Kinetic Study of Hydride Transfer of a Caffeine Derivative

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Abstract:

A synthetic heterocyclic compound 7, 8-dihydro-9-methylcaffiene(CAFH) can go through the process of a hydride transfer. The kinetic data showed that the mechanism was not a simple one-step process but contained a transition step. The mechanism demonstrated that the reaction first produced a cation intermediate and then a hydrogen transfer from CAFH to $AcrH^+ClO_4^-$. The further steps for this mechanism are to find a way to use it for a purpose such as to explore biological reactions.
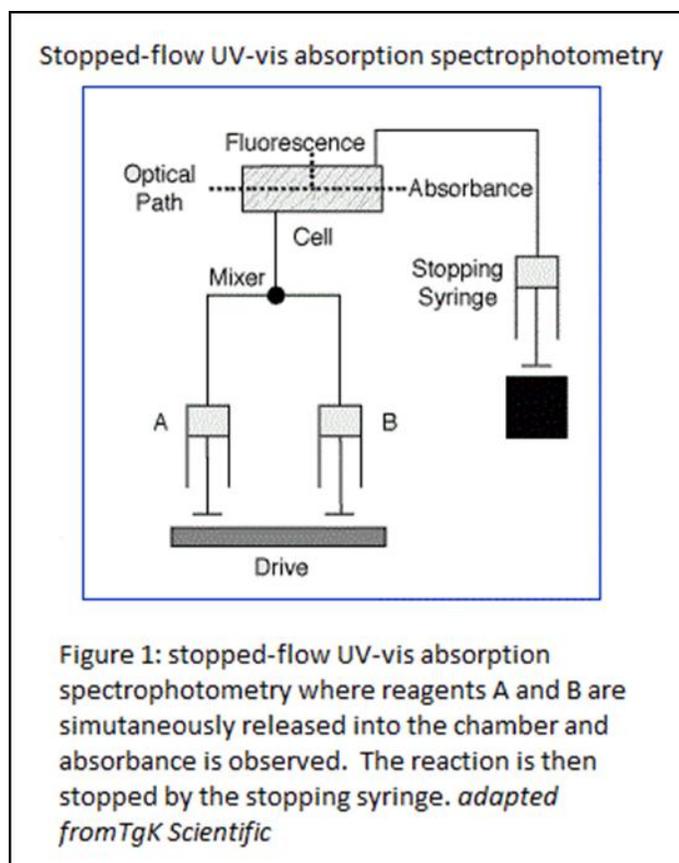
Introduction:

Hydride transfer is one of the most common chemical reactions. The hydride ion is the simplest anion and is a strong reducing agent. A hydride is a hydrogen atom that has two electrons and one proton. The hydride is a strong reducing agent because it has two electrons and is able to easily give up one of the electrons to another molecule. Therefore, hydride transfers are in a lot of biological reactions. Some natural organic hydride donors are NADPH, $FADH_2$, and ascorbic acid (Vitamin C)[1].

The focus of interest in hydride transfers is now in man-made hydride donors. Many of the synthetic hydride donors are 5 or 6-membered heterocyclic compounds. The reason that these heterocyclic donors are studied is because they have important applications, such as models to examine the kinetics and thermodynamics of some natural organic hydride donors[2].

Though 5 and 6-membered heterocyclic compounds are both extensive, the studies on thermodynamics, kinetics, and mechanism of the 5-membered heterocyclic compounds are not as in-depth as the 6-membered heterocyclic compounds[3].

Some of the ways to study the 5-memebered heterocyclic compounds is through thermodynamic and kinetic experiments. Thermodynamics is the study of transformations of energy. The physical properties of thermodynamics are work, heat and energy. Thermodynamics can be used in experiments to determine the enthalpy change in a reaction which can determine the driving force for the hydride transfer.

Kinetics is the study chemical reaction rates. There are many ways to monitor the kinetics of a reaction but one major ways is to use the stopped-flow UV-visual absorption spectrophotometry. A diagram of a stopped-flow system is shown below in figure 1.

Figure 1: stopped-flow UV-vis absorption spectrophotometry where reagents A and B are simultaneously released into the chamber and absorbance is observed. The reaction is then stopped by the stopping syringe. *adapted fromTgK Scientific*

As shown above in Figure 1, the stopped-flow technique is when reagents are mixed very quickly in a small chamber. The reagents are then stopped by a syringe instead of allowed to travel out of the outlet tube. As the solution fills the stopping syringe the plunger hits a block which cause the flow to be stopped immediately causing the reaction to continue in the mixed solutions[4]. The stopped-flow technique allows for the reaction to be studied at the millisecond to second timescale. This is possible when the reagents are driven from syringes (shown in Figure 1 and A and B) into the mixing chamber and then the volume is limited by the stopping syringe. This provides the mixing chamber with solution that is only milliseconds old. Some of the common observation instruments are UV-visible absorption, circular dichroism, and fluorescence emission. The fluorescence emission and UV-visible absorption are both shown in

Figure 1. As shown in figure 1, the reagents are pushed quickly into the mixing chamber by the driving syringes. Then the observation instrument is used to monitor the concentrations over time[5]. In this paper, the UV-visual absorption would be used to determine the kinetics of the reaction. UV-visual absorption is used to identify compounds based on what light it absorbs. This happens when the sample molecules are exposed to light energy and if the light energy matches the energy needed to cause an electronic transition (when an electron from the highest occupied molecular orbital, HOMO jumps to the lowest unoccupied molecular orbital, LUMO) then the light is absorbed causing the electron to be promoted to a higher energy orbital. The optical spectrometer then records the wavelength that was absorbed. This method is used often with biochemical reactions.

The study of 5-membered heterocyclic compounds have been studied before but not as in-depth as some other hydride transfer reactions, such as 6-membered heterocyclic compounds.

In this paper, the chemical kinetics of 7, 8-dihydro-9-methylcaffeine (CAFH) would be studied. The kinetic study of CAFH and N-methylacridinium in acetonitrile would determine the mechanism of hydride transfer.

Results and Discussion:

The kinetics of the hydride transfer is important to determining the mechanism of the hydride transfer. Kinetics is the study of chemical process rates. Kinetics uses different experimental conditions to see how the conditions influence the speed of the chemical reaction. This data can provide information on the transition states and the reactions mechanism. In Parker et al., the kinetics of 7,8-dihydro-9-methylcaffeine (CAFH) to $AcrH^+ClO_4^-$ were studied using stopped-flow UV-visual absorption spectrophotometry[7]. The kinetics of the reaction can be determined by UV-visual absorption spectrophotometry because it collects data of the absorbance of the reaction over time. The time component is what helps to determine the kinetics because kinetics studies the time it takes for the reaction to occur. It was achieved by looking at the decay of $AcrH^+ClO_4^-$ to $AcrH_2$ (9,10-dihydroacridine) at $\lambda_{max} = 415$ nm[7]. The decay of $AcrH^+$ to $AcrH_2$ determines the reaction kinetics because it measures the loss of concentration over time. This shows how fast the reaction takes place by showing how fast the reactant turns into the product. The first step to determine is the rate law. The general form of the rate law in this experiment is:

$$Rate = -d[CAFH]/dT = k[CAFH]^m * [AcrH^+ClO_4^-]^n$$

The m and n stand for the order due to CAFH and $AcrH^+ClO_4^-$. The equation is negative because it is showing the decay of CAFH or the loss of concentration of CAFH over time. The k in the rate law equation stands for the rate constant. A rate constant is independent of the concentrations but is dependent on temperature. The rate law equation shown above shows the rate of reaction as a function of the concentrations of

the species present in the chemical reaction. It is assumed, in this paper, that the concentration of CAFH is much greater than the concentration of $AcrH^+ClO_4^-$, because 2 mM of CAFH were used in the experiment and only 0.2 mM of $AcrH^+ClO_4^-$ were used [5]. Therefore, the lower concentration of dye is determined as a function of time. This is called the pseudo-first-order rate constant because the assumption is that a greater concentration CAFH of exists than $AcrH^+ClO_4^-$. Pseudo-first-order rate constant is when one reactant is in large concentration compared to the other reactant, which therefore allows for the assumption that the large concentration reactant stays constant throughout the reaction. It is called a pseudo-first-order rate constant because the rate constant isn't really a first-order rate law. The first-order rate law is used because one of the reactants is being displaced from the rate law by assuming it stays constant, therefore it is called a pseudo-first-order rate law. The pseudo-first-order rate law is beneficial because it allows the study of each reactant separately.

The pseudo-first-order rate constants were determined by using Guggenheim's method[5]. Guggenheim's method is when concentration data is taken at constant time increments, Δt. This is a convenient method to use with modern technology since the data can be taken at any time. The equation used is $-kt + \ln(A_{end} - A_o)(1-e^{-k\Delta t})$. This equation uses the initial concentration of the reactant and the final concentration of the reactant and the time it takes to happen. Δt is constant, which makes the equation a straight line. The slope of the line provides the rate constant, k. The Δt should be large so that the relative error will be small, because the smaller time increments looked at the less data will be looked at compared to larger increments of time where the larger amount of data is studied. The ideal Δt is infinity[5].

To find out more about the rate constants for the hydride transfer between CAFH and $AcrH^+ClO_4^-$ the successive correlation method is used. The successive correlation method involves the collection of 2000 points of data over the first half-life[7]. A half-life is when the initial concentration of the reactant is cut in half so that only a half of the initial concentration is left. The half-life is important, because it shows how fast the reactant is used up in the reaction which provides how fast the reaction is taking place. The data collected is on the absorbance-time of the reaction of CAFH and $AcrH^+ClO_4^-$ which was converted to the extent of reaction -time profile. This means that the extent of the reaction is now going to be studied to see how much of the reactants are used before the reaction reaches equilibrium. It results in twenty-four rate constants that show any changes in the pseudo-first-order rate constants during the reaction[7]. The successive correlation method data is shown below in Table 1.

Rate Constants as a Function of Wavelength										
Table 1: Shows the rate constants for the hydride transfer between CAFH and $AcrH^+ClO_4^{4-}$. It shows the rate constants at various wavelengths. *Adapted from Parker et. al.*										
395 nm		**405 nm**		**415 nm**		**425 nm**		**435 nm**		
k_{app}/s^{-1}	±	k_{app}/s^{-1}	±	k_{app}/s^{-1}	±	k_{app}/s^{-1}	±	k_{app}/s^{-1}	±	segment
0.522	0.0478	.0499	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	0.0106	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

Table 1 shows the rate constants of the reaction between CAFH and $AcrH^+ClO_4^-$. The ideal process for the experiment is that at the wavelengths 395 nm, 405 nm, 415 nm, 425 nm, and 435 nm are that only CAFH and the product concentrations are present so that an accurate reading can obtained. K_{app} stands for the pseudo-first-order rate constant. The k_{app} values are significant because it will determine if the reaction is a single step reaction by showing if the rate constant values will change over time[7]. If the reaction takes place in one step then the k_{app} values will be time and wave-independent, because if the reaction happens in one step then the rate constant values would vary over time and wouldn't just decrease steadily over time and the rate constants should vary between the different wavelengths instead of being pretty much the same to show that there was a change in concentration of the reactant to the product[8]. Table 1 demonstrates that the values in the right hand column under each wavelength show the pseudo-first-order rate constant over time. The left hand columns, under each wavelength, show the standard deviation values.

The k_{app} values in table 1 show that at each wavelength the rate constant values decrease with time. The k_{app} values, for the 395 nm, shows that the k_{app} value starts high. Then decreases until around 0.0393/0.0392 and appears to have reached a steady-state. A steady-state is when all components of a reaction are constant as time changes. The same happens for all the rest of the wavelengths. This demonstrates that the reaction is not a single-step reaction because k_{app} was time-dependent, because the rate constants started out high and then decreased over time to a steady-state which indicated that there is a presence of an intermediate since the rate constants would stay

the same if it was a simple single step because as the concentration of the reactant decreased the product would increase and therefore not affect the rate constant [7].

A first order reaction is time- independent because the time taken for the reaction concentration to fall to half its original concentration is shown in this equation below.

$$Kt_{1/2} = -\ln((1/2[A]_o)/([A]_o)) = -\ln (1/2) = \ln 2$$

Therefore: $T_{1/2} = \ln 2/k$

This equation shows that the half-life of the reactant is independent from the reactants initial concentration[5]. In a second-order reaction, the half-life equation is derived from the second-order rate law and the equation is shown below.

$$d[A]/dt = -k[A]^2$$

$$-\int_{[A]_o}^{[A]} d[A]/[A]^2 = k \int_0^t dt$$

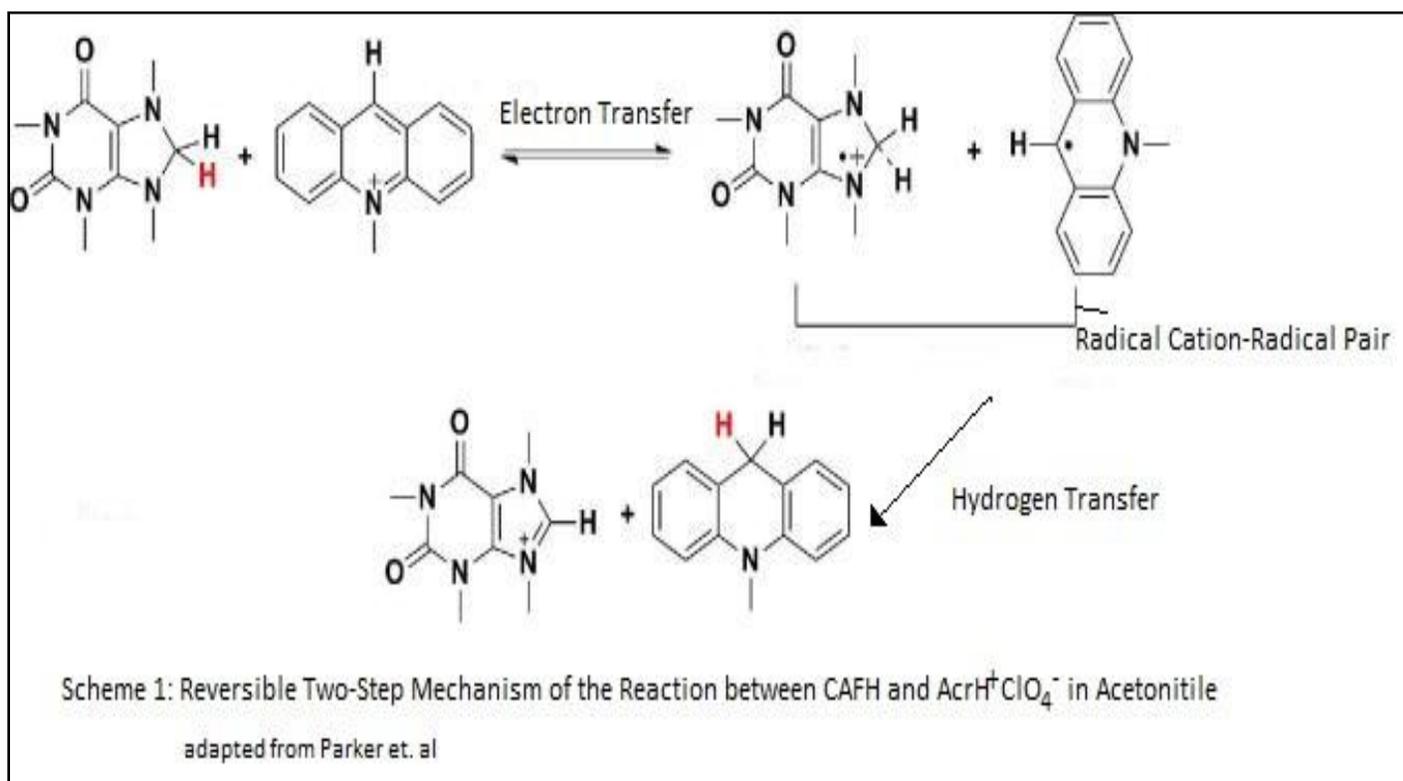$$\frac{1}{[A]_o} \lim_{[A]_o \to [A]} = \frac{1}{[A]} - \frac{1}{[A]_o} = kt$$

$$T1/2 = 1/k[A]_o$$

This equation shows that the half-life of the reactant varies with the initial concentrations[5]. So, the data in table 1 shows that the rate constant of CAFH is dependent on time which signifies that there is some intermediate that takes place during the reaction.

The mechanism for the hydride transfer is a transfer of electrons followed by a hydrogen transfer. The mechanism shows that there is an intermediate which means that the reaction is not a single step reaction. An intermediate is when a chemical

substance is produced during a conversion of a reactant to a product. Based on the

kinetic data, an intermediate is part of the mechanism because the k_{app} showed a time

dependancy.

The proposed mechanism for the hydride transfer from CAFH to $AcrH^+ClO_4^-$ is

shown below in scheme 1.

Scheme 1: Reversible Two-Step Mechanism of the Reaction between CAFH and $AcrH^+ClO_4^-$ in Acetonitile

adapted from Parker et. al

Scheme 1 shows that the nitrogen from the pyrrole on the compound CAFH was

photoinduced to give up an electron[9]. This causes the nitrogen on the pyrrole to become

a radical cation. The nitrogen from $AcrH^+ClO_4^-$ was photoinduced to give up an electron

causing the loss of its positive charge and creating the radical anion[7]. The ClO4- is not

shown in scheme 1 because for this reaction it is does not contribute anything to

breaking or forming of new bonds and is a spectator ion in the mechanism. The

hydrogen on the pyrrole of CAFH gives up its electron to the carbon attached to the

radical cation nitrogen which then causes a double bond to form between the nitrogen

and the carbon. This causes the nitrogen to have a positive charge[7]. The hydrogen

from CAFH then becomes H^+, which then becomes attracted to the carbon radical.

A pyrrole is a heterocyclic ring that has four carbons and nitrogen. It is aromatic

only when the lone pair is located in the p orbital of the nitrogen this is because the lone

pair is able to travel around the ring displacing the double bonds and reforming the

double bonds between different atoms in the molecule.

A cation radical is formed by ionization of a single electron from a neutral

molecule. An example is the nitrogen on the pyrrole of CAFH. This ionization therefore

gives the nitrogen a positive charge by taking away and electron from nitrogen's lone

pair and transferring it to the connecting carbon. This leaves nitrogen with a lone

electron and a positive charge. The hydrogen the gets knocked off because the carbon

has to many electrons and a nitrogen-carbon double bond is formed making CAD^+ [7].

The anion radical is formed breaking a carbon-carbon double bond of $AcrH^+ClO_4^-$

. This results in one electron going to the one carbon and the other carbon which

causes a chain of carbon-carbon double bond breakage until the positively charged

nitrogen gains another electron causing the nitrogen to become neutral[7]. The carbon

anion is now is able to attract the H^+ that came from CAFH. The H^+ shares the radical

with the carbon creating a bond between carbon and hydrogen.

The kinetics of a reaction is what determines how fast a reaction will proceed.

The collision theory states that two molecules must collide in order to react with each

other. This means that the concentrations should have an impact on how much the molecules collide. Finding out how much the molecules collide is how the reaction rate in calculated.

In a two-step reaction, shown in scheme 1, the first step is the intermediate. This is not a product of the reaction but just a stepping stone to get to the final product. The intermediate shows how the final product is reached. In this experiment the intermediates have radicals which allow for the hydrogen to transfer from CAFH to $AcrH^+ClO_4^-$.

Most two-step reactions happen with one reaction happening fast and the other reaction happening slow which is why the intermediate is hard to detect. This is why the UV-visual spectrophotometer was used to capture the absorbance over time to be able to determine if the reaction had an intermediate.

This mechanism shows a charge-transfer complex. This is where the electron transfer occurs. The electron transfer is not observed because it most likely is caused by photo induction. A charge-transfer complex has been present in other hydride transfer mechanisms, so it is plausible that it is also present in the hydride transfer of CAFH and $AcrH^+ClO^{4-7}$. This signifies that this mechanism of an electron transfer followed by a hydrogen transfer is very possible for the reaction of CAFH and $AcrH^+ClO_4^-$.

Conclusion:

In this paper, the hydride transfer reaction between 7, 8 dihydro-9-methylcaffeine (CAFH) and $AcrH^+ClO_4^-$ was studied using kinetics to find out how the reaction mechanism worked. The kinetic data showed that the reaction was not a simple one step process, but had an intermediate step in the mechanism. This was shown from the fact that k_{app} was greater during short intervals of time but then decreased at longer intervals of time. This demonstrated that the k_{app} started to change indicating that there was another reaction taking place instead of a direct reaction from CAFH to CAF^+. The reaction mechanism was then possible to predict. The proposed mechanism showed that the intermediate was a radical cation that opened up the possibility for a hydrogen transfer[7].

The results from this experiment were accurate and contributed directly to figuring out how the mechanism worked. Knowing the mechanism of the hydride transfer of CAFH gives scientists a better understanding on how synthetic heterocyclic hydride donors work in vivo[1]. Since the mechanism is now proposed for CAFH, which is a 7, 8-dihydro purine derivative, the future study of how CAFH can contribute to biological functions needs to be evaluated. The 7, 8-dihydro purine derivative has already been shown to help with the study of reduction and oxidation of coenzymes[10].

Some of the things that can be the next step for this experiment are looking into whether CAFH can be used to reduce aldehydes or ketones for organic synthesis[11]. One way to look into the possibility of using CAFH to reduce aldehydes or ketones is to mix the two compounds together and then take to product that is formed from the

reaction and place it in the gas chromatographer to see what product is formed and to determine if the CAFH was able to reduce the aldehydes or ketones. Also a reaction equation would be proposed based on the results from the gas chromatographer.

There are a bunch of possibilities to take the next step for this research on hydride transfer of synthetic heterocyclic compounds. The important thing is to not stop with this mechanism until a way to use it someway is found.

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