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A Thermodynamic and Kinetic Study of Hydride Transfer of a Caffeine Derivative

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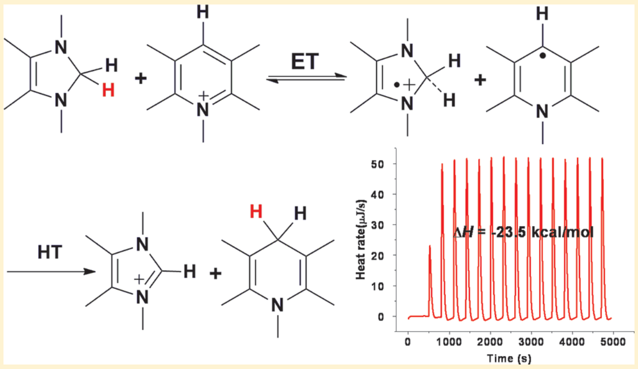
S Supporting Information

ABSTRACT: One representative type of heterocyclic compound that can release a hydride ion is 7,8-dihydro-9-methylcaffeine (CAFH). The one-electron oxidation potential of CAFH [−0.294 (V vs $Fc^{+/0}$)] and the one-electron reduction potential of CAF^+ [−2.120 (V vs $Fc^{+/0}$)] were obtained using two different methods, CV and OSWV. Applying titration calorimetry data in thermodynamic cycles, the enthalpies of CAFH releasing a hydride ion [57.6 kcal/mol] and releasing a hydrogen atom [80.3 kcal/mol] and of its radical cation $CAFH^{\bullet+}$ releasing a proton [33.0 kcal/mol] and releasing a hydrogen atom [38.4 kcal/mol] have been determined. Several conclusions can be drawn from the thermodynamic results: (1) CAFH is a very good single-electron donor whose single-electron oxidation potential is much less positive than that of NAD(P)H model compound BNAH [$E_{ox} = 0.219$ V vs $Fc^{+/0}$]. (2) The single-electron reduction potential of CAF^+ is much more negative than that of BNA^+ [$E_{red} = -1.419$ V], which means that CAF^+ is not a good electron acceptor. Furthermore, CAFH is a very good hydride donor compared to BNAH. The results of non-steady-state kinetic studies, for the reaction of CAFH and $AcrH^+ClO_4^-$, show that the ratio of $t_{0.50}/t_{0.05}$ is larger than 13.5 and the ratio of k_{init}/k_{pfo} is larger than 1. The pseudo-first-order rate constants obtained at different reaction stages decrease with the time, and the kinetic isotope was observed to be small at a short reaction time and slowly increases to 3.72 with the progress of the reaction. These kinetic results clearly display that the hydride transfer of CAFH to $AcrH^+$ in acetonitrile is not a one-step mechanism, while the thermodynamic results show that CAFH is a very good electron donor. The combination of the kinetic results with the thermodynamics analysis shows that the hydride transfer of the caffeine derivative CAFH takes place by a two-step reversible mechanism and there is an intermediate in the reaction.

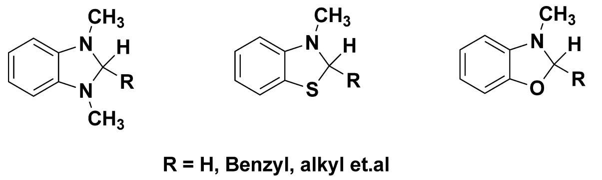


■ INTRODUCTION

Hydride transfer is one of the fundamental chemical and biological reactions. The mechanism of hydride transfer from naturally produced organic hydride donors, such as NAD(P)H,[1] $FADH_2$,[2] tetrahydrofolate,[3] and ascorbic acid (vitamin C),[4,5] to the surrounding substrates has been a fascinating subject to chemists and biochemists and has attracted the attention of many researchers around the world.

Recently, many man-made organic hydride donors have been designed and synthesized, which has been a focus of interest. In 2008, Zhu's group published a paper[6] dealing with synthetic organic hydride donors, five-membered heterocyclic compounds, such as 2,3-dihydrobenzo-imidazoles, 2,3-dihydrobenzo-thiazoles, and 2,3-dihydrobenzo-oxazoles[7−13] (Scheme 1). In this article, the driving forces for the release of a hydride ion of the five-membered hydride donors, as well as that for release of an electron and hydrogen atom, were determined. The ability of the intermediates of these compounds to release protons, hydrogen atoms, and electrons were also reported.

Scheme 1



The reason why synthetic heterocyclic hydride donors have received so much attention is that they possess important chemical and biochemical properties and serve in multiple applications, such as models for some important natural organic hydride donors to allow for the examination of the thermodynamics, kinetics, and mechanisms of hydride transfers in vivo.[14−20] In 1975, Sidney[21] reported the reduction of 7,9-disubstituted purine and related heterocycles by borohydride to

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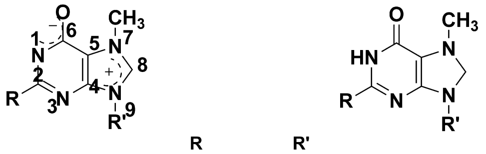
afford the corresponding 7,8-dihydro species (Scheme 2). He found that the reduced species could reoxidize quantitatively under the influence of water or oxygen and that, in solutions, the reduced species could selectively reduce imines and immonium salts via hydride transfer. Most importantly, he observed that the treatment of NAD(P)$^+$ with an excess of reduced 7,8-dihydro-9-methylcaffeine at pH = 10 could afford NAD(P)H. This procedure is expected to be of considerable utility to biochemists during the study of the reduction and oxidation of coenzymes in the human body. Undoubtedly, Sidney opened up a new field for synthetic hydride donors that have biological activity. However, his investigation was quantitatively limited to the hydride transfer properties of 7,8-dihydro purine derivatives.

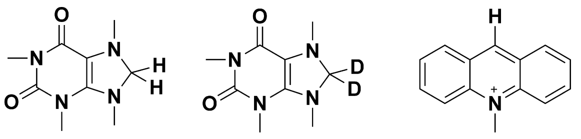
Scheme 2



	R	R'	
1a	NH2	CH3	1b
2a	H	CH3	2b
3a	OH	CH3	3b

In this article, we will partially fill the gap in the knowledge of the chemical thermodynamics and kinetics of the hydride transfer reactions of 7,8-dihydro purine derivatives shown in Scheme 2 as organic hydride donors, an area to which rather scant attention was paid in the past. Analysis of the thermodynamic and kinetic data obtained from the hydride transfer reaction of the model compound (7,8-dihydro-9-methylcaffeine, CAFH) provides quantitative data to describe the chemical properties of CAFH as a hydride donor. The thermochemical cycles also provide similar data to describe CAFH as a hydrogen atom and an electron donor in acetonitrile solution. A detailed kinetic study will be coupled with the thermochemical data to explore the mechanism of hydride transfer between CAFH and NAD$^+$ model compound *N*-methylacridinium cation (AcrH$^+$ClO$_4^-$) in acetonitrile (Scheme 3).

Scheme 3



CAFH CAFD AcrH$^+$ClO$_4^-$

■ RESULTS

Thermodynamic Results. The caffeine derivative 7,8-dihydro-9-methylcaffeine (CAFH) was prepared by known procedures.[22] The target products were identified by ^{1}H NMR and IR. Redox potentials of CAFH were determined in acetonitrile by using two electrochemical methods, CV and OSWV (Figures 1 and 2, respectively). It is obvious from the voltammograms shown in Figures 1 and 2 that both charge-transfer processes are electrochemically irreversible. We use the potentials measured by the OSWV method simply because of the ease of measurement and estimate the error in the potential determined to be ±5 mV. Electrode processes, followed by rapid chemical reactions, can be shifted by as much as 200 mV from the reversible potential (Nicholson and Shain 1964).[23] However, when using thermochemical cycles, we are usually computing the potential change for a bimolecular electron-transfer reaction. The two-electrode potential determinations needed often involve irreversible charge-transfer reactions, as in this case, and are associated with their respective electrode potential shifts. These electrode potential shifts are most often in the same direction for the two half-reactions, which results in a potential difference for the two processes being much closer to the reversible potential difference and a large decrease in error associated with the use of irreversible electrode potentials in the thermodynamic cycle. For these reasons, we suggest that the error in the Δ*E* values are considerably lower than the maximum value and are small.

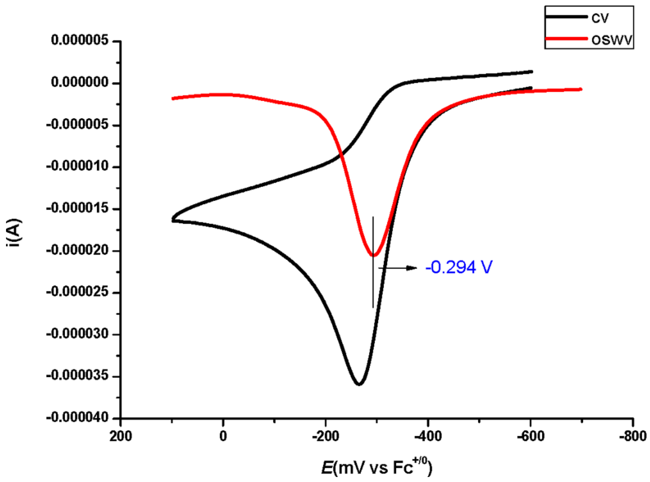


Figure 1. Cyclic voltammetry (CV) and Osteryoung square wave voltammetry (OSWV) of CAFH in deaerated acetonitrile containing 0.1 M ^{n}Bu$_4$NPF$_6$ as supporting electrolyte. The black line, CV graph (sweep rate = 0.1 V/s); the red line, OSWV graph.

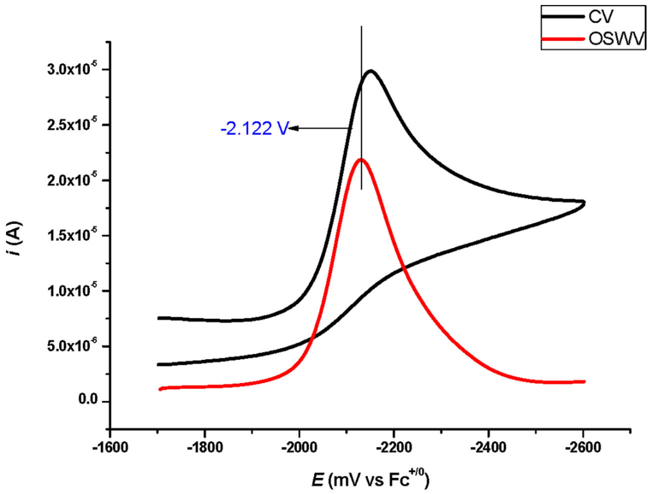


Figure 2. Cyclic voltammetry (CV) and Osteryoung square wave voltammetry (OSWV) of CAF$^+$ in deaerated acetonitrile containing 0.1 M ^{n}Bu$_4$NPF$_6$ as supporting electrolyte. The black line, CV graph (sweep rate = 0.1 V/s); the red line, OSWV graph.

The detailed experimental results are summarized in Table 1. The molar enthalpy changes (ΔH_r) of hydride transfer from the organic hydride donor CAFH to the acceptor *N*-methylacridi-

Table 1. Reaction Enthalpy Changes of Caffeine Derivative CAFH with $AcrH^+ClO_4^-$ as Well as the Redox Potentials of Relative Species in Acetonitrile Together with the Redox Potentials of Some Well-Known Six-Membered Heterocyclic Organic Hydride Donors and the Corresponding Salts for Comparison

		$E_{ox}(ZH)^b$		$E_{red}(Z^+)^b$	
ZH	$\Delta H_r{}^a$	CV	OSWV	CV	OSWV
CAFH	−23.5	−0.267	−0.294	−2.160	−2.120
		references			
BNAH[c]		0.260	0.219	−1.448	−1.419
HEH[d]		0.509	0.478	−1.144	−1.112
$AcrH_2$[e]		0.493	0.460	−0.817	−0.787

[a] ΔH_r was obtained from the reaction heats of 1 and 2 by switching the sign; the latter were measured by titration calorimetry in dry acetonitrile at 298 K. The data, given in kcal/mol, were average values of at least three independent runs. The reproducibility of ΔH_r was observed to be ±0.5 kcal/mol. [b] Measured by CV and OSWV methods in dry acetonitrle at room temperature, the unit in volts vs $Fc^{+/0}$ and reproducible to 5 mV or better. [c] BNAH is 1-benzyl-1,4-dihydronicotinamide. [d] HEH is Hantzsch 1,4-dihydropyridine. [e] $AcrH_2$ is 10-methyl-9,10-dihydroacridine.

nium ion ($AcrH^+ClO_4^-$) (eq 3) were calculated from data obtained in acetonitrile using titration calorimetry (Figure 3).

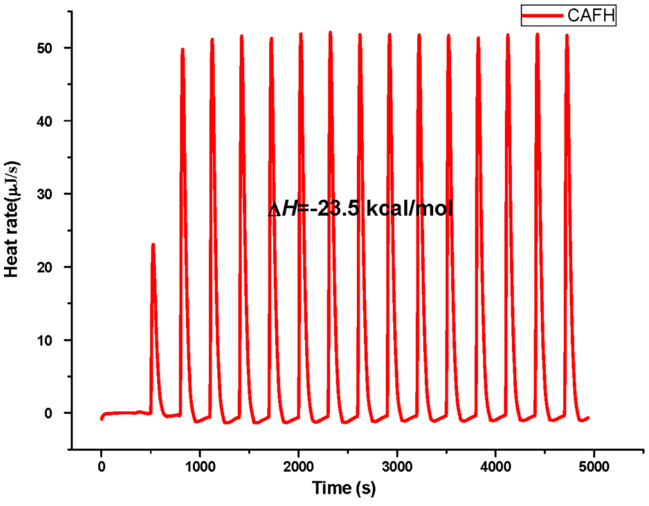
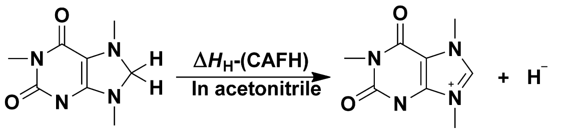


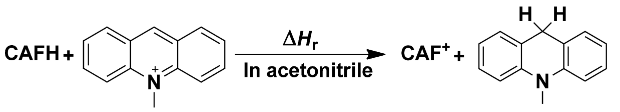
Figure 3. Isothermal titration calorimetry (ITC) for the reaction heat of CAFH with N-methylacridinium ($AcrH^+ClO_4^-$) in acetonitrile at 298 K.

The thermodynamic driving force of the five-membered heterocyclic compound (CAFH) to release a hydride anion in acetonitrile is defined as the enthalpy change of the half-reaction for hydride transfer (eqs 1 and 2). The determination



(1)

of the enthalpy change for that reaction was obtained according to eq 4, which was derived by consideration of the hydride-exchange reactions of CAFH with the strong hydride acceptor N-methylacridinium ($AcrH^+ClO_4^-$) (eq 3) in acetonitrile. The enthalpy change was determined by using titration calorimetry



(3)

(see Figure 3); $\Delta H_{H^-}(AcrH_2)$ is the enthalpy change for release of a hydride ion from 9,10-dihydroacridine ($AcrH_2$) in acetonitrile, which is available from our previous work.[24]

$$\Delta H_{H^-}(\mathrm{CAFH}) = H_f(\mathrm{CAF}^+) + H_f(\mathrm{H}^-) - H_f(\mathrm{CAFH}) \tag{2}$$

$$\Delta H_{H^-}(\mathrm{CAFH}) = \Delta H_{H^-}(\mathrm{AcrH_2}) + \Delta H\mathrm{r} \tag{4}$$

The thermodynamic driving force for CAFH to release a hydrogen atom and that for $CAFH^{•+}$ to release a proton and to release a hydrogen atom in acetonitrile is also defined as the enthalpy changes of the corresponding half-reaction, respectively. It is evident that these enthalpy changes can be used to measure the hydrogen-donating ability of CAFH and the proton-donating ability and hydrogen-donating ability of $CAFH^{•+}$ when coupled to appropriate acceptor molecules. To assess these enthalpies, three thermodynamic cycles were constructed according to the chemical processes in which CAFH releases a hydride anion in acetonitrile (Scheme 4). Equations 5−7[25] were derived according to Hess' law from the three thermodynamic cycles. In eqs 5−7, ΔH_{H^-}(CAFH) and ΔH_H(CAFH) are the enthalpy changes of CAFH to release a hydride anion and a neutral hydrogen atom in acetonitrile, respectively. The $\Delta H_P(CAFH^{•+})$ and $\Delta H_H(CAFH^{•+})$ are the enthalpy changes of $CAFH^{•+}$ to release a proton in acetonitrile and to release a neutral hydrogen atom in acetonitrile, respectively. The $E°(CAF^{+/0})$, $E°(CAFH^{+/0})$, $E°(H^{0/-})$, and $E°(H^{+/0})$ are the standard redox potentials of CAF^+, CAFH, H^+, and H^- in acetonitrile, respectively. In acetonitrile, the enthalpy changes of CAFH to release a neutral hydrogen and that of $CAFH^{•+}$ to release a proton and to release a neutral hydrogen atom can be obtained using thermochemical cycles once ΔH_{H^-}(CAFH), $E°(CAF^{+/0})$, $E°(CAFH^{+/0})$, $E°(H^{0/-})$, and $E°(H^{+/0})$ are available. Also, ΔH_{H^-}(CAFH) is then available from the data in Table1. The standard redox potentials of $E°(H^{0/-})$ and $E°(H^{+/0})$ were obtained from the literature,[26] while $E°(CAF^{+/0})$ and $E°(CAFH^{+/0})$ were obtained from experimental measurements (Table 1). The detailed values of ΔH_H(CAFH), $\Delta H_P(CAFH^{•+})$, and $\Delta H_H(CAFH^{•+})$ in acetonitrile are summarized in Table 2.

$$\Delta H_H(\mathrm{CAFH}) = \Delta H_{H^-}(\mathrm{CAFH}) - F[E°(\mathrm{CAF}^{+/0}) - E°(\mathrm{H}^{0/-})] \tag{5}$$

$$\Delta H_P(\mathrm{CAFH}^{•+}) = \Delta H_H(\mathrm{CAFH}) - F[E°(\mathrm{CAFH}^{+/0}) - E°(\mathrm{H}^{+/0})] \tag{6}$$

$$\Delta H_H(\mathrm{CAFH}^{•+}) = \Delta H_{H^-}(\mathrm{CAFH}) - F[E°(\mathrm{CAFH}^{+/0}) - E°(\mathrm{H}^{0/-})] \tag{7}$$

Kinetic Results. The kinetics of hydride transfer from7,8-dihydro-9-methylcaffeine (CAFH) and 7,8-dideuterium-9-methylcaffeine (CAFD) to $AcrH^+ClO_4^-$ were conveniently monitored with stopped-flow or conventional UV−vis absorption spectrophotometry by following the decay of reactant ($AcrH^+ClO_4^-$) at λ_{max} = 415 nm for the reaction in more than 10-fold excess (Figure 4). The pseudo-first-order

Scheme 4. Three Thermodynamic Cycles Constructed on the Basis of the Heterolytic C_7−H Bond Dissociation Process of CAFH and Electrode Potentials

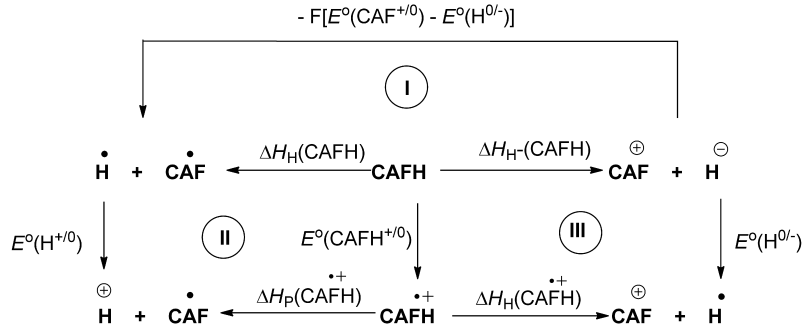


Table 2. Enthalpy Changes of CAFH To Release a Hydride Anion and To Release a Neutral Hydrogen Atom as Well as the Enthalpy Changes of $CAFH^{•+}$ To Release a Proton and To Release a Neutral Hydrogen Atom in Acetonitrile (kcal mol^{-1})

ZH	$\Delta H_{H^-}(ZH)^a$	$\Delta H_H(ZH)^b$	$\Delta H_P(ZH^{•+})^b$	$\Delta H_H(ZH^{•+})^b$
CAFH	57.6	80.3	33	38.4
		references		
BNAH	64.2	70.7	12.4	32.9
HEH	69.3	68.7	4.5	32.0
$AcrH_2$	81.1	73.0	9.2	44.2

[a] $\Delta H_{H^-}(ZH)$ values for ZH = CAFH, BNAH, HEH, and $AcrH_2$ were derived from eq4, taking $\Delta H_{H^-}(AcrH_2)$ = 81.1 kcal/mol in acetonitrile. The uncertainities are all smaller than 1 kcal/mol. [b] $\Delta H_H(ZH)$, $\Delta H_P(ZH^{•+})$, and $\Delta H_H(ZH^{•+})$ were estimated from eqs 5−7, respectively, taking $E°(H^{0/-}) = -1.128$ V vs Fc and $E°(H^{+/0}) = -2.298$ V vs Fc in acetonitrile from Zhang's work. The relative uncertainties were estimated to be smaller than or close to 1 kcal/mol in each case.

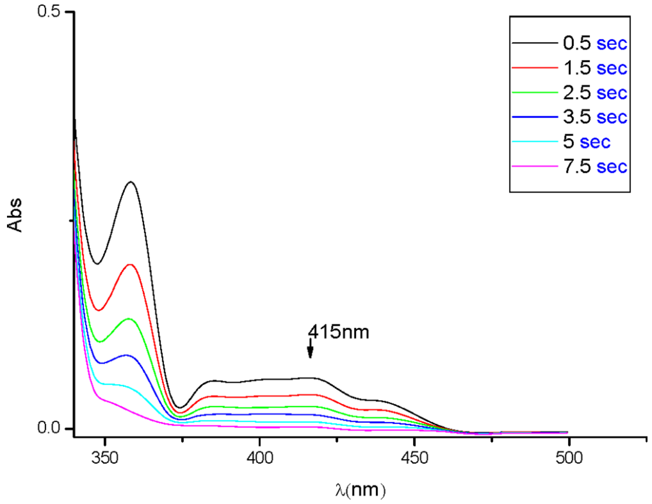


Figure 4. UV−vis spectra change obtained from the reaction of CAFH (2 mM) with $AcrH^+ClO_4^-$ (0.2 mM) in dry acetonitrile at 298 K.

Table 3. Dependence of the Hydride-Transfer Rates from CAFH and CAFD to $AcrH^+ClO_4^-$ in Acetonitrile on the Reaction Temperature

	k_2 (M^{-1} s^{-1})^a				
ZH	298 K	303 K	308 K	313 K	318 K
CAFH	92.4	110.0	130.7	156.9	184.2
CAFD	22.5	27.5	33.7	41.2	50.6

[a] Second-order rate constants k_2 for the hydride transfer from CAFH and CAFD to $AcrH^+ClO_4^-$ were obtained from the corresponding pseudo-first-order rate constants by the linear correlation against the concentration of the $AcrH^+ClO_4^-$; the experimental error is within 5%.

rate constants were calculated by Guggenheim's method.[27] The second-order rate constants (k_2) at different temperatures between 298 and 318 K are given in Table 3, which were derived from plots of the pseudo-first-order rate constants versus the concentrations of CAFH. Eyring activation parameters, activation enthalpy ($\Delta H^{‡}$), and activation entropy ($\Delta S^{‡}$) for the hydride transfer from CAFH to $AcrH^+ClO_4^-$ are summarized in Table 4; They were derived from Eyring plots of $\ln(k_2/T)$ versus the reciprocal of the absolute temperature ($1/T$), respectively.

Table 4. Comparison of Activation Parameters of Hydride Transfer from CAFH and CAFD to $AcrH^+ClO_4^-$

ZH	$\Delta H^{‡a}$	$\Delta S^{‡b}$	$-T\Delta S^{‡c}$	$\Delta G^{‡d}$
CAFH	5.7	−30.5	9.1	14.8
CAFD	7.0	−28.9	8.6	15.6

[a] From the slopes of the Eyring plots; the unit is kcal/mol. The uncertainty is smaller than 0.05 kcal/mol. [b] From the intercepts of the Eyring plots; the unit is cal mol^{-1} K^{-1}. [c] The unit is kcal/mol. [d] From the equation, $\Delta G^{‡} = \Delta H^{‡} - T\Delta S^{‡}$; the unit is kcal/mol.

More detailed kinetic analysis was employed using methods developed by the Parker group.[28] The time ratio ($t_{0.50}/t_{0.05}$) and rate constant ratio (k_{init}/k_{pfo}) are very useful probes to analyze the mechanism of hydride transfer.[28a] For a pseudo-first-order reaction taking place in a single step regardless of whether reactant or product is monitored, the time ratio ($t_{0.50}/t_{0.05}$) and rate constant ratio (k_{init}/k_{pfo}) are equal to 13.5 and 1.00, respectively ($t_{0.50}$, half-life; $t_{0.05}$, the time necessary to reach the extent of reaction equal to 0.05; k_{init}, pseudo-first-order rate constants measured in the extent of reaction ranges from 0 to 0.05; k_{pfo}, pseudo-first-order rate constants). However, for a reaction taking place by a complex mechanism, when the decay of reactant is monitored, the time ratio is greater than 13.5 and the rate constant ratio is larger than 1.00, whereas when the evolution of product is monitored, the time ratio is smaller than 13.5 and the rate constant ratio is smaller than 1.00. The data in Tables 5 and 6 were obtained upon analysis of the reactions of CAFH and CAFD with $AcrH^+ClO_4^-$ over a range of wavelengths.

Table 5. Time and Rate Constant Ratios for the Hydride-Transfer Reactions between CAFH and $AcrH^+ClO_4^-$ in Acetonitrile at 298 K over a Range of Wavelengths

wavelengths (nm)	k_{init}/k_{pfo}[a]	$t_{0.50}/t_{0.05}$[a]	$k_{s.s.}$/s^{-1}[a]
395	1.19	15.6	0.393
405	1.07	14.2	0.380
415	1.11	14.6	0.389
425	1.05	15.1	0.381
435	1.11	15.5	0.371
445	1.14	16.0	0.379

[a] [CAFH] = 2 mM; [$AcrH^+ClO_4^-$] = 0.2 mM.

Table 6. Time and Rate Constant Ratios for the Hydride-Transfer Reactions between CAFD and $AcrH^+ClO_4^-$ in Acetonitrile at 298 K over a Range of Wavelengths

wavelengths (nm)	k_{init}/k_{pfo}[a]	$t_{0.50}/t_{0.05}$[a]	$k_{s.s.}$/s^{-1}[a]
395	1.61	17.8	0.0931
405	1.52	17.1	0.0934
415	1.38	15.4	0.0934
425	1.42	16.3	0.0957
435	1.59	16.9	0.0886
445	1.87	18.2	0.0881

[a] [CAFD] = 2 mM; [$AcrH^+ClO_4^-$] = 0.2 mM.

Another analysis method was to collect 2000 points of absorbance−time (Abs-t) data over about the first half-life of the reaction of CAFH with $AcrH^+ClO_4^-$. This was followed by conversion to an extent of reaction (E.R.)−time profile. Carrying out 24 different least-squares linear correlations over different point segments resulted in 24 rate constants. These segments involve points 1−11, 1−21, 1−31, 1−41, 1−51, 1−101, 1−201,...1−1801, and 1−1901. The times of the 24 rate constants are that at the midpoints of the segments. This method is called the successive correlation method,[28d,g,h] and it gives a clear indication of any changes in the value of the apparent pseudo-first-order rate constant (k_{app}) as the reaction proceeds. If a reaction takes place in a single step, the values of k_{app} for all of the point segments are expected to be time- and wavelength-independent. The data in Table 7 and Tables S2 and S3 (Supporting Information) were obtained by this method under different wavelengths. The ideal experimental situation is when measurements can be made at wavelengths where reactant and product are the only absorbing species. In any event, the observation that mechanism probe values are dependent upon the wavelength at which measurements are made is convincing evidence that the kinetics of the reaction are inconsistent with the simple mechanism.

The procedure described in the previous paragraph was applied to the reaction of CAFD and $Acr^+ClO_4^-$ using the same time periods as those used for CAFH. The results of the successive correlation method for the latter reaction, divided by those obtained when CAFH was the substrate, gave the apparent kinetic isotope effects (KIE_{app}) as a function of time. The data in Figure 5 illustrate the time dependence of KIE_{app} for the hydride-transfer reaction between CAFH/CAFD and $AcrH^+ClO_4^-$, and the corresponding data are summarized in Table 8. These data suggest that KIE_{app} approaches 1 as time nears 0, indicating that there is no KIE for the first step in the reaction.

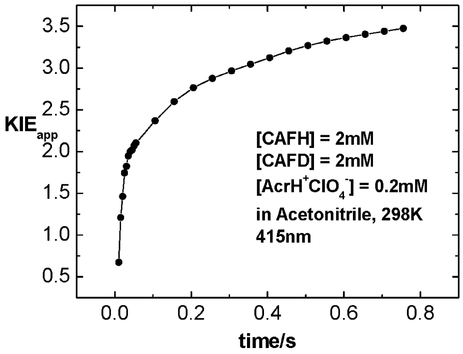


Figure 5. Apparent KIE for the reaction between CAFH/CAFD and $AcrH^+ClO_4^-$ in acetonitrile at 298 K as a function of time.

DISCUSSION

The chemical processes of hydride transfer are often proposed to involve multistep mechanisms in addition to the hydride

Table 7. Apparent Rate Constants for the Hydride-Transfer Reaction between 2 mM CAFH and 0.2 mM $AcrH^+ClO_4^-$ in Acetonitrile over the First Half-Life at 298 K as a Function of Wavelengths[a]

395 nm		405 nm		415 nm		425 nm		435 nm		
k_{app}/s^{-1}	±[b]	k_{app}/s^{-1}	±	k_{app}/s^{-1}	±	k_{app}/s^{-1}	±	k_{app}/s^{-1}	±	segment
0.522	0.0478	0.499	0.0403	0.546	0.0596	0.534	0.0056	0.491	0.0084	1
0.490	0.0287	0.487	0.0139	0.497	0.0252	0.501	0.0054	0.456	0.0157	2
0.477	0.0378	0.469	0.0174	0.467	0.0124	0.478	0.0156	0.449	0.0088	3
0.463	0.0348	0.452	0.0175	0.458	0.0201	0.455	0.00928	0.441	0.0079	4
0.449	0.0321	0.447	0.0180	0.450	0.0177	0.436	0.00813	0.439	0.0081	5
0.447	0.0289	0.432	0.0125	0.449	0.0186	0.432	0.00817	0.435	0.0011	6
0.439	0.0241	0.430	0.0137	0.447	0.0217	0.431	0.00989	0.430	0.0399	7
0.434	0.0243	0.428	0.0109	0.442	0.0234	0.427	0.00827	0.424	0.00667	8
0.429	0.0249	0.424	0.0100	0.431	0.0265	0.419	0.00739	0.422	0.00759	9
...	...	...	...	...	...	....	...	...	...	...
0.394	0.0104	0.395	0.0054	0.400	0.0028	0.402	0.0123	0.383	0.0075	21
0.393	0.0105	0.394	0.0053	0.399	0.0021	0.400	0.0124	0.381	0.0077	22
0.393	0.0106	0.395	0.0052	0.397	0.0014	0.401	0.0124	0.380	0.0077	23
0.392	0.0106	0.395	0.0052	0.396	0.0076	0.400	0.0126	0.378	0.0078	24

[a] Average of 3 sets of 20 stopped-flow repetitions. [b] "±" is the standard deviation of three sets of experiments.

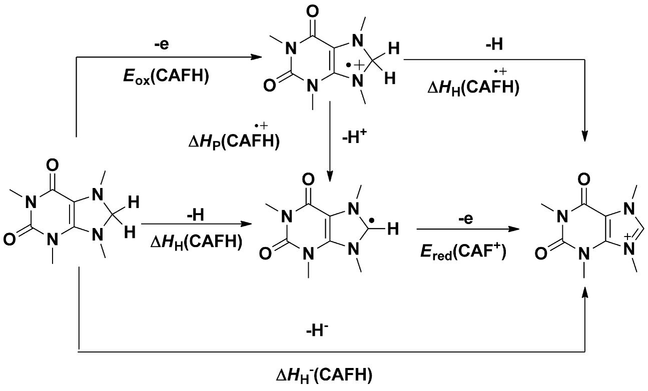
Table 8. Apparent KIE for the Reaction of CAFH/CAFD with $AcrH^+ClO_4^-$ in Acetonitrile at 298 K and 415 nm

no.	time (s)	k^H_{app} $(s^{-1})^a$	k^D_{app} $(s^{-1})^b$	KIE_{app}
1	0.01049	0.404	0.600	0.673
2	0.01549	0.449	0.371	1.21
3	0.02049	0.438	0.299	1.46
4	0.02549	0.434	0.249	1.74
5	0.03049	0.435	0.238	1.82
6	0.03549	0.435	0.223	1.95
7	0.04049	0.434	0.217	2.00
8	0.04549	0.433	0.214	2.01
9	0.05049	0.431	0.208	2.07
...	...	...	...	...
24	0.75549	0.399	0.115	3.48

[a] [CAFH] = 2 mM; $[AcrH^+ClO_4^-]$ = 0.2 mM. [b] [CAFD] = 2 mM; $[AcrH^+ClO_4^-]$ = 0.2 mM.

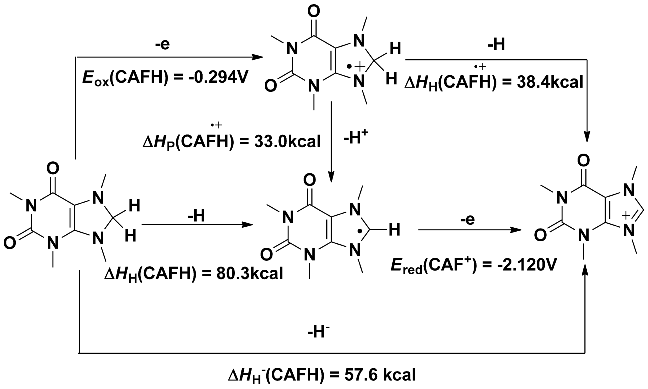
one-step transfer mechanism (Scheme 5). It is conceivable that the following chemical processes take place in vivo: (1) CAFH releases either a hydride ion or a hydrogen atom and an electron. (2) The intermediate $CAFH^{•+}$ releases either a hydrogen atom or a proton. (3) The intermediate $CAF^•$ releases an electron. To quantitatively describe the characteristic chemical behaviors of CAFH as well as its corresponding reaction intermediates in vivo, the thermodynamic driving forces of CAFH to release a hydride, hydrogen atom, and electron, the thermodynamic driving forces for $CAFH^{•+}$ to release a hydrogen atom and proton, and the thermodynamic driving force of $CAF^•$ to release an electron in acetonitrile need to be known. We have obtained all of these data, which are summarized in Table 2. According to this data, the chemical properties of CAFH as well as its various reaction intermediates could be conveniently shown by constructing the thermodynamic relations chart for CAFH (Scheme 6), which can be defined as the Molecule ID Card of CAFH.[29] From the Molecule ID card of CAFH, three different characteristic thermodynamic parameters are available for CAFH, which can then be used to quantitatively describe the three different characteristic chemical properties of other members in the caffeine derivative family at the same time. The results are listed in Table 9.

Scheme 5. Possible Pathways of the Hydride Transfer from Caffeine Derivatives CAFH



The hydride-transfer reaction between CAFH and $AcrH^+ClO_4^-$ could take place by a number of different mechanisms, including one step or multiple steps. The sequences of multistep mechanisms could be electron–proton–electron, electron–hydrogen, or hydrogen–electron transfers. The most likely mechanism based on thermodynamics for the reaction of CAFH to $AcrH^+ClO_4^-$ can be determined from the data obtained by the thermodynamic cycles. These data are now available from the Molecule ID Card of CAFH and $AcrH^+ClO_4^-$, as shown in Scheme 7.

Scheme 6. Molecule ID Cards of CAFH in Acetonitrile

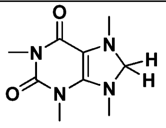
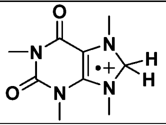
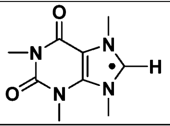
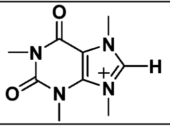


From Scheme 7, it is easy to see that, for the hydride transfer between CAFH and $AcrH^+ClO_4^-$, the energy change for the three initial steps (steps a, b, and c) in the four possible pathways are 11.4 kcal/mol for the electron transfer (step a), 36.1 kcal/mol for the hydrogen transfer (step b), and −23.5 kcal/mol for the concerted hydride transfer (step c). The energy change for the hydrogen atom transfer is quite high, and the energy change for the electron transfer is smaller than 12 kcal/mol,[30] while that for the direct hydride transfer is very negative. It is reasonable to suggest that the hydrogen atom transfer process can be ruled out as the initial step for the reaction of CAFH with $AcrH^+ClO_4^-$. As a result, the remaining concerted hydride transfer step and the initial electron transfer are both energetically reasonable pathways for the reaction of CAFH with $AcrH^+ClO_4^-$. If the electron transfer is the first step, this would be expected to be followed by a hydrogen atom transfer since the energy change for proton transfer from $CAFH^{•+}$ to $AcrH^•$ is very large compared with the latter.

To further verify that the reaction mechanism for the hydride transfer of CAFH to $AcrH^+ClO_4^-$ in acetonitrile, the kinetics of the reaction were examined. The activation free energy ($\Delta G^‡$) for the hydride transfer from CAFH to $AcrH^+ClO_4^-$ was observed to be equal to 14.8 kcal/mol (Table 4), which is much smaller than the standard energy change (ΔG^0) of the initial hydrogen atom transfer (step b) as expected. Furthermore, the experimental $\Delta G^‡$ for the hydride transfer reaction is larger than ΔG^0 for the initial electron transfer (step a), and also larger than ΔG^0 for the concerted hydride transfer (step c). According to transition-state theory, $\Delta G^‡$ for a reaction is always larger than, or at least equal to, the corresponding ΔG^0 for that reaction.[31] On the basis of the latter, it is evident that step b must be ruled out as the initial reaction step (Figure 6). However, the two remaining mechanisms (a and c) are thermodynamically possible for this reaction.

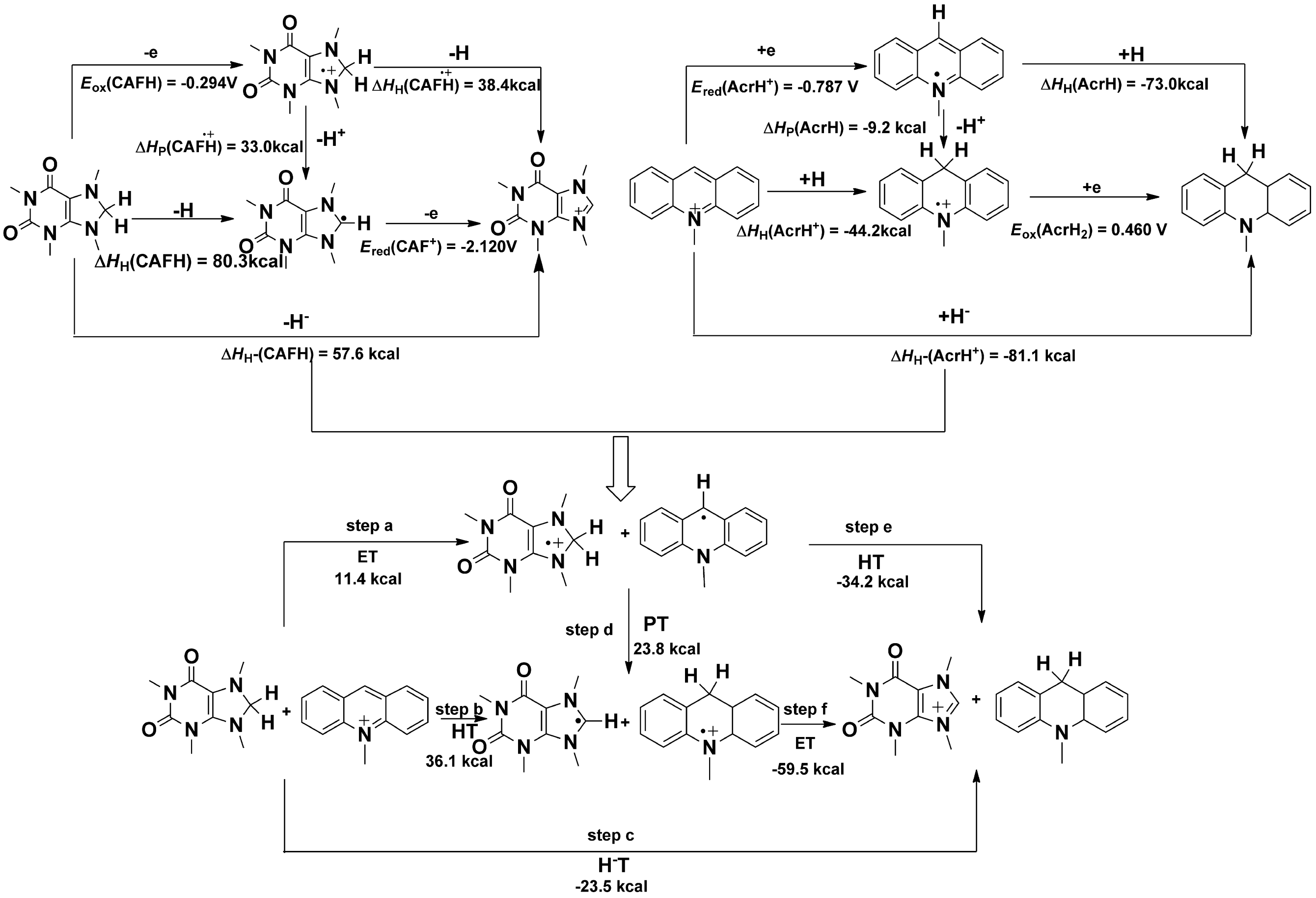
The greatest difference between the concerted hydride transfer and the initial electron transfer is that there is an intermediate in the latter mechanism. If the intermediate could be detected, the mechanism of hydride transfer of CAFH to $AcrH^+ClO_4^-$ can be proposed to be the initial electron transfer, followed by hydrogen atom transfer. If a reaction has an

Table 9. Diagnoses of Chemical Properties for Caffeine Derivatives According to the Molecule ID Card of CAFH

Species	thermodynamic parameters*	diagnoses of the characteristic properties
	$\Delta H_{H^-}(CAFH) = 57.6$ kcal $\Delta H_H(CAFH) = 80.3$ kcal $E_{ox}(CAFH) = -0.294$ V	strong hydride donor, strong nucleophilic agent weak hydrogen donor and antioxidant strong one-electron reductant
	$\Delta H_P(CAFH^{\bullet+}) = 33.0$ kcal $\Delta H_H(CAFH^{\bullet+}) = 38.4$ kcal $E_{red}(CAFH^{\bullet+}) = -0.294$ V	weak organic acid good hydrogen donor and antioxidant poor one-electron oxidant
	$\Delta H_P(CAF^{\bullet}) = -33.0$ kcal $\Delta H_H(CAF^{\bullet}) = -80.3$ kcal $E_{ox}(CAF^{\bullet}) = -2.120$ V	strong base good hydrogen acceptor, good antioxidant strong one-electron donor
	$\Delta H_{H^-}(CAF^+) = -57.6$ kcal $\Delta H_H(CAF^+) = -38.4$ kcal $E_{red}(CAF^+) = -2.120$ V	weak hydride acceptor and electrophilic agent weak hydrogen acceptor weak one-electron oxidant

*Note: $\Delta H_P(CAF^{\bullet})$, $\Delta H_H(CAF^{\bullet})$, $\Delta H_{H^-}(CAF^+)$, and $\Delta H_H(CAF^+)$ are defined as the enthalpy changes of $CAF^{\bullet}$ to obtain proton, and to obtain hydrogen atom, and the enthalpy changes of CAF^+ to obtain hydride anion and to obtain hydrogen in acetonitrile, respectively. The values are equal to the enthalpy changes of the corresponding opposite species to release proton, to release hydrogen atom, and to release hydride anion in acetonitrile by switching the signs.

Scheme 7. Thermodynamic Analysis Platform on the Mechanism of Hydride Transfer from CAFH to $AcrH^+ClO_4^-$ in Acetonitrile



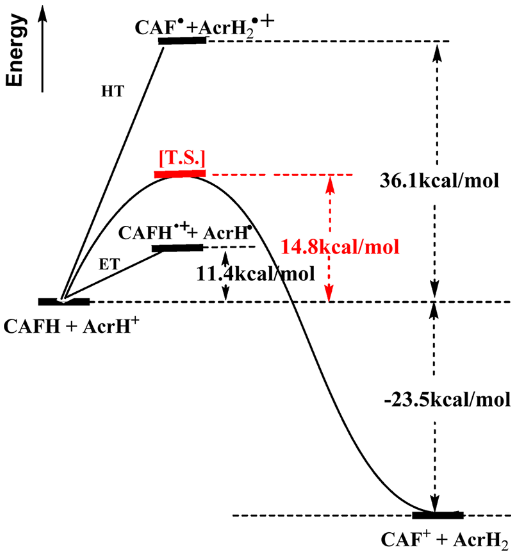


Figure 6. Comparison of state energy changes for the three possible initial steps of the hydride transfer from CAFH to $AcrH^+ClO_4^-$ and the activation free energy of the hydride transfer.

intermediate, the initial rate of decay of the reactant will be larger than the initial rate of the product evolution in the presteady-state time period. Whether or not an intermediate is involved in a reaction is addressed readily by the kinetic methods used in this study.[28]

The data in Tables 5 and 6 show that the time ratio ($t_{0.50}/t_{0.05}$) is larger than 13.5 and the rate constant ratio (k_{init}/k_{pfo}) is greater than 1.0. This is the case for a complex mechanism when the decay of reactant is monitored. A pseudo-first-order reaction taking place in a single step, regardless of whether reactant or product is monitored, results in time ratios and rate constant ratios equal to 13.5 and 1.0, respectively. The data summarized in Tables 5 and 6 are inconsistent with the simple single-step mechanism for the hydride transfer of CAFH and $AcrH^+ClO_4^-$. Furthermore, the data in Table 7 and Tables S2 and S3 (Supporting Information) clearly display that the k_{app}–time profiles begin at relatively high values of k_{app} and decay with time toward steady-state values, which requires that there is an intermediate in the reaction since a reaction taking place in a single step results in apparent rate constants that are expected to be time-independent. In addition, the wavelength-dependent apparent rate constants indicate that absorbance by an intermediate is involved, which is inconsistent with the simple single-step mechanism. The apparent deuterium kinetic isotope effects for CAFH were observed to be time-dependent, with a low value at the beginning, and to increase with increasing time. This is illustrated in Figure 5 and Table 8. It should be pointed out that KIE_{app} at the shortest time is smaller than 1.0. There is considerable error associated with this initial value since absorbance changes are small especially for the D substrate.

The data discussed in the previous paragraphs clearly rule out the direct hydride-transfer mechanism for the reaction between CAFH and $AcrH^+ClO_4^-$. Therefore, some form of the reversible consecutive mechanism (Scheme 8) is the only mechanism tested that is consistent with the experimental data. No significant deuterium kinetic isotope is expected for the electron-transfer step since the molecules are large aromatics and π electrons are involved in the electron-transfer reaction.

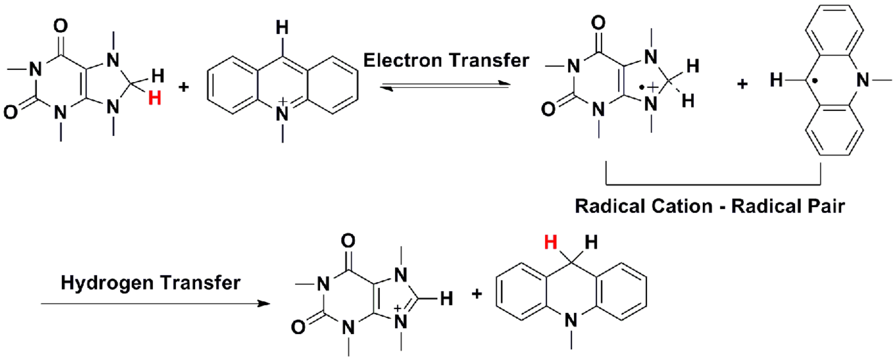
Although we did not observe the formation of a charge-transfer (CT) complex, it is likely that electron transfer takes place within the CT complex or a similar nonbonded reactant complex, which is kinetically significant. In fact, it was proposed several years ago that the CT complex is related in a similar hydride-transfer reaction.[32]

■ EXPERIMENTAL SECTION

Materials. Solvents and reagents were obtained from commercial sources and used as received unless otherwise noted. Caffeine was purchased from a chemical supplier. Tetrabutylammonium hexafluorophosphate was recrystallized three times from CH_2Cl_2/Et_2O and dried in vacuo at 110 °C for 10 h before preparation of a supporting electrolyte solution. 7,8-Dihydro-9-methylcaffeine and CAFD were prepared according to the previously described procedures[22] and were identified by NMR and IR, respectively. The results are listed for CAFH: ^1H NMR (400 MHz, CD_3CN): δ 2.62 (s, 3H), 2.93 (s, 3H), 3.19 (s, 3H), 3.41 (s, 3H), 4.18 (s, 2H). IR (KBr): 2943, 2837, 1616, 1521, 1379, 1321, 740 cm^{-1}. For CAFD: ^1H NMR (400 MHz, CD_3CN): δ 2.63 (s, 3H), 2.94 (s, 3H), 3.21 (s, 3H), 3.41(s, 3H).

Electrochemistry. The electrochemical experiments were carried out by cyclic voltammetry (CV) and Osteryoung square wave voltammetry (OSWV) using a BAS-100B electrochemical apparatus in deaerated acetonitrile under an argon atmosphere. The electrodes used were the following: working electrode, glassy carbon; reference electrode, 0.01 M $Ag/AgNO_3$ in $^nBu_4NPF_6/CH_3CN$ electrolyte solution; and auxiliary electrode, platinum wire. The ferrocene/ferrocenium redox couple (Fc/Fc^+) was used as an internal reference for all measurements. Scans were taken at 100 mV s^{-1}. The concentration of the substrate is approximately 1 mM with 0.1 M $^nBu_4NPF_6$ in acetonitrile. The estimated errors are smaller than 5 mV.

Scheme 8. Two-Step Reversible Consecutive Mechanism Applied to the Hydride-Transfer Reaction between CAFH and $AcrH^+ClO_4^-$ in Acetonitrile



Isothermal Titration Calorimetry (ITC). The titration experiments were performed on a CSC4200 isothermal titration calorimeter in acetonitrile at 298 K. 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 (~3 mM) into the reaction cell (1.30 mL) containing 1 mL of other concentrated reactant (~10 mM). The injection volume (10 μL) was delivered in a 0.5 s time interval with 300 s between every two injections. The reaction heat was obtained by integration of each peak except the first.

Kinetic Measurements. Kinetic experiments were carried out using a Hi-Tech SF-61 stopped-flow spectrometer installed in a glovebox and kept under a nitrogen atmosphere. The temperature was controlled at 25 °C using a constant temperature flow system connected directly to the reaction cell in the return pathway to a bath situated outside of the glovebox. All stopped flow experiments included recording at least 20 absorbance−time profiles at each wavelength. Each experiment was repeated at least three times. The 2000 point absorbance−time curve data were collected over one half-life.

CONCLUSIONS

In this article, 7,8-dihyro-9-methylcaffeine (CAFH) was synthesized as a type of heterocycle that can release a hydride ion. The thermodynamics, kinetics, and mechanism of CAFH as hydride, hydrogen atom, and electron sources to react with $AcrH^+ClO_4^-$ in acetonitrile were examined in detail. Several conclusions can be safely drawn from the thermodynamic and kinetic data: (1) CAFH is a strong electron donor and hydride donor to this acceptor since the one-electron oxidation potential of CAFH [−0.294 V vs $Fc^{+/0}$)] is significantly lower than that of $AcrH_2$ [E_{ox} = 0.460 V vs $Fc^{+/0}$] and the enthalpy of CAFH releasing a hydride ion [57.6 kcal/mol] is also smaller than that of $AcrH_2$ [81.1 kcal/mol]. (2) The reaction between CAFH and $Acr^+ClO_4^-$ in acetonitrile takes place by a complex mechanism. This conclusion is supported by thermodynamic analysis and kinetic analysis. For this reaction, thermodynamic data display that the hydride transfer has two possible routes: single-step concerted hydride transfer or an initial electron transfer, followed by hydrogen atom transfer; at the same time, the kinetic data show that a number of facts require that there is an intermediate in the reaction. These include that (a) the time ratio ($t_{0.50}/t_{0.05}$) is larger than 13.5, (b) the rate constant ratio (k_{init}/k_{pfo}) is greater than 1.0, (c) k_{app} is observed to be relatively large at short times and to decrease toward a steady-state value at longer times, and (d) the observed KIE is time-dependent, approaching unity near zero time and increasing toward a plateau value as steady state is achieved. A reversible consecutive mechanism is proposed with a radical cation intermediate, followed by hydrogen transfer, for the hydride transfer between CAFH and $AcrH^+ClO_4^-$.

ASSOCIATED CONTENT

Ⓢ Supporting Information

UV/vis and ^{1}HNMR spectra of substrates and tables and figures of kinetic data under various conditions. 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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(25) Equations 5, 6, and 7 were constructed from the thermodynamic cycles (I), (II), and (III) in Scheme 4, respectively. Note that we used the term free-energy change ΔG_{et} to replace the enthalpy change ΔH_{et} in eqs 5−7 for the electron-transfer processes. The justification of this treatment is that entropies associated with electron transfer are negligible, as verified by Arnett et al: Arnett, E. M.; Amarnath, K.; Harvey, N. G.; Cheng, J.-P. *J. Am. Chem. Soc.* **1990**, *112*, 344.

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