

Full Paper

Subscriber access provided by BIU Pharmacie | Faculté de Pharmacie, Université Paris V

Thermodynamics and Kinetics of Click Reaction between Benzyl Azide and Different Alkynes by Microcalorimetry

Xiaoyi Li, Bo Jin, Zhicheng Guo, Shijin Chu, and Rufang Peng

Org. Process Res. Dev., Just Accepted Manuscript • DOI: 10.1021/acs.oprd.9b00435 • Publication Date (Web): 30 Dec 2019 Downloaded from pubs.acs.org on January 3, 2020

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

1	
2	
3	
4	Thermodynamics and Kinetics of Click Reaction between Benzyl
5	
6	Azide and Different Alkynes by Microcalorimetry
/	The for the protocol of the former of the fo
9	Xiaovi Li ^a Bo Jin ^{a,*} Zhicheng Guo Shijin Chu Rufang Peng ^{a,*}
10	macht Er, Boom , Emonong Suc, Shijin Shu, Kutung Pong
11	
12	"State Key Laboratory of Environmental-friendly Energy Materials, Southwest University of Science and
13	Technology Sichuan Mianyang 621010 China
14	reennology, stendar manyang 021010, enna
15	
16	
17	
19	
20	
21	
22	
23	
24	
25	
20	
28	
29	
30	
31	
32	
33	
34 25	
36	
37	
38	
39	
40	
41	
42	
45 ΔΔ	
45	
46	
47	
48	
49	
50	
51 52	
52 53	
54	
55	
56	
57	* Corresponding author.
58	E-mail address: iinbo0428@163.com (B. Jin), rfpeno2006@163.com (R. Peno)
59	
00	

Abstract: The copper(I)-catalyzed 1,3-dipolar cycloaddition of azides and alkynes provides diverse building blocks for chemical synthesis, biochemistry, pharmaceutical industries, and materials science. In order to provide a good theoretical support for industrial amplification reaction, it is significant to study the catalytic properties and the corresponding kinetics of a given reaction. In this article the reaction kinetics and thermodynamics of "Click reaction" between benzyl azide and different alkynes were investigated by microcalorimetry. Benzyl azide and ethyl propiolate were used as model reactions. The effects of a variety of parameters were studied in a calorimeter to establish the kinetics and mechanism of the reaction under isothermal conditions. The activation energies for the reaction of benzyl azide with 4-nitrophenylacetylene, ethyl propiolate, and 3-butyyne-2-one were 22.99 \pm 0.13, 55.81 \pm 0.74, and 56.75 \pm 0.65 kJ mol⁻¹, respectively. The difference of reaction kinetics of different alkynes was explained by the reaction mechanism combined with theoretical calculations, and the reaction is intrinsically kinetically controlled.

Keywords: Azide, Alkyne, Microcalorimetry, Kinetics, Thermodynamics

1. Introduction

Since the groups of Sharpless¹ and Meldal² independently reported the "click chemistry" of copper-catalyzed azide and alkyne cycloaddition (CuAAC) in 2002, it has become an area of interest for scientists. The 1,3-dipolar cycloaddition of azides and alkynes³ is an effective way to form connections between structures that bear various functional groups.⁴ The discovery of copper(1) catalysis of this process² has been widely used in bioconjugation,⁵⁻¹⁰ organic synthesis,¹¹⁻¹⁴ materials and surface science,¹⁵⁻¹⁷ and combinatorial chemistry. In the field of fine chemical industry, in order to prevent accidents in batch and semi-batch reactors, especially in the case of highly exothermic reaction or thermal unstable compounds, the selection of safe operating conditions plays an important role in the chemical production process. In the past few decades, a lot of research has been carried out on this issue, and most of which are based on the knowledge of reaction kinetics and thermodynamics.¹⁸ Unfortunately, due to its expensive, time-consuming and equipment limitations, there are few reports on the reaction kinetics and thermodynamics.¹⁹⁻²⁰

Binauld et al. successfully synthesized oligomers and polymers containing triazole units by the

copper(I)-catalyzed 1,3-dipolar cycloaddition reaction. ¹H NMR was used to monitor the stepgrowth click polymerization, and the activation energy of the reaction was 45 ± 5 kJ mol⁻¹.²¹ Sheng et al. studied the kinetics of Cu(I)-catalyzed polymerization by differential scanning calorimetry (DSC).²² Wu et al. used the real-time infrared analysis technology based on ATR-FTIR principle to monitor the designed ligand-accelerated CuAAC reaction. The experiment also determined that the rate-determining step of the CuAAC reaction was the transition of azide-alkyne 1:1 complex to the preproduct 1,2,3-triazole.²³ However, it is difficult to determine the detailed kinetic model of the reaction because of the influence of the reaction mixture system composition on the activity of the reagents and products. Therefore, it is particularly important to find an optimal method to obtain accurate kinetic parameters of these reactions.

The microcalorimeter (MC) is an experimental device for detecting the change of micro-heat level. Compared with differential scanning calorimeter (DSC), microcalorimeter offer a specific sensitivity that is approximately 1000 higher. For a long time, it has been used to study biological processes²⁴⁻²⁶ and molecular interactions^{27,28} in life sciences. As an essential thermal analysis method, microcalorimetry was used to study the kinetics and thermodynamics of curing reaction.²⁹⁻³² Compared with the traditional method, the advantage of microcalorimetry is that it can determine the thermodynamic and kinetic parameters simultaneously. In this work, we investigated the thermochemical process of the "Click reaction" between benzyl azide with different alkynes, such as ethyl propiolate, 4-nitrophenylacetylene, and 3-butyne-2-one, by using microcalorimetry, and obtained the kinetics and thermodynamics data for the reaction of benzyl azide with different alkynes was explained from the perspective of reaction mechanism and theoretical calculation. Meanwhile, the mechanism function of the title reaction was obtained by the model-fitting method. At 295.15 - 307.15 K, all the models conform to the Jander equation, with n = 1/2 described as 3D diffusion, which indicates that the reaction interface advances at a constant velocity in three dimensions.³³

2. Experimental

2.1. Materials

Benzyl azide (Aladdin, China), ethyl propiolate (Aladdin, China), DIPEA (Aladdin, China), 4-

nitrophenylacetylene (Shanghai Macklin Biochemical, China), 3-butyne-2-one (Shanghai Macklin Biochemical, China), dichloromethane (Xinjie Trade Company, China), acetic acid (Xinjie Trade Company, China), and all of reagents were used as supplied without further purification.

2.2. Measurements

RD496-2000 Calvet microcalorimeter (MC) (Mianyang CAEP Thermal Analysis Instrument Company, China) was used to measure the thermokinetics of the title reaction. At 298.15K, the sensitivity of the instrument is 64.53 μ V mW⁻¹.^{34.36} Before each experiment, the microcalorimeter was calibrated based on the Joule effect. RD496-2000 Calvet microcalorimeter was used to measure the standard molar enthalpy of dissolution of KCl (spectral purity) is 17.237 ± 0.028 kJ mol⁻¹, compared with the literature value of 17.241 ± 0.018 kJ mol⁻¹, ³⁷ the relative error is less than 0.02%, which indicates the reliability of the measuring device.

2.3 Experimental Details

Before the experiment, we designed the glass casing for the reaction. Fig. 1. shows the structural schematic of glass tube. The outer tube has a length of 67 mm and a diameter of 15 mm; the inner tube has a length of 43 mm and a diameter of 13 mm. The bottom of the inner tube is very thin, which makes it very easy to be broken by a platinum pushrod. The heat generated during the process of smashing the inner tube is about 200 mJ, which is eliminated by the differential method.

The reaction system was composed of alkyne and azide with a molar ratio of 1:1. Benzyl azide (0.5 mmol), DIPEA (0.02 mmol, 0.04 equiv), HOAc (0.02 mmol, 0.04 equiv), CuI (1.9 mg, 0.02 equiv) were added to the outer glass tube and were diluted to 2 mL CH₂Cl₂. Alkyne (0.5 mmol) was added to the inner glass bubble and was diluted to 2 mL CH₂Cl₂. In each experiment, the glass tube with the reactants was placed in a calorimeter measuring cell. Another glass tube containing the same volume of CH_2Cl_2 was placed in the reference cell. After the temperature and baseline were stabilized, the inner glass tubes in the measuring cell and the reference cell were simultaneously ruptured and the reaction enthalpy was detected.



Fig. 1. The structural schematic of glass reaction tube.

3 Results and Discussion

3.1 Mechanism

In recent years, people have focused on the research of CuAAC reaction mechanism. Sharplees and his colleagues have proposed a widely accepted three-step catalytic cycle mechanism.¹ As shown in Fig. 2., first, the π -electron complexing of Cu(I) with acetylenic bonds reduces the pKa of the terminal alkyne and is further converted to Cu(I) acetylide (2). Then the Cu(I) acetylide (2) is coordinated to the azide (3) to form a 5-Cu-substituted 1,2,3-triazole (4) which is rearranged to form a Cu-substituted triazole intermediate. Finally, the triazole product (5) is obtained by protonation.

Catalysts are considered to be one of the main factors affecting the efficiency of organic reactions. CuI is the most commonly used catalyst in CuAAC reactions. In this paper, the combination of CuI/DIPEA (*N*,*N*-diisopropylethylamine)/HOAc was considered as a highly efficient catalytic system.³⁸ In the reaction system, the functions of DIPEA and HOAc were assigned, HOAc not only accelerated the conversions of the intermediates, but also buffered the basicity of DIPEA.



Fig. 2. Three-step mechanism of CuAAC reaction.

3.2. Effect of Temperature

The reaction between benzyl azide and ethyl propiolate is chosen as a model system to determine the behavior of azide-alkyne systems. The reaction between benzyl azide and ethyl propiolate is given in Scheme 1, as follows:

$$\bigvee_{N_3} + HC \equiv C \qquad O \qquad CH_3 \qquad CuI, DIPEA \qquad N \qquad N \\ HOAc, CH_2Cl_2 \qquad HC \equiv C \qquad O \qquad CH_3$$

Scheme. 1. The reaction equation of benzyl azide and propiolate.

The reactions were studied at different temperatures under otherwise similar conditions. The isothermal temperatures set as 295.15, 299.15, 303.15, and 307.15 K because the CuAAC reaction can take place at room temperature. Fig. 3(a). shows the corresponding heat flow curves for the reaction of the benzyl azide and ethyl propiolate at four different temperatures. Each curve is a smooth and single exothermic peak. According to the heat flow curve, it can be seen that the increase of the reaction temperature leads to the acceleration of the reaction rate. As the temperature increased, the exothermic peak moved towards the higher peak of heat flow and reached a certain value at the end of the reaction. As shown in Fig. 3(b), the reaction was completed after 17300, 10800, 9300, and 8100 s at 295.15, 299.15, 303.15, and 307.15 K, respectively. Changes in reaction temperature had a greater impact on reaction rates. By integrating the heat flow curves, the total heat can be obtained. The total reaction heat at 295.15, 299.15, 303.15, and 307.15 K were 176959.1, 175776.5, 172980.0, and 167969.7 mJ, respectively.



$$\alpha = \frac{H_t}{H_o} \tag{1}$$

The reaction degree and reaction rate versus time obtained at four different isothermal temperatures are shown in (Figs. 3(c) and3(d)). The conversion was found to increase with temperature. The curves displayed in Fig. 3(d) indicate that the reaction occurs rapidly at the initial stage, this phenomenon was attributed to more azide and alkyne molecules involved in the reaction. Alkynes can be rapidly converted into Cu-intermediates, thus accelerating the formation of triazole products. At the late stage of the reaction, the reactants were consumed, so the reaction rate decreased gradually. There was no significant change in the time required to reach the maximum reaction rate at different temperatures.



Fig. 3. (a) Heat flow curves of the reaction between benzyl azide and ethyl propiolate at different temperatures; (b)The histogram describing the heat and time at different temperatures; (c) Degree of

reaction (α) vs. time (t) of the reaction between benzyl azide and ethyl propiolate at different temperatures; (d) Reaction rate vs. time (t) of the reaction between benzyl azide and ethyl propiolate at different temperatures.

The model-fitting method was used to calculate the rate constants. In the isothermal method, the rate constant k(T) is a constant; thus, k is separated with the reaction model $G(\alpha)$. Hence, the kinetic parameters can be evaluated by using the model-fitting method as follows:

$$G(\alpha) = kt \tag{2}$$

The isothermal kinetics processing software presents 41 kinds of line of $G(\alpha)$ vs. time by leastsquare method. the most proper form of $G(\alpha)$ is selected on the basis of the fitting line with the maximum correlation coefficient and the minimum intercept.³³ The reaction rate constant k is obtained through the slope. The plots of $G(\alpha)$ against t are fitted as shown in Fig. 4(a). At 295.15 -307.15 K, all the models conform to the Jander equation, with n = 1/2 described as 3D diffusion. The mechanism function No.5 is $G(\alpha) = [1-(1-\alpha)^{1/3}]^{1/2}$. The Arrhenius equation (Eq. (3)) can be employed to calculate the activation energy and the pre-exponential factor of the reaction of between benzyl and alkynes. By plotting ln k versus 1/T, the values of activation energy, E_{α} , and preexponential factor, A, can be estimated by calculating the slope of the linear fit and the y-intercept, as shown in Fig. 4(b), which exhibits a fine linear relationship. Thus, the reaction is kinetically controlled. The value of (ΔG^{\neq}) is obtained by Eq. (4) and the values of (ΔH^{\neq}) and (ΔS^{\neq}) are obtained by Eq. (5).³⁹

$$\ln k = \ln A - \frac{E_a}{RT} \tag{3}$$

$$\Delta G^{\neq} = RT \ln \frac{RT}{Nhk} \tag{4}$$

$$\ln\frac{k}{T} = -\frac{\Delta H^{\neq}}{RT} + \frac{\Delta S^{\neq}}{R} + \ln\frac{k_B}{h}$$
(5)

where *R* is the gas constant (8.314 J mol⁻¹ K⁻¹); *T* is the absolute temperature, *h* is the Planck's constant (6.626 × 10⁻³⁴ J s⁻¹), *N* is the Avogadro number (6.024 × 10²³ mol⁻¹), and k_B is the Boltzmann's constant (1.3807 × 10⁻²³ J K⁻¹). The original data of the reaction of benzyl azide and ethyl propiolate with different temperatures are shown in Table S1 and the kinetic parameters are listed in Table 1, and the ΔH^{\ddagger} , ΔS^{\ddagger} , and ΔG^{\ddagger} values for the reaction between benzyl azide and ethyl propiolate in the temperature range of 295.15 - 307.15 K were 54.24 ± 0.82 kJ mol⁻¹, -141.22 ± 1.25J mol⁻¹ K⁻¹, and 96.77 ± 0.73 kJ mol⁻¹, respectively.

2 3 4 5		Table 1	. Values of	$\ln k, A, E, \Delta G^{\neq},$	$\Delta H^{\neq}, \Delta S^{\neq}, \text{ and }$ at different	<i>r</i> for the r temperat	reaction between ures	azide and ethyl p	propiolate	
6 7	<i>T</i> /K	ln k	r	<i>E_a</i> /kJmol ⁻¹	$\ln A$	r	$\Delta G^{\neq}/\text{kJ} \text{ mol}^{-1}$	$\Delta H^{\neq}/kJ \text{ mol}^{-1}$	$\Delta S^{\neq}/J \text{ mol}^{-1} \text{ K}^{-1}$	r
8	295.15	-9.66±0.01	0.996	56.75±0.65	13.48±0.97	0.997	95.96±1.70	54.24±0.82	-141.22±1.25	0.996
9 10	299.15	-9.31±0.01	0.998				96.43±1.62			
11 12	303.15	-9.03±0.02	0.999				97.05±1.70			
13	307.15	-8.75±0.02	0.999				97.64±1.24			
14 15	mean						96.77±0.73			
16										
17										
18										
19		(a)		(b)					
20		(^{1.0}			-8.6			1	
22						-8.8	•	 Testing data 		
23			····			-		—— Fitting curve		



Fig. 4. (a) Plots of $G(\alpha)$ vs. time (t) at different temperatures; (b) Plots of $\ln k$ vs. T^{-1} for the benzyl azide and ethyl propiolate system.

3.3. Effect of Catalyst

To research the influence of catalyst on the reaction rate, the reaction systems with different contents of CuI were studied at 303.15 K. Fig. 5(a) shows the corresponding heat flow curves. The exothermic peak value of the heat flow curve increased while the content of CuI increased. The increased content of CuI caused a decreased time to reach the maximum reaction rate. As seen in Fig. 5(b), the reaction was completed after 9300, 7200, 6600, and 5100 s and the total reaction heat values were 172980, 170204, 175635.6 and 175569.8 mJ, whereas the contents of CuI were 2 mol%, 3 mol%, 4 mol%, and 5 mol%, respectively, which demonstrated that the contents of catalyst do not affect the total heat of the reaction and only the reaction rate. The conversion is plotted against time for different contents of the catalyst under otherwise similar conditions (Figure 5(c)). As the content

 of the catalyst is increased, there is an increase in conversion. In the presence of a large contents of CuI, the formation of the C-Cu bond-containing intermediates can be accelerated. Analogously, the reaction rate gradually slowed down as the reaction progressed. The relationship between ln *k* and the contents of CuI is shown in Fig. 5(d). Higher contents of catalyst can enhance the rate constant. Original data of the reaction of benzyl azide and ethyl propiolate at 303.15 K with different contents of CuI are shown in Table S2, the ln *k* values are -9.04 ± 0.01 , -8.72 ± 0.02 , -8.60 ± 0.01 , and -8.34 ± 0.02 at the contents of CuI were 2 mol%, 3 mol%, 4 mol%, and 5 mol%, respectively.



Fig. 5. (a) Heat flow curves of the reaction between benzyl azide and ethyl propiolate at different contents of CuI; (b) The histogram describing the heat and time at different contents of CuI; (c) Degree of reaction (α) *vs.* time (*t*) of the reaction between benzyl azide and ethyl propiolate at different contents of CuI; (d) The histogram describing the relationship between ln *k* and CuI contents.

3.4. Effect of Concentration of Ethyl propiolate

The reaction rate constant was studied by varying the content of ethyl propiolate at 303.15 K. The effect of reactant concentration was studied at five levels of $-C \equiv C/-N_3$ ratio (0.4, 0.8, 1.0, 1.4, and 1.8). The curves at five different concentrations are shown in Fig. 6 and the original data are displayed in Table S3. From Fig. 6(a), with the increase of ethyl propiolate content, the peak value

of heat flow curve increased. The total reaction heat values were 67899, 138689.6, 172980, 167771.8, and 178485.6 mJ whereas the $-C \equiv C/-N_3$ molar ratios were 0.4, 0.8, 1.0, 1.4, and 1.8, respectively. The heat of reaction increased as the ethyl propiolate content increased at the same temperature, with the exception of the ratio of 1.4, and this finding may be due to the influence of intermediate in the reaction. As exhibited in Fig. 6(b), the degrees of reaction at different proportions are similar. Fig. 7 shown the relationship between ln *k* and the molar ratio of the $-C \equiv C$ and $-N_3$ groups. As listed in Table S3, the ln *k* values are -8.97 ± 0.01 , -8.99 ± 0.02 , -9.04 ± 0.02 , -8.89 ± 0.01 , and -8.79 ± 0.02 at $-C \equiv C/-N_3$ molar ratios of 0.4, 0.8, 1.0, 1.4, and 1.8, respectively. The time to complete the reaction are 7500, 8500, 9300,7900, and 7300s at $-C \equiv C/-N_3$ molar ratios of 0.4, 0.8, 1.0, 1.4, and 1.8, respectively. The results show that ln *k* has an inverse relationship with the reaction time. The reason is that when one of the reactants is excessive, the other reactant will be rapidly consumed and the reaction rate is fast, thus, the reaction time is shortened with the decrease of reactant content.



Fig. 6. (a) Heat flow curves of the reaction between benzyl azide and different contents of ethyl propiolate at 303.15 K; (b) Degree of reaction (α) *vs* time (*t*) of the reaction between benzyl azide and different contents of ethyl propiolate at 303.15 K.



Fig. 7. The histogram describing the relationship between $\ln k$ and the molar ratio of $-C \equiv C$ to $-N_3$.

3.5. Effect of different alkynes

 The stereoelectronic effect of substituents has a significant effect on the rate of CuAAC click reaction. Matyjaszewski studied the effects of electronic and steric effects on the reaction rate. They found that for reactants with electron-withdrawal capacities and less sterically congested, the reaction rate was fastest.⁴⁰ Alkynes with α -carbonyl groups are more reactive than alkynes for the Huisgen reaction. Moreover, the solubility of the substrates is also a key factor for a successful outcome.⁴¹ To study the effect of different groups on the reaction rate, we selected the other two different alkynes to react with benzyl azide and obtained their thermodynamics and kinetics parameters.

Tables S4 and S5 listed the original data of the reactions between benzyl azide and 4nitrophenylacetylene, 3-butyne-2-one at four temperatures. Fig. 8(a) shown the heat flow of the reactions between benzyl azide and different alkynes at 303.15 K, and Fig. 8(b) shown the heat and time of three different reaction systems. At 303.15 K, the reaction process of benzyl azide with 4nitrophenylacetylene is the fastest growing reaction, followed by 3-butyne-2-one and ethyl propiolate with almost similar behavior. The thermokinetic parameters of the reaction between benzyl azide and 4-nitrophenylacetylene, 3-butyne-2-one at four temperatures were derived from the Arrhenius equation, as shown in (Figs. 8(c) and (8d)), respectively. Tables 2 and 3 showed the values of ln *k*, *A*, *E_a*, ΔG^{\ddagger} , ΔH^{\ddagger} , and ΔS^{\ddagger} , and the correlative coefficient *r* values for the reaction between azide and 4-nitrophenylacetylene, 3-butyne-2-one at different temperatures. As shown in Tables 1, 2, and 3, the activation energies of the reaction of benzyl azide with 4-nitrophenylacetylene,

ethyl propionate, and 3-butyne-2-one are 22.99 ± 0.13 , 55.81 ± 0.74 , and 56.75 ± 0.65 kJ mol⁻¹, respectively, which indicate that the order of reaction rate of the three different alkynes with benzyl azide is 4-nitrophenylacetylene > 3-butyne-2-one > ethyl propiolate.

To understand the difference in reaction kinetics between different alkynes, the click reaction mechanism combined with theoretical calculations was used to study the difference in reactivity between benzyl azide and different alkynes. The CuAAC reaction catalytic cycle proposed by Sharpless is widely accepted.¹ Generally, copper-catalyzed azide-alkyne cycloaddition is 7 to 8 orders of magnitude faster than non-catalytic thermal cycloaddition.⁴² Therefore, the step of the copper catalyst acting on the alkyne to form the intermediate (2) is highly critical and directly affects the rate of the azide-alkyne cycloaddition reaction. By reducing the electron density on the sp carbon atom, the activity of alkynyl ligand was increased, and the π -complexation of the δ -alkynyl-CuI species was invoked.⁴³⁻⁴⁶ To verify our results, the compound structure was optimized by using density functional theory with B3LYP method and 6-311G(d,p) basis set. Subsequently, the atomic dipole moment-corrected Hirshfeld charge (ADCH)47 was calculated to study atomic charge distribution. Additionally, the electrostatic potential (ESP) on molecular van der Waals (vdW) surface was implemented via Multiwfn soft ⁴⁸ to predicate the reaction site. Based on the Bader ⁴⁹ point of view, vdW surface denotes the isosurface of electron density ρ =0.001 e/bohr³. As presented in Figs. 9 and 10 the charge density of 4-nitrophenylacetylene is -0.24, and the electrostatic potential is -0.40, indicating that a more negative charge facilitates interaction with the copper ion. The conjugate electron effect of aromatic ring structure enhances the reaction activity of the terminal alkynes and facilitates the formation of the corresponding intermediates with the copper ion, which is beneficial to the reaction. Therefore, the activation energy of *p*-nitrophenylene acetylene is the lowest and its reaction rate is the fastest. Furthermore, ethyl propiolate and 3-butyn-2-one have a similar behavior. From the above, the calculated results are in good agreement with our experimental results.



Fig. 8. (a) Heat flow curves of the reaction between benzyl azide and different alkynes at 303.15 K; (b) The histogram describing the heat and time of the reaction benzyl azide with different alkynes at 303.15 K; (c) Plot of ln *k vs. T*¹ for the benzyl azide and 4-nitrophenylacetylene system at different temperatures; (d) Plot of ln *k vs. T*¹ for the benzyl azide and 3-butyne-2-one system at different temperatures.

Table 2. Values of ln k, A, E, ΔG^{\neq} , ΔH^{\neq} , ΔS^{\neq} , and r for the reaction between azide and 4-nitrophenylacetylene at different temperatures

<i>T</i> /K	ln k	r	E_a /kJ mol ⁻¹	$\ln A$	r	$\Delta G^{\neq}/\text{kJ mol}^{-1}$	$\Delta H^{\neq}/\text{kJ mol}^{-1}$	$\Delta S^{\neq}/J \text{ mol}^{-1} \mathrm{K}^{-1}$	r
295.15	-8.43±0.01	0.999	22.99±0.13	0.93±0.28	0.974	92.95±1.95	20.48±0.79	-245.60±1.63	0.968
299.15	-8.34±0.01	0.997				94.02±2.40			
303.15	-8.17±0.01	0.994				94.88±1.27			
307.15	-8.08 ± 0.01	0.985				95.93±2.05			
mean						94.45±1.27			

Table 3. Values of $\ln k$, A, E, ΔG^{\neq} , ΔH^{\neq} , ΔS^{\neq} , and r for the reaction between azide and 3-butyne-2-one at different temperatures

T/K	ln k	r	E_a /kJ mol ⁻¹	$\ln A$	r	$\Delta G^{\neq}/\text{kJ} \text{ mol}^{-1}$	$\Delta H^{\neq}/\text{kJ} \text{ mol}^{-1}$	$\Delta S^{\neq}/J \text{ mol}^{-1} \text{ K}^{-1}$	r
 295.15	-9.42±0.01	0.994	55.81±0.74	13.34±0.21	0.994	95.38±1.98	53.31±2.03	-142.36±1.26	0.993
299.15	-9.04 ± 0.02	0.988				95.81±1.86			
303.15	-8.80 ± 0.01	0.995				96.47±1.84			
307.15	-8.52 ± 0.02	0.993				97.06±1.57			
mean						96.18±0.74			



Fig. 9. Charge distribution of compound (a)3-butyne-2-one; (b)ethyl propiolate; (c)4-

nitrophenylacetylene.



Fig. 10. Electrostatic potential (ESP) on molecular vdW surface of compound (a) 3-butyne-2-one; (b) ethyl propiolate; (c) 4-nitrophenylacetylene; Surface local minima and maxima of ESP are represented as cyan and orange spheres, respectively

4. Conclusions

The protocol based on microcalorimetry which is described in this paper offers a kinetic and thermodynamic model in CuAAC reactions. Microcalorimetry can accurately measure the heat change in the reaction process. This method facilitates the rapid screening of catalytic process steps, as well as the study of the thermodynamics and kinetics of organic reactions. In this paper, the thermodynamic properties of the reaction were investigated by changing the reaction conditions. Temperature and catalyst content have great influence on the reaction rate. The experimental results also show that CuI/DIPEA/HOAc system is an efficient catalytic system, which has the advantages of short reaction time and mild reaction conditions.

Acknowledgments

We are grateful for financial support from the Science Challenge Project (project no. TZ2018004), Natural Science Foundation of China (21875192), Outstanding Youth Science and Technology Talents Program of Sichuan (No. 19JCQN0085), National Defense Technology Foundation Project (project no. JSJL2016404B002), Key Projects of the Pre-research Fund of the General Armament Department (No. 6140720020101) and the Institute of Chemical Materials, China Academy of Engineering Physics (project no. 18zh0043).

Supporting Information

Original data of the reaction of benzyl azide and different alkynes under different conditions (PDF)

References

 Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective Ligation of Azides and Terminal Alkynes. Angew. Chem. Int. Ed. 2002, 41, 2596-2599.

 [2] Tornoe, C. W.; Christensen, C.; Meldal, M. Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides. J. Org. Chem. 2002, 67, 3057-3064.

[3] Huisgen, R. 1,3-Dipolar Cycloaddition Chemistry; Wiley: New York, America, 1984; pp 273-278.

[4] Lewis, W. G.; Green, L. G.; Grynszpan, F.; Radic, Z.; Carlier, P. R.; Taylor, P.; Finn, M. G.; Sharpless, K. B. Click Chemistry in Situ: Acetylcholinesterase as a Reaction Vessel for the Selective Assembly of a Femtomolar Inhibitor from an Array of Building Blocks. Angew. Chem. Int. Ed. 2002, 41, 1053-1055.
[5] Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. K.; Finn, M. G. Bioconjugation by Copper(I)-Catalyzed Azide-Alkyne [3 + 2] Cycloaddition. J. Am. Chem. Soc. 2003, 125, 3192-3193.

[6] Speers, A. E.; Cravatt, B. F. Profiling Enzyme Activities in vivo using Click Chemistry Methods.Chem. Biol. 2004, 11, 535-546.

[7] Speers, A. E.; Cravatt, B. F. Activity-Based Protein Profiling in vivo using a Copper(I)-Catalyzed Azide-Alkyne [3 + 2] Cycloaddition. J. Am. Chem. Soc. 2003, 125, 4686-4687.

[8] Lee, L. V.; Mitchell, M. L.; Huang, S. J.; Fokin, V. V.; Sharpless, K. K.; Wong, C. H. A Potent and Highly Selective Inhibitor of Human α-1,3-Fucosyltransferase via Click Chemistry. J. Am. Chem. Soc. 2003, 125, 9588-9589.

[9] Deiters, A.; Cropp, T. A.; Mukherji, M.; Chin, J. W.; Anderson, J. C.; Schultz, P. G. Adding Amino Acids with Novel Reactivity to the Genetic Code of Saccharomyces Cerevisiae. J. Am. Chem. Soc. 2003, 125, 11782-11783.

[10] Seo, T. S.; Li, Z.; Ruparel, H.; Ju, J. Y. Click Chemistry to Construct Fluorescent Oligonucleotides for DNA Sequencing. J. Org. Chem. 2003, 68, 609-612.

[11] Fazio, F.; Bryan, M. C.; Blixt, O.; Paulson, J. C.; Wong, C. H. Synthesis of Sugar Arrays in Microtiter Plate. J. Am. Chem. Soc. 2002, 124, 14397-14402.

[12] Bodine, K. D.; Gin, D. Y.; Gin, M. S. Synthesis of Readily Modifiable Cyclodextrin Analogues via Cyclodimerization of an Alkynyl-Azido Trisaccharide. J. Am. Chem. Soc. 2004, 126, 1638-1639.

[13] Zhou, Z.; Fahrni, C. J. A Fluorogenic Probe for the Copper(I)-Catalyzed Azide-Alkyne Ligation Reaction: Modulation of the Fluorescence Emission via $3(n,\pi^*)-1(\pi,\pi^*)$ Inversion. J. Am. Chem. Soc. 2004, 126, 8862-8863.

[14] Jin, T.; Kamijo, S.; Yamamoto, Y. Copper-Catalyzed Synthesis of N-Unsubstituted 1,2,3-Triazoles from Nonactivated Terminal Alkynes. Eur. J. Org. Chem. 2004, 35, 3789-3791.

[15] Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, G. J.; Scheel, A.; Voit, B.; Pyun, J.; Frechet, J. M.; Sharpless, K. K.; Fokin, V. V. Efficiency and Fidelity in a Click-Chemistry Route to Triazole Dendrimers by the Copper(I)-Catalyzed Ligation of Azides and Alkynes. Angew. Chem. 2004, 43, 3928-3932.

2	
3 4	[16] Li, C.; Finn, M. G. Click Chemistry in Materials Synthesis. II. Acid-Swellable Crosslinked Polymers
5 6	Made by Copper-Catalyzed Azide-Alkyne Cycloaddition. J. Polym. Sci. Part A. 2006, 44, 5513-5518.
7	[17] Collman, J. P.; Devaraj, N. K.; Chidsey, C. E. "Clicking" Functionality onto Electrode Surfaces.
9	Langmuir. 2004, 20, 1051-1053.
10	[18] Westertern K R · Molga E J Safety and Runaway Prevention in Batch and Semibatch Reactors—
12 13	
14	A Review. J. Chem. Eng. Res. Des. 2006, 84, 543-552.
16	[19] Balland, L.; Mouhab, N.; Cosmao, J. M.; Estel, L. Kinetic Parameter Estimation of Solvent-Free
17 18	Reactions: Application to Esterification of Acetic Anhydride by Methanol. Chem. Eng. Process. 2002,
19 20	41, 395-402.
21	[20] Steensma, M.; Westerterp, K. R. Thermally Safe Operation of a Cooled Semi-Batch Reactor. Slow
22	Liquid-Liquid Reactions. Chem. Eng. Technol. 1991, 14, 367-375.
24 25	[21] Binauld, S.; Boisson, F.; Hamaide, T.; Drockenmuller, D.; Fleury, E. Kinetic Study of Copper(I)-
26 27	Catalyzed Click Chemistry Step-Growth Polymerization. J. Polym. Sci. Pol. Chem. 2010, 46, 5506-5517.
28 29	[22] Sheng, X.; Mauldin, T. C.; Kessler, M. R. Kinetics of Bulk Azide-Alkvne "Click" Polymerization.
30 31	I Polym Sci Pol Chem 2010 48 4093-4102
32	[22] Sum S. T., Wy, D.V. Machanistic Insights into Cu(I). Catalyzad Asida Allerma "Cliple" Cycloadditian
34	[25] Sun, S. I., wu, F. I. Mechanistic hisights into Cu(1)-Catalyzed Azide-Aikyne Chek Cycloaddition
35 36	Monitored by Real Time Infrared Spectroscopy. J. Phys. Chem. A. 2010, 114, 8331-8333.
37	[24] Nyström, T.; Larsson, C.; Gustafsson, L. Bacterial Defense Against Aging: Role of the Escherichia
39	Coli Arca Regulator in Gene Expression, Readjusted Energy Flux and Survival During Stasis. Embo. J.
40 41	1996, 15, 3219-3228.
42 43	[25] Bäckman, P.; Kimura, T.; Schön, A.; Wadsö, I. Effects of Ph-Variations on the Kinetics of Growth
44 45	and Energy Metabolism in Cultured T-Lymphoma Cells: A Microcalorimetric Study. J. Cell. Physiol.
46	1992, 150, 99-103,
47 48	
49 50	[26] Wadso, I. Isothermal Microcalorimetry for the Characterization of Interactions between Drugs and
51	Biological Materials. Thermochim. Acta. 1995,267, 45-59.
52 53	[27] Lin, F. Y.; Chen, W. Y. Microcalorimetric Studies on the Interaction Mechanism Between Proteins
54 55	and Hydrophobic Solid Surfaces in Hydrophobic Interaction Chromatography: Effects of Salt,
56	Hydrophobicity of the Sorbent, and Structure of the Protein. Anal. Chem. 2001, 73, 3875-3883.
58	[28] Jansson, M.; Hallén, D.; Koho, H.; Andersson, G.; Berghard, L.; Heidrich, J.; Nyberg, E.; Uhlén,
59 60	

M.; Kördel, J.; Nilsson, B. Characterization of Ligand Binding of a Soluble Human Insulin-Like Growth Factor I Receptor Variant Suggests a Ligand-Induced Conformational Change. J. Biol. Chem. 1997, 272, 8189-8197.

 [29] Li, N.; Zhao, F. Q.; Luo, Y.; Mo, H. C.; Gao, H. X.; Xiao, L. B.; Yao, E. G.; Hu, R.Z. Study on Curing Reaction Thermokinetics of Azide Binder/Bispropargyl Succinate by Microcalorimetry. Propell. Explos. Pyrot. 2015, 40, 808-813.

[30] Xiao, Y. Y.; Jin, B.; Peng, R. F.; Zhang, Q. C.; Liu, Q. Q.; Guo, P. L.; Chu, S. J. Kinetic and Thermodynamic Analysis of the Hydroxyl-Terminated Polybutadiene Binder System by Using Microcalorimetry. Thermochim. Acta. 2018, 659, 13-18.

[31] Tao, J. J.; Jin, B.; Peng, R. F.; Chu, S. J. Isothermal Curing of the Glycidyl Azide Polymer Binder System by Microcalorimetry. Polym. Test. 2018, 71, 231-237.

[32] Chen, J. J.; Jin, B.; Luo, G.; Liu, H. H.; Zhang, Q. C.; Huang, Q.; Peng, R. F. Thermodynamics and Kinetics of Polyglycidyl Nitrate-Based Urethane Network Formation by Microcalorimetry. J. Chem. Thermodyn. 2019, 132, 397-404.

[33] Hu, R. Z.; Gao, S. L.; Zhao, F. Q.; Shi, Q. Z.; Zhang, T. L.; Zhang, J. J. Thermal Analysis Kinetics; second ed., Science Press: Beijing, China, 2008; pp 151-155.

[34] Li, N.; Zhao, F. Q.; Gao, H. X.; Hu, R. Z.; Xiao, L. B.; Yao, E. G.; Huang, X. P.; Chang, P. Thermokinetics of the Formation Reactions of Metal (Li, Na, Pb, Cu) Salts of 3-Nitro-1,2,4-Triazol-5-One, Acta. Phys-Chim. Sin. 2013, 29, 112-113.

[35] Xiao, L. B.; Xing, X. L.; Zhao, F. Q.; Xue, L.; Xu, K. Z.; Yi, J. H.; Hu, R. Z. Dissolution Properties of 2-(Dinitromethylene)-5-Methyl-1,3-Diazacyclo-Pentane in Dimethyl Sulfoxide and N-Methyl Pyrrolidone. Chem. Res. Chinese. U. 2012, 28, 743-746.

[36] Li, N.; Zhao, F. Q.; Luo, Y.; Hao, H. X.; Gao, H. X.; Yao, E. G.; Xiao, L. B.; Hu, R. Z.; Yi, J. H. Study on Thermodynamics and Kinetics for the Reaction of Aluminum Hydride and Water by Microcalorimetry. J. Therm. Anal. Calorim. 2015, 120, 1847-1851.

[37] Kilday, M. V. The Enthalpy of Solution of Srm-1655 (KCl) in H₂O. J. Res. Nat. Bur. Stand. 1980,
 85, 467-481.

[38] Shao, C.W.; Wang, X.Y.; Zhang, Q.; Luo, S.; Zhao, J. C.; Hu, Y. F. Acid-Base Jointly Promoted Copper(I)-Catalyzed Azide-Alkyne Cycloaddition. J. Org. Chem. 2011, 76, 6832-6836.

1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
21	
22	
23	
24	
25	
26	
27	
28	
29	
30	
31	
32	
33	
34	
25	
22	
20	
3/	
38	
39	
40	
41	
42	
43	
44	
45	
46	
<u>⊿</u> 7	
+/ ∕0	
40	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
50	
23	
nυ	

[39] Li, N.; Zhao, F. Q.; Luo, Y.; Gao, H. X.; Xiao, L. B.; Hu, R. Z.; Ju, R. H. Dissolution Property of N-Guanylurea Dinitramide (GUDN) in Dimethyl Sulfoxide and N-Methyl Pyrrolidone. J. Therm. Anal. Calorim. 2014, 115, 869-873.

[40] Golas, P. L.; Matyjaszewski, K. Marring Click Chemistry with Polymerization: Expanding the Scope of Polymeric Materials. Chem. Soc. Rev. 2010, 39, 1338-1354.

[41] Molander, G. A.; Ham, J. Synthesis of Functionalized Organotrifluoroborates via the 1,3-Dipolar Cycloaddition of Azides. Org. Lett. 2006, 8, 2767-2770.

[42] Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. Copper(I)-Catalyzed Synthesis of Azoles. DFT Study Predicts Unprecedented Reactivity and Intermediates. J. Am. Chem. Soc. 2005, 127, 210-216.

[43] Rodionov, V. O.; Presolski, S. I.; Díaz, D. D.; Fokin, V. V.; Finn, M. G. Ligand-Accelerated Cu-Catalyzed Azide-Alkyne Cycloaddition: A Mechanistic Report. J. Am. Chem Soc. 2007, 129, 12705-12712.

[44] Hein, J. E.; Fokin, V. V. Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC) and Beyond: New Reactivity of Copper(I) Acetylides. Chem. Soc. Rev. 2010, 39, 1302-1303.

[45] Ahlquist, M.; Fokin, V. V. Enhanced Reactivity of Dinuclear Copper(I) Acetylides in Dipolar Cycloadditions. Organometallics. 2007, 26, 4389-4391.

[46] Liang, L.; Astruc, D. The Copper(I)-Catalyzed Alkyne-Azide Cycloaddition (CuAAC) "Click" Reaction and Its Applications. An overview. Coordin. Chem. Rev. 2011, 255, 2933-2945.

[47] Lu, T.; Chen, F. W. Atomic Dipole Moment Corrected Hirshfeld Population Method. J. Theor.Comput. Chem. 2012, 11, 163-183.

[48] Lu, T.; Chen, F. W. Multiwfn: A Multifunctional Wavefunction Analyzer. J. Comput. Chem, 2012, 33, 580-592.

[49] Bader, R. F. W.; Carroll, M. T.; Cheeseman, J. R.; Chang, C. Properties of Atoms in Molecules: Atomic Volumes. J. Am. Chem. Soc. 1987, 109, 7968-7979.



Table of Contents graphic

295x155mm (150 x 150 DPI)