Delta H_{rxn} + \mathrm{F}[E_{red}(\mathrm{TX}^+) - E_{ox}(\text{G-PDH})] \tag{6}$$

$$\Delta G(\text{step } f) = \mathrm{F}[E_{red}(\text{G-PD}^+) - E_{ox}(\mathrm{TXH})] \tag{7}$$

From Table 4, it is clear that for the six hydride transfer reactions with different substituents, the state energy changes of the three initial steps range from −24.7 to −29.2 kcal/mol for step *a* (hydride transfer in one step), from 15.3 to 13.8 kcal/mol for step *b* (electron transfer), and from 26.4 to 24.3 kcal/mol for step *c* (hydrogen atom transfer). Since the state energy changes of step *b* and step *c* are all quite large positive values (greater than 13.8 and 24.3 kcal/mol, respectively), it is reasonable to suggest that the processes of electron transfer (step *b*) and hydrogen atom transfer (step *c*) can be all ruled out as the initial step of the hydride transfer from G-PDH to TX^+ in acetonitrile whether the substituent is an electron-donating group or an electron-withdrawing group. As a result, the remaining step *a* (the concerted hydride transfer in one step) should be the merely viable process for the hydride transfer from G-PDH to TX^+ in acetonitrile because the state

Scheme 1. Possible Reaction Pathways of the Hydride Transfer from G-PDH to TX^+ in Acetonitrile

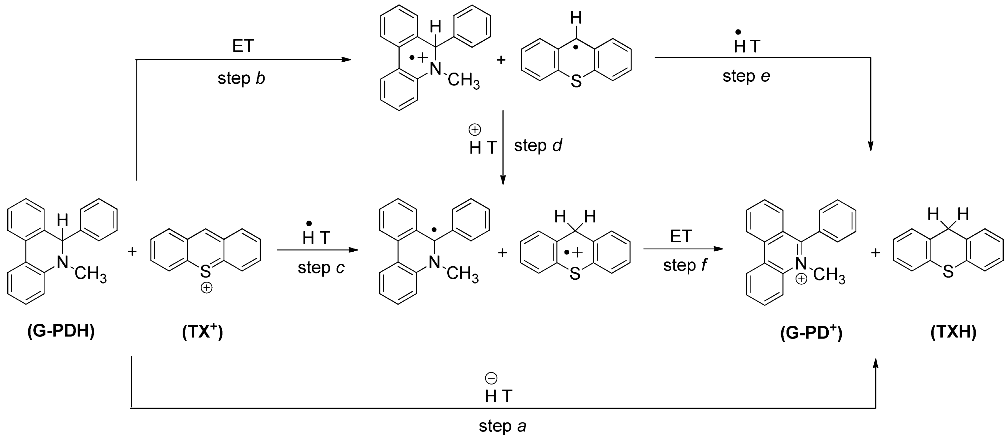


Table 4. Energetics of Each Mechanistic Step of the Hydride Transfer from G-PDH to TX^+ Shown in Scheme 1 (kcal/mol)[a,b]

	ΔH (or ΔG) (kcal/mol)					
groups	step *a*	step *b*	step *c*	step *d*	step *e*	step *f*
p-CF_3	−24.7	15.3	26.4	11.2	−40.0	−51.1
p-Cl	−26.4	14.7	25.6	10.8	−41.1	−52.0
m-CH_3O	−26.6	14.4	25.8	11.4	−41.0	−52.4
p-H	−27.5	14.3	25.2	10.9	−41.8	−52.7
p-CH_3	−28.1	14.1	25.1	11.1	−42.2	−53.2
p-CH_3O	−29.2	13.8	24.3	10.5	−43.0	−53.5

[a] The state energy changes are scaled by using enthalpy changes for steps *c*−*e* and by using free energy changes for steps *b* and *f*. [b] The standard redox potentials in acetonitrile were derived from the experimental results by using CV method, but if the electrochemical redox is irreversible, the standard redox potentials in acetonitrile were derived from the OSWV results, because OSWV has been verified to be a more exact electrochemical method for evaluating the standard one-electron redox potentials of analyte with irreversible electrochemical processes than CV.[22]

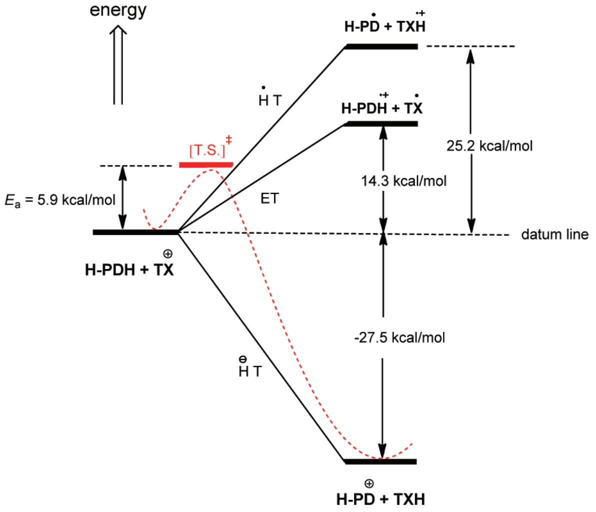


Figure 8. Comparison of state energy changes for the three possible initial steps of the hydride transfer from H-PDH to TX^+ and the activation energy of the hydride transfer in acetonitrile.

energy changes of step *a* are all quite negative (more negative than −24.7 kcal/mol). That is to say, whether the substituent is an electron-donating group or an electron-withdrawing group, the mechanism of the hydride transfer from G-PDH to TX^+ should be the same; i.e., the hydride transfers all take place in one-step. In fact, the one-step mechanism of the hydride transfer can be further verified from the comparison of the state energy changes of the three possible initial steps of the hydride transfer and the Arrhenious activation energy of the hydride transfer reaction. Table 2 shows that the value scale of the Arrhenious activation energies (E_a) of the reactions range from 4.73 to 6.63 kcal/mol when H atom was used as the isotopic atom. Since the Arrhenious activation energies of the reactions (4.73−6.63 kcal/mol) are much smaller than the corresponding standard state energy changes of the initial electron transfer (step *b*) (15.3−13.8 kcal/mol) and the corresponding standard state energy changes of the initial hydrogen transfer (step *c*) (26.4−24.3 kcal/mol), but larger than the corresponding standard state energy changes of the concerted hydride transfer (step *a*) (−29.2 ∼ −24.7 kcal/mol), the initial electron transfer and the initial hydrogen atom transfer as the isolated reaction step in the hydride transfer from G-PDH to TX^+ both are impossible to take place according to the *collision theory* as one of the most fundamental reaction laws that the Arrhenious activation energy is always larger than or at least equal to the corresponding standard state energy change for any elemental reaction.[23] It is evident that both of the two reaction steps *b* and *c* must be ruled out as the initial reaction steps in the reactions of G-PDH with TX^+ in acetonitrile; the only remaining step *a* is suitable for the reaction law (Figure 8). As such, a convincing conclusion can be made that the mechanisms of the hydride transfer from G-PDH to TX^+ in acetonitrile should be the same to each other whether the substituent group is electron-withdrawing or electron-donating. On the basis of the statement above, it is clear that the discovery that the reactions of G-PDH with TX^+ in acetonitrile have two different temperature dependences of KIE seems to have nothing to do with the mechanism of the hydride transfer. As such, the real reason that makes the hydride transfer reaction to have two different temperature dependences of KIE is still a conundrum.

From the discussion given above, it is sure that the hydride transfers all took place via one-step mechanism from G-PDH to TX^+ in acetonitrile whether the substituent (G) is an electron-withdrawing group or an electron-donating group. However, according to Arrhenious equation, it is impossible that an elementary reaction has an abnormal temperature dependence of KIE, and the reason is that $E^D - E^H$ is always larger than zero in the equation of $k^H/k^D = A^H/A^D \exp[(E^D - E^H)/RT]$, which indicates that the transfer of the hydride anion from G-PDH to TX^+ in acetonitrile by one step mechanism is not an elementary chemical reaction. In fact, from Figure 7, we clearly find that when the substituent groups are electron-donating, the line slope is −1.67, but when the substituent groups are electron-withdrawing, the line slope is −3.67; the marked difference between the two line slopes evidently indicates that the one-step of the hydride transfer from G-PDH to TX^+ in acetonitrile is not a single, discrete reaction step (i.e., an elementary chemical reaction step). Since the hydride anion can be divided into two electrons and one hydrogen atomic nucleus (or proton), and the mass of electron is much smaller than that of hydrogen atomic nucleus, it is conceived that during the hydride transfer, the electron transfer should be more favorable than the hydrogen atomic nucleus transfer; i.e., the transfer of electron and the transfer of the hydrogen atomic nucleus could not be at same time during the hydride transfer, which, of course, also can receive the strong support from *Franck−Condon principle*.[24] So, it is reasonable to suggest that the charge-transfer complex (CT-complex) could be formed as an reaction intermediate during the hydride transfer in one-step. The most likely reaction mode for the hydride transfer from G-PDH to TX^+ in acetonitrile may be proposed as shown in Scheme 2. In this mode, the process of the hydride transfer

Scheme 2. Two-Stage Mechanism of the Hydride Transfer from G-PDH to TX^+

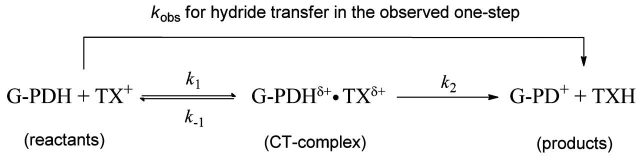


Table 5. Suitable Values of β and γ Together with Theoretic Values of Observed KIE at Different Temperatures; The Latter Were All Derived from the Fitting Curves at α = 1.08 kcal/mol

				k_{obs}^H/k_{obs}^D [d]				
groups	α [a]	β [b]	γ [c]	298 K	303 K	308 K	313 K	318 K
p-CF$_3$	1.08	1.84	3.58×10^{-2}	3.30	3.16	3.02	2.90	2.79
p-Cl	1.08	0.67	2.27×10^{-1}	3.14	3.04	2.95	2.87	2.79
m-CH$_3$O	1.08	−2.66	6.39×10	3.17	3.18	3.19	3.20	3.20
p-H	1.08	−4.07	7.11×10^{2}	3.21	3.27	3.32	3.37	3.41
p-CH$_3$	1.08	−6.59	5.09×10^{4}	3.23	3.38	3.51	3.63	3.72
p-CH$_3$O	1.08	−10.78	4.22×10^{7}	2.80	3.09	3.37	3.62	3.83

[a] $\alpha = E_2^D - E_2^H$, the unit is kcal/mol. [b] $\beta = E_2^H - E_{-1}^H$, the unit is kcal/mol. [c] $\gamma = A_{-1}^H/A_2^H$. [d] The theory data of the observed KIE at different temperatures.

Table 6. Suitable Values of β and γ Together with Theoretic Values of Observed KIE at Different Temperatures; The Latter Were All Derived from the Fitting Curves at α = 1.36 kcal/mol

				k_{obs}^H/k_{obs}^D [d]				
groups	α [a]	β [b]	γ [c]	298 K	303 K	308 K	313 K	318 K
p-CF$_3$	1.36	1.12	5.26×10^{-2}	3.30	3.16	3.02	2.90	2.79
p-Cl	1.36	0.23	2.13×10^{-1}	3.13	3.03	2.94	2.86	2.78
m-CH$_3$O	1.36	−2.28	1.53×10	3.16	3.17	3.18	3.18	3.19
p-H	1.36	−3.26	8.08×10	3.21	3.27	3.32	3.37	3.41
p-CH$_3$	1.36	−4.90	1.30×10^{3}	3.23	3.37	3.49	3.62	3.73
p-CH$_3$O	1.36	−8.12	2.26×10^{5}	2.81	3.06	3.33	3.59	3.85

[a] $\alpha = E_2^D - E_2^H$, the unit is kcal/mol. [b] $\beta = E_2^H - E_{-1}^H$, the unit is kcal/mol. [c] $\gamma = A_{-1}^H/A_2^H$. [d] The theoretic data of the observed KIE at different temperatures.

from G-PDH to TX$^+$ in acetonitrile may be divided into two isolated different stages: the first stage is that the two reactants approach to each other to form a CT-complex by charge transfer (i.e., partial electron transfer); in this stage, there are no bonds formed or broken. The second stage is that the transfer of hydrogen atom with partial negative charge takes place from GPDH-moiety to TX-moiety to form the products. In fact, this reaction pattern has been widely verified and accepted.[25−30]

From Scheme 2, it is clear that the observed rate constant (k_{obs}) of the hydride transfer from G-PDH to TX$^+$ in the observed one-step actually consists of three rate constants: k_1, k_{-1} and k_2, where k_1 is the rate constant of the charge transfer from G-PDH to TX$^+$ to form CT-complex, k_{-1} is the rate constant of the reverse process, and k_2 is the rate constant of the hydride transfer in the second stage, i.e., the transfer of hydrogen atom with partial negative charge.

If the amount of the CT-complex as a reaction intermediate during the hydride transfer is constant, the observed rate constant k_{obs} can be expressed by eq 8 with k_1, k_{-1}, and k_2 according to the steady state assumption.

$$k_{obs} = \frac{k_1 k_2}{k_{-1} + k_2} \tag{8}$$

Since the first stage (*charge transfer*) of the hydride transfer was not involved with the break or formation of C−H(D) bonds, the corresponding rate constants k_1 and k_{-1} should be insensitive to the change of isotopic atoms. Only the second stage, represented by k_2, has a primary hydrogen kinetic isotope effect. And the observed isotope effect, k_{obs}^H/k_{obs}^D, can be expressed by eq 9, which was directly derived from eq 8. In eq 9, k_{-1}^H is equal to k_{-1}^D. If $k_{-1} \gg k_2$, eq 9 can be reduced into eq 10; if $k_{-1} \ll k_2$, eq 11 can be obtained from eq 9. Obviously, neither of the two cases have the abnormal temperature dependence of KIE. The only possible case that can produce the abnormal temperature dependence of KIE for the reactions of the hydride transfer from G-PDH to TX$^+$ in acetonitrile is that k_{-1} and k_2 are comparable in magnitudes.

$$\frac{k_{obs}^H}{k_{obs}^D} = \frac{k_2^H(k_{-1}^D k_2^D)}{k_2^D(k_{-1}^H k_2^H)} \tag{9}$$

$$\frac{k_{obs}^H}{k_{obs}^D} \approx \frac{k_2^H}{k_2^D} \tag{10}$$

$$\frac{k_{obs}^H}{k_{obs}^D} \approx 1 \tag{11}$$

According to Arrhenious equation, eq 9 can be rewritten as:

$$\begin{aligned}\frac{k_{obs}^H}{k_{obs}^D} &= \frac{k_{-1}^D/k_2^D + 1}{k_{-1}^H/k_2^H + 1}\\ &= \frac{A_{-1}^D/A_2^D\exp[(E_2^D - E_{-1}^D)/RT] + 1}{A_{-1}^H/A_2^H\exp[(E_2^H - E_{-1}^H)/RT] + 1}\end{aligned} \tag{12}$$

where A and E are Arrhenious parameters and R and T are molar gas constant and temperature, respectively. Equation 12 describes the special relationship between the KIE and the temperature for the reaction of the hydride transfer from G-PDH to TX$^+$ in acetonitrile.

Since $A_{-1}^H \approx A_{-1}^D$ and $A_2^H \approx A_2^D$, eq 12 can be replaced by eq 13:

$$\frac{k_{obs}^H}{k_{obs}^D} = \frac{A_{-1}^H/A_2^H\exp[(E_2^D - E_{-1}^D)/RT] + 1}{A_{-1}^H/A_2^H\exp[(E_2^H - E_{-1}^H)/RT] + 1} \tag{13}$$

If $E_2^D - E_2^H = \alpha$, $E_2^H - E_{-1}^H = \beta$, and $A_{-1}^H/A_2^H = \gamma$, eq 13 can be rewritten into eq 14:

$$\frac{{k_{\text{obs}}}^{\text{H}}}{{k_{\text{obs}}}^{\text{D}}} = \frac{\gamma\,\exp[(\beta + \alpha)/RT] + 1}{\gamma\,\exp(\beta/RT) + 1} \tag{14}$$

From eq 14, it is clear that the specific relationship between the KIE and the temperature is not only dependent on β and γ, but also dependent on α. Since the second process of the hydride transfer in Scheme 2 is an elementary reaction process, the α value should be a constant. If the difference of zero-point energies of the two bonds (C−H and C−D) for stretching vibrations was considered, the α value should be 1.08 kcal/mol.[4a] But if the difference of zero-point energies between the two bonds for the bending vibrations together with stretching vibrations were considered, the α value should be 1.36 kcal/mol.[4a]

In order to explore and derive the possible and suitable values of β and γ that make the observed hydride transfer reaction to have two different temperature dependences of KIE, the experimental data of KIE against the temperature for the hydride transfer from G-PDH to TX^+ in acetonitrile (Table 3) were modeled using eq 14 by adjusting β and γ at α = 1.08 and 1.36 kcal/mol, respectively; the related fitting results were summarized in Tables 5 and 6, respectively.

From Tables 5 and 6, it is clear that whether α is equal to 1.08 kcal/mol or equal to 1.36 kcal/mol, when β is positive value and γ is smaller than 1, the reactions of the hydride transfer from G-PDH to TX^+ in acetonitrile have normal temperature dependences of KIE, but when β is negative value and γ is larger than 1, the reactions of the hydride transfer from G-PDH to TX^+ in acetonitrile have abnormal temperature dependences of KIE; i.e., if the activation energy of the hydride transfer in the second stage is larger than that of the hydride transfer in the first revered stage and the A-value of the hydride transfer in the second stage is larger than that of the hydride transfer in the first revered stage, the reactions of the hydride transfer from G-PDH to TX^+ have normal temperature dependences of KIE. On the contrary, if the activation energy of the hydride transfer in the second stage is smaller than that of the hydride transfer in the first revered stage and the *A*-value of the hydride transfer in the second stage is smaller than that of the hydride transfer in the first revered stage, the reactions of the hydride transfer from G-PDH to TX^+ have abnormal temperature dependences of KIE. Since the model data of KIE in Tables 5 and 6 are quite in agreement with the corresponding experimental results in Table 3, it is believable that the proposed reaction pattern of the hydride transfer reaction shown in Scheme 2 should be reasonable and true; i.e., the one-step process of the hydride transfer from G-PDH to TX^+ in acetonitrile actually consists of two different elementary stages: "*transfer of charge (partial electron)*" and "*transfer of hydrogen atom with partial negative charge*". When the substituent is p-CF_3, p-Cl, and m-CH_3O, the electron-withdrawing potential of the substituents is favorable to the return of charge (partial electron) in the CT-complex, but unfavorable to the hydride transfer in the second stage; the result is to make the KIE of the hydride transfer to show normal temperature dependence. But when the substituent is p-CH_3O, p-CH_3, and p-H, the electron-donating potential of the substituents is favorable to the hydride transfer in the second stage, but unfavorable to the return of charge (or partial electron) in the CT-complex; the result is to make the KIE of the hydride transfer to exhibit abnormal temperature dependence. Clearly it is the multistage mechanism of the hydride transfer as the real root that results in the two different temperature dependences of KIE. Meanwhile, the result of this work should be also a safe response to the skepticism of some chemists about the multistage mechanism of the hydride transfer reactions.[31]

Herein, it is worthwhile to point out that although the hydride transfer reaction from G-PDH to TX^+ in acetonitrile has abnormal temperature dependence of KIE in the temperature region between 298 and 318 K, this does not mean that in all temperature regions the reaction has abnormal temperature dependence of KIE. From Figure 9, it is clear that for the reaction of the hydride transfer from G-PDH to TX^+ with p-CH_3O as the substituent, the reaction has no abnormal temperature dependence of KIE when the temperature is larger than 372.5 K. The temperature at 372.5 K is a temperature turning point, and the values of the turning point of temperature are varied as the substituents changed.

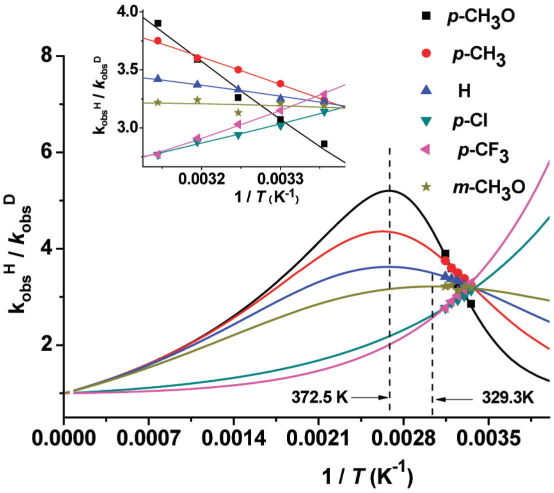


Figure 9. Fitting curves of eq 14 according to the experimental data and using α = 1.36 kcal/mol. The points represent the experimental data. Inset: Enlarging figure of the curves in temperature regions between 298 and 318 K.

■ CONCLUSIONS

In this work, the values of the kinetic isotope effect for the reactions of the hydride transfer from the substituted 5-methyl-6-phenyl-5,6-dihydrophenanthridine (G-PDH) to thioxanthylium (TX^+) in acetonitrile were determined at various temperatures. Results show that the KIE of the reactions has two different temperature dependences, which are controlled by the nature of the substituents. By detailed examination of the thermodynamics, kinetics, and mechanism of the hydride transfer reactions as well as the effects of the substituents on the temperature dependence of KIE, the following conclusions can be made: (1) Reactions of the hydride transfer from G-PDH to TX^+ in acetonitrile take place by a concerted one-step hydride transfer mechanism, but the concerted one-step hydride transfer reaction is not an elementary chemical reaction in kinetics, which includes two different elementary stages: "*transfer of partial electron*" and "*transfer of hydrogen atom with partial negative charge*". It may be a common phenomenon that the hydride transfer in one-step actually is carried out by formation of CT-complex as an intermediate. (2) The KIE of the hydride transfer from G-PDH with TX^+ in acetonitrile is an apparent kinetic behavior of the reaction. The abnormal dependence of KIE on the temperature for the hydride transfer from G-PDH with electron-donating groups to TX^+ in acetonitrile is due to the kinetic competition between the return of charge and forward transfer of hydrogen atom with partial negative charge in the CT-complex during the hydride transfer. (3) The root that the temperature dependence of KIE for hydride transfer can be transformed by changing the nature of the substituents is that, in the CT-complex, the effects of the substituents on the kinetics of the hydride transfer in the second stage are different from that on the kinetics of the hydride transfer in the first reversed stage. Generally, electron-withdrawing groups can make the KIE of the reaction to have normal temperature dependence, but the electron-donating groups can make the KIE of the reaction to have abnormal temperature dependence. (4) The abnormal temperature dependence of KIE for hydride transfer is not only dependent on the nature of the substituent mechanism of the reaction but also dependent on the temperature regions. If the practice temperature is beyond the temperature regions, the KIE of the reaction has no abnormal temperature dependence.

In one word, the most significant contribution of this work is not only to dig out the root that makes the KIE of the hydride transfer reaction to have the abnormal temperature dependence for the first time, but also further verify the complex process of the hydride transfer by the concerted one-step mechanism.

■ EXPERIMENTAL SECTION

Materials. All reagents were of commercial quality from freshly opened containers or were purified before use. Reagent-grade acetonitrile was refluxed over $KMnO_4$ and K_2CO_3 for several hours and was doubly distilled over P_2O_5 under argon before use. The commercial tetrabutylammonium hexafluorophosphate (Bu_4NPF_6, Aldrich) was recrystallized from CH_2Cl_2 and was dried in vacuo at 110 °C overnight before preparation of supporting electrolyte solution. The substituted 5-methyl-6-phenylphenanthridinium perchlorate (G-$PD^+ClO_4^-$) was prepared by the reaction of the corresponding substituted 6-phenylphenanthridine with methyl iodide in acetone, followed by metathesis with $NaClO_4$.[32] The substituted 6-phenylphenanthridine were synthesized according to conventional synthetic strategies.[33] The substituted 5-methyl-6-phenyl-5,6-dihydrophenanthridine (G-PDH) and the substituted [6-^{2}H]-5-methyl-6-phenyl-5,6-dihydrophenanthridine (G-PDD) were prepared by reduction of the corresponding iodide salts with $NaBH_4$ and $NaBD_4$, respectively. The thioxanthylium perchlorate ($TX^+ClO_4^-$) was synthesized according to literature method.[34] All the final products were identified by ^{1}H NMR and MS. G-PDH (G = *p*-CF_3): ^{1}H NMR (δ, ppm, CD_3CN, 400 M) 2.94 (s, 3H); 5.62 (s, 1H); 6.70 (d, 1H); 6.88 (t, 1H); 7.23−7.41 (m, 6H); 7.52 (d, 2H); 7.84 (d, 1H); 7.91 (d, 1H); ESI-MS/[M + 1] = 340.87. G-PDH (G = *p*-Cl): ^{1}H NMR (δ, ppm, CD_3CN, 400 M) 2.88 (s, 3H); 5.48 (s, 1H); 6.65 (d, 1H); 6.83 (t, 1H); 7.09 (d, 2H); 7.08−7.26 (m, 5H); 7.34 (t, 1H); 7.80 (d, 1H); 7.86 (d, 1H); ESI-MS/[M + 1] = 306.14. G-PDH (G = *m*-OCH_3): ^{1}H NMR (δ, ppm, CD_3CN, 400 M) 2.93 (s, 3H); 3.65 (s, 3H); 5.46 (s, 1H); 6.71 (s, 2H); 6.75 (t, 2H); 6.86 (t, 1H); 7.13 (t, 1H); 7.24 (m, 3H); 7.36 (t, 1H); 7.83 (d, 1H); 7.88 (d, 1H); ESI-MS/[M + 1] = 302.42. G-PDH (G = *p*-H): ^{1}H NMR (δ, ppm, CD_3CN, 400M) 2.92 (s, 3H); 5.50 (s, 1H); 6.67 (d, 1H); 6.85 (t, 1H); 7.15−7.26 (m, 8H); 7.36 (t, 1H); 7.83 (d, 1H); 7.89 (d, 1H); ESI-MS/[M + 1] = 272.48. G-PDH (G = *p*-CH_3): ^{1}H NMR (δ, ppm, CD_3CN, 300 M) 2.23 (s, 3H); 2.90 (s, 3H); 5.45 (s, 1H); 6.65 (d, 1H); 6.84 (t, 1H); 7.01 (s, 4H); 7.17 (d, 1H); 7.24 (q, 2H); 7.34 (t, 1H); 7.82 (d, 1H); 7.88 (d, 1H); ESI-MS/[M + 1] = 286.15. G-PDH (G = *p*-OCH_3): ^{1}H NMR (δ, ppm, CD_3CN, 400 M) 2.87 (s, 3H); 3.67 (s, 3H); 5.41 (s, 1H); 6.62 (d, 1H); 6.71 (d, 2H); 6.82 (t, 1H); 7.01 (d, 2H); 7.13 (d, 1H); 7.21 (q, 2H); 7.32 (t, 1H); 7.79 (d, 1H); 7.85 (d, 1H); ESI-MS/[M + 1] = 302.13. $TX^+ClO_4^-$: ^{1}H NMR (δ, ppm, CD_3CN, 300 M) 8.25 (t, 2H); 8.47 (t, 2H); 8.80 (d, 2H); 8.89 (d, 2H); 10.31 (s, 1H); ESI-MS/[M^+] = 197.34.

Measurement of Redox Potentials. The electrochemical experiments were carried out by CV and OSWV using a BAS-100B electrochemical apparatus in deaerated acetonitrile under argon atmosphere at 298 K as described previously.[35] *n*-Bu_4NPF_6 (0.1 M) in acetonitrile was employed as the supporting electrolyte. A standard three-electrode cell consists of a glassy carbon disk as work electrode, a platinum wire as a counter electrode, and 0.1 M $AgNO_3$/Ag (in 0.1 M *n*-Bu_4NPF_6/acetonitrile) as reference electrode. The ferrocenium/ferrocene redox couple (Fc^+/Fc^0) was taken as the internal standard. The reproducibilities of the potentials were usually ≤5 mV for ionic species and ≤10 mV for neutral species.

Isothermal Titration Calorimetry (ITC). The titration experiments were performed on a CSC4200 isothermal titration calorimeter in acetonitrile at 298 K as described previously.[36] The performance of the calorimeter was checked by measuring the standard heat of neutralization of an aqueous solution of sodium hydroxide with a standard aqueous HCl solution. Data points were collected every 2 s. The heat of reaction was determined following 10 automatic injections from a 250 μL injection syringe containing a standard solution (2 mM) into the reaction cell (1.30 mL) containing 1 mL of other concentrated reactant (~10 mM). Injection volumes (10 μL) were delivered in 0.5 s time intervals with 300−450 s between every two injections. The reaction heat was obtained by integration of each peak except the first. Note: typically the first injection shows less heat than expected. This is often due to diffusion across the tip of the needle or to difficulties in positioning the buret drive.

Kinetic Measurements. The kinetics of the hydride transfer reactions were conveniently monitored with an Applied Photophysics SX.18MV-R stopped-flow, which was thermostatted at 298−318 K under strict anaerobic conditions in dry CH_3CN. The rates were determined from disappearance of the absorbance due to the hydride acceptor (TX^+) at λ = 500 nm. The method of the kinetic measurement was pseudofirst-order method. The concentration of a hydride donor was maintained at more than 20-fold excess of the hydride acceptor to attain pseudofirst-order conditions. The kinetic traces were recorded on an Acorn computer and analyzed by Pro-K Global analysis/simulation software or translated to PC for further analysis. The well data fitting used the equation of $\mathrm{Abs} = \mathrm{P1}{*}\mathrm{EXP}(-\mathrm{P2}{*}x) + \mathrm{P3}$, which integrated in the Pro-K Global analysis/simulation software or Origin Software, and P2 was the pseudofirst-order rate constants k_1. Thus the second-order observed rate constants (k_{obs}) were derived from plots of the pseudofirst-order rate constants versus the concentrations of the excessive reactants. In each case, it was confirmed that the rate constants derived from 5−7 independent measurements agreed within an experimental error of ±5%.

■ ASSOCIATED CONTENT

Supporting Information

Three thermodynamic cycles, which were used to construct eqs 4−6, and copies of ^{1}H MNR spectra of the hydride donors G-PDH(D) and $TXClO_4$. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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