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Mechanism and Kinetics of the Synthesis of 1,7-Dibromoheptane

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Mechanism and the kinetic model for the synthesis of 1,7-dibromoheptane was studied. During the synthesis process of 1,7-dibromoheptane (D) from 1,7-heptanediol (A) and hydrobromic acid (B) by using acid as the reaction catalyst, the product distributions were measured. It was found that the concentration variations of components with reaction time followed the regularity of consecutive reaction. The first step is the formation of 7-bromo-1-heptanol (C) from A and B was a slow step. The second step, formation of 1,7-dibromoheptane from C and B was a fast step. Based on the S_N2 reaction mechanisms, a kinetic model of the reaction was established. The reaction rate constants (k) and activation energy (E_a) were calculated in various reaction conditions. The kinetic model was tested and verified by the experiments. At the same time, the curve between activation energy (E_a) *versus* mass fraction of sulphuric acid (m) gave the straight line in the reaction system. Because acid strength (H) can be expressed by mass fraction of sulphuric acid, so the reaction activation energy could be changed by adjusting acid strength (H) of catalyst.

Key Words: 1,7-Dibromoheptane, Consecutive reaction, Reaction mechanism, Kinetics, Acid strength.

INTRODUCTION

1,7-Dibromoheptane is an important pharmaceutical intermediate, commonly used in drugs, chiral macrocyclic ligands, long-chain fatty alcohol and the synthesis of cationic surfactant and is widely used in the fields of pharmacy, bionic chemical, petroleum, food, cosmetics[1]. 1,7-Dibromoheptane is not only a extremely important intermediates, but also a product developed urgently by organic intermediate enterprises. At present, the synthesis of the 1,7-dibromoheptane is not reported earlier and no domestic manufacturers of 1,7-dibromoheptane in China. In this paper, the mechanism and the kinetic model for the synthesis of 1,7-dibromoheptane is studied.

It is generally believed that the bromination of the aliphatic primary alcohols is based on the classical S_N2 mechanism. Since the 1,ω-diol is a primary alcohol, its reaction mechanism is as follows:

The first step:

$$HO\text{-}(CH_2)_n\text{ - }OH + H^+ \rightleftharpoons O^+H_2\text{-}(CH_2)_n\text{-}OH \quad (1)$$

$$O^+H_2-(CH_2)_n-OH+Br^- \xrightarrow{k_1} Br-(CH_2)_n-OH \quad (2)$$

The second step:

$$Br\text{-}(CH_2)_n\text{-}OH + H^+ \rightleftharpoons Br\text{-}(CH_2)_n\text{-}O^+H_2 \quad (3)$$

$$Br-(CH_2)_n-O^+H_2+Br^- \xrightarrow{k_2} Br-(CH_2)_n-Br \quad (4)$$

The hydroxyl is a difficult leaving group, firstly, an alcohol hydroxyl group needs be protonated by strong acid, it is rapidly converted into an equilibrium mixture and can be used as a good leaving group and then the nucleophilic reagent, bromide anion, reacts to form intermediate according to S_N2 reaction mechanism. Secondly, the intermediate continued to be protonated and then be brominated to produce final products. They can be represented simply as follows:

$$A+B \xrightarrow{k_1} C \quad (5)$$

$$C+B \xrightarrow{k_2} D \quad (6)$$

Supposed that the both steps are carried out based on S_N2 mechanism, then the rate equation is proposed as follows:

$$\text{Loss rate of A: } r_A=-\frac{dc_A}{dt}=k_1c_Ac_B \quad (7)$$

$$\text{Formation rate of C: } r_C=\frac{dc_B}{dt}=k_1c_Ac_B-k_2c_Cc_B \quad (8)$$

$$\text{Formation rate of D: } r_D=\frac{dc_D}{dt}=k_2c_Cc_B \quad (9)$$

Where k_1 represents the reaction rate constant of the first step; k_2 represents the reaction rate constant of the second step; c_A, c_B, c_C represents the concentration of 1,7-heptandiol, hydrobromic acid and intermediate, respectively, mol L^{-1}.

In order to verify the mechanism and calculate the kinetic data, the changes of content of components A, C and D with reaction time are measured at different experimental conditions.

EXPERIMENTAL

Hydrobromic acid (40 %, Tianjin Chemical Reagent Co., Ltd.). Other reagents including 1,7-heptandiol, sulphuric acid, *etc.* were of AR grade. 1,7-Dibromoheptane and 7-bromo-1-heptanol were purchased from the Sigma-Aldrich Co.

Experimental procedures: A mixture of 1.65 g of 1,7-heptandiol (12.5 mmol) and 5.5 mL hydrobromic acid was stirred in a 50 mL flask equipped with a magnetic stirrer, a oil bath, a dropping funnel and a 14-in glass helices-packed column having a variable reflux ratio still-head. The pot temperature was cooled by ice-water mixture and sulphuric acid was added slowly through the dropping funnel. Heat was applied to the reaction flask and total reflux continued until the heat temperature became constant. During the reaction process, samples were collected after every 0.5 h, the organic phase was separated, the aqueous phase was extracted using ethyl acetate and then organic phases were combined together. The combined organic phase was washed, neutralized and dried, ethyl acetate was remove using a rotary evaporator under vacuum and then the obtained product was weighed and analyzed with gas chromatography.

Analytical methods: Products were analyzed by using GC 9800-type gas chromatograph and the mass percent concentration of A, C and D were determined with area normalization method. The changes of content of components A, C and D with reaction time were measured under different experimental conditions. (Chromatographic conditions: the temperature of detector and vaporization chamber was 270 ºC, respectively; carrier gas was nitrogen; the initial column temperature was 170 ºC and maintained for 4 min, temperature programed was 170-250 ºC at a rate of 20 ºC/min; the injection volume was 0.5 μL; the split ratio was 50:1).

RESULTS AND DISCUSSION

Exclusion of external diffusion and the volume changes: As the 1,7-heptandiol could be dissolved in hydrobromic acid to form a homogeneous reaction, while the synthetic product could not be dissolved in water phase, thus the volume change had little impact on the reaction. External diffusion effects could be eliminated by adjusting the stirring rate. It could be found by experiment that the effect of external diffusion could be eliminated when the stirring rate was more than 200 rotation min^{-1}.

Relationship of the content of components with reaction time: The relationship of the content of component with reaction time was measured under the different experimental condition. The results were shown in Fig. 1. It revealed that the reaction was a typical consecutive reaction in the condition of hydrobromic acid as brominating agent and sulphuric acid as catalyst and the reaction rate constant k_1 of the first step was far smaller than the reaction rate constant k_2 of the second step[2], *i.e.*, the bromination reaction of the first step was the control step.

Establishment of mathematical model: As the first step reaction is a slow one, the whole process is controlled by the first step. It can be considered that after A forms C, C immediately generates D. The rate equation can be expressed as follows:

$$r_D = r_A = -\frac{dc_A}{dt} = k_1 c_A c_B = k c_A c_B \tag{10}$$

Supposed that Δ is the loss concentration of A, $\Delta = c_{A,0} - c_A$; then the loss of hydrobromic acid is 2Δ; $c_B = c_{B,0} - 2c_{A,0} + 2c_A$, let $F = c_{B,0} - 2c_{A,0}$, we insert the parametric formula F into the eqn. 10 to get the rate equation after integral calculus,

$$\ln\frac{F + 2c_A}{2c_A} + \ln\frac{2c_{A,0}}{F + c_{A,0}} = Fkt \tag{11}$$

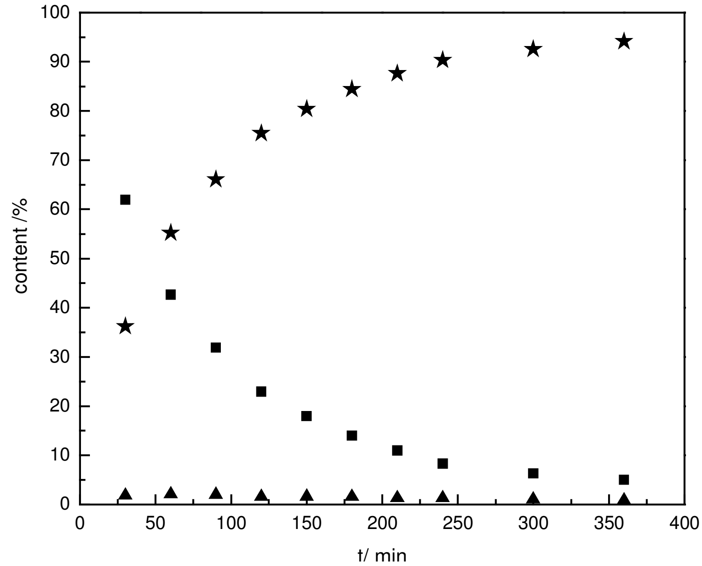

Fig. 1. Variation of component distribution with reaction time. ★: 1,7-dibromoheptane, ■:1,7-heptanediol, ▲: 7-bromo-1-heptanol

where $c_{A,0}$/mol L^{-1} and $c_{B,0}$/mol L^{-1} represents the initial concentration of 1,7-heptanediol and hydrobromic acid, respectively; k/L mol^{-1} min^{-1} is the apparent rate constant; T/K is temperature of reaction; t/min represents reaction time.

Experimental data and the discussion of fitting results: Based on the relation of the concentrations of 1,7-heptanediol with the reaction time, the rate constant k under the different reaction conditions could be calculated from the least square method. The objective function that was used to determine the parameters k in eqn. 11 by optimization was $F = \min \sum_{i=1}^{N} (c_A - c_{A,i})^2$. The experimental data were shown in Tables 1 and 2. The experimental value and the fitting results were shown in Figs. 2 and 3.

TABLE-1
CONCENTRATION OF 1,7-HEPTANEDIOL (mol L^{-1}) IN VARIOUS REACTION TIME AND TEMPERATURE

t (K)	30 min	60 min	90 min	120 min	150 min	180 min	210 min	240 min
353.15	2.033	1.942	1.872	1.805	1.740	1.670	1.610	1.560
363.15	1.925	1.747	1.590	1.447	1.320	1.208	1.110	1.022
373.15	1.737	1.420	1.175	0.993	0.838	0.717	0.613	0.530
383.15	1.387	0.953	0.683	0.500	0.373	0.283	0.217	0.167
388.15	1.140	0.667	0.427	0.280	0.187	0.128	0.087	0.060

Volume of sulfuric acid is 1 mL at different reaction temperature. The molar ratio of diol/HBr is 3:1.

TABLE-2
CONCENTRATION OF 1,7-HEPTANEDIOL (mol L^{-1}) IN VARIOUS REACTION TIME AND VOLUME OF SULFURIC ACID

t (mL)	30 min	60 min	90 min	120 min	150 min	180 min	210 min	240 min
0.4	1.722	1.400	1.162	0.968	0.830	0.707	0.618	0.530
0.6	1.602	1.220	0.960	0.770	0.623	0.508	0.422	0.352
0.8	1.393	0.963	0.692	0.510	0.383	0.293	0.225	0.173
1.0	1.137	0.667	0.427	0.280	0.187	0.127	0.087	0.060
1.2	0.930	0.480	0.267	0.155	0.092	0.055	0.330	0.020

Reaction temperature is 388.15 K; the molar ratio of diol/HBr is 3:1.

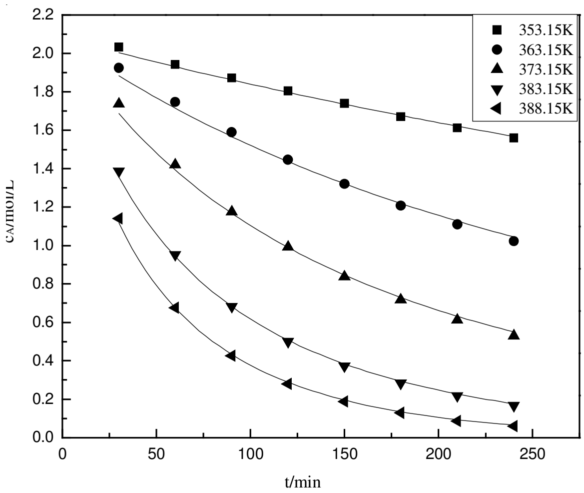

Fig. 2. Experimental data and regression curves of the rate equation at the different reaction temperature

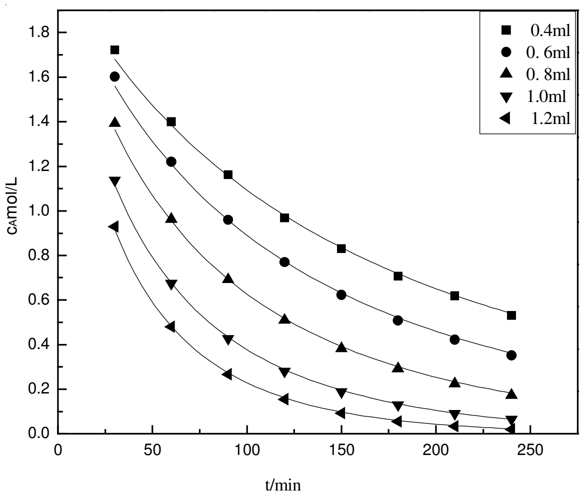

Fig. 3. Experimental data and regression curves of the rate equation in various volume of sulfuric acid

The rate constants k and correlation coefficient were shown in Tables 3 and 4. It showed that the established mathematical model with the S_N2 mechanism had good agreement with the experimental data. At the same time, in the reaction of charge reduction, polar solvents could hinder the reaction while non-polar solvents could accelerate the reaction according to S_N2 mechanism[3]. This reaction was a reaction of charge reduction (protonated alcohol and bromide ions generated neutral molecules). As the synthetic 1,7-dibromoheptane had small polarity and 7-bromo-1-heptanol could be reacted in a micro-environment of small polarity, while 1,7-heptanediol reacted in water of large polarity, thus, k_2 was greater than k_1, which was also consistent with the experimental results.

TABLE-3
RATE CONSTANT AND CORRELATION COEFFICIENT
AT VARIOUS TEMPERATURE

T (K)	k × 10^3 (L mol^{-1} min^{-1})	R^2
353.15	0.19	0.992
363.15	0.43	0.993
373.15	0.93	0.996
383.15	1.99	0.998
388.15	3.03	0.999

TABLE-4
RATE CONSTANT AND CORRELATION COEFFICIENT
IN VARIOUS VOLUME OF SULFURIC ACID

V (mL)	m	k × 10^3 (L mol^{-1} min^{-1})	R^2
0.4	0.096	0. 94	0.998
0.6	0.137	1.30	0.998
0.8	0.175	1.96	0.997
1.0	0.209	3.03	0.999
1.2	0.241	4.17	0.999

From the above-mentioned results, it could be found that the polarity change of the solvent and brominating agent could relatively change the value of k_1 and k_2, thus the different products could be obtained by changing the polarity of the solvent and brominating agent according to different reaction conditions.

Determination of apparent activation energy of reaction: When the dosage of sulphuric acid was 1 mL, the calculated apparent rate constant k values and correlation coefficient at various temperatures was listed in Table-3. The temperature dependence of the chemical reactions could be given in the Arrhenius equation:

$$\ln k = \frac{-E_a}{RT} + \ln A \qquad (12)$$

where k is rate constant; A is a pre-exponential factor; E_a represents activation energy; R is gas constant; T represents temperature.

The curve of ln k - 1/T was drawn according to the eqn. 12 and shown in Fig. 4. According to eqn. 12, the slope of the curve between ln k *versus* 1/T should give a straight line whose slope equals to -E_a/R. The apparent activation energies and pre-exponential factor derived from these curves were found as, $E_a = 10771.1 \times 8.3145 = 89556$ J/mol = 89.56 KJ/mol; $A = e^{21.91} = 3.28 \times 10^9$. This was in good agreement with the literature value of activative energy for the bromination reaction of medium-chain fatty alcohols[4].

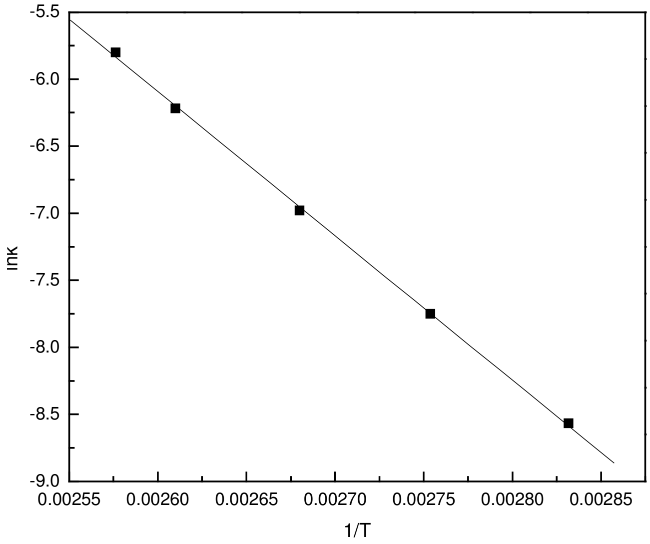

Fig. 4. Relationship between the rate constant ln k and temperature T

Relation of mass fraction 'm' of sulphuric acid (acid strength H) with the activation energy: It was found in the experiment that the dosage of acid had a great effect on the rate of the reaction. Therefore the changes of raw materials with reaction time were determined under the same experimental condition as ever but changing the dosage of acid, the experimental results were shown in Fig. 3 and Tables 2 and 4. The experimental results were also in good agreement with the proposed rate equation. It revealed from the result in Table-5 and Fig. 5 that the mass fraction 'm' of sulphuric acid had a good linear relationship with the activative energy E_a (correlation coefficient R = 0.996). According to the theories of catalysis[5], there was correspondence between the mass fraction 'm' of sulphuric acid and the acid strength of H. So it was reasonable to use the mass fraction 'm' of sulphuric acid in the aqueous phase to represent the acid strength H, then substituted the calculated rate constants into the Arrhenius equation, the activation energy under different acid strength could be calculated. The activation energy of reaction could be lowered with the increase of the acid strength, which made the reaction could be carried out smoothly under mild conditions. Meanwhile replacing the traditional liquid catalysts with solid acid catalysts would made the process environmentally benign[6,7]. In light of this, the present study could have an important environmental impact on the synthesis of 1,7-dibromoheptane.

TABLE-5
MASS FRACTION OF SULFURIC ACID (ACID STRENGTH) H AND E_a

V (mL)	m	$k \times 10^3$ (L mol^{-1} min^{-1})	R^2
0.4	0.096	0.94	93.20
0.6	0.137	1.30	92.16
0.8	0.175	1.96	90.83
1.0	0.209	3.03	89.43
1.2	0.241	4.17	88.39

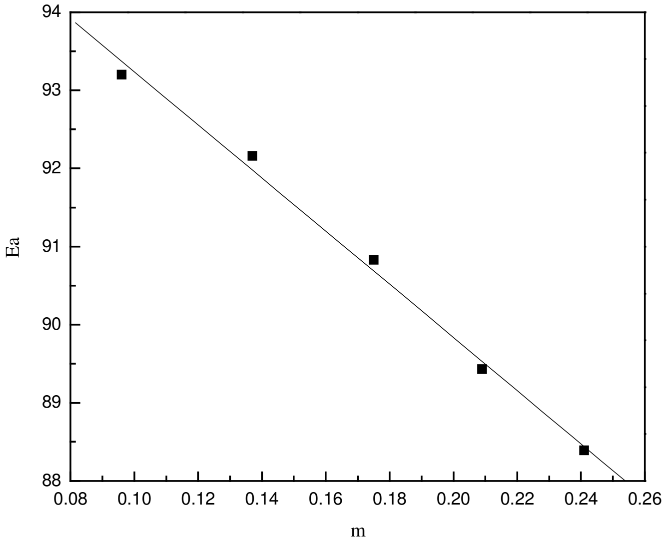

Fig. 5. Relationship between the mass fraction of sulfuric acid and activation energy (E_a)

Based on the calculations with the least squares method above-mentioned, the linear equation related to the activation energy E_a and the mass fraction 'm' of sulphuric acid was obtained:

$$E_a = 96.64 - 34.01m \tag{13}$$

Apparent kinetic equation: Put the Arrhenius equation and the correlation equation about the mass fraction m of sulphuric acid (acid strength) and the activative energy into the rate eqn. 11, then the apparent kinetic equation was obtained as follows:

$$c_A = \frac{F/2}{\exp\left(FA\exp\left(\frac{34.01m - 96.64}{8.3145T}\right)t - \ln\left(\frac{2c_{A,0}}{F + 2c_{A,0}}\right)\right) - 1} \tag{14}$$

Relative deviations (RD) were calculated according to:

$$RD = \frac{c_{A\,exp} - c_{A\,cal}}{c_{A\,cal}} \tag{15}$$

where $c_{A\,exp}$ represents experimental data; $c_{A\,cal}$ represents calculated value.

From Figs. 2 and 3, it was found that the rate equation was consistent with the experimental data. The rate equation was checked with a group of minimum data (correlation coefficient is the worst) of the correlation coefficient R in this experiment. And the results were shown in Table-6, from which it could be known that the experimental data had much higher precision and less errors compared with the calculated ones. The calculated results agreed well with the experimental data. It indicated that the proposed mechanism and the established model for the calculation of this system was appropriate.

TABLE-6
COMPARISON BETWEEN THE EXPERIMENTAL
DATA AND CALCULATED VALUES

t (min)	30	60	90	120	150	180	210	240
$c_{A\,exp}$ (mol L^{-1})	2.073	1.987	1.900	1.827	1.743	1.677	1.593	1.543
$c_{A\,cal}$ (mol L^{-1})	1.991	1.906	1.827	1.753	1.683	1.617	1.555	1.496
100 RD	3.95	4.07	3.84	4.05	3.44	3.57	2.38	3.04

Conclusion

The mechanism and kinetics of synthesis of 1,7-dibromoheptane was studied. The results indicated that the reaction of 1,7-dibromoheptane was a typical consecutive one by measuring the concentration changes of each component with reaction time under different conditions. In the reaction system of hydrobromide as brominating agent and sulphuric acid as catalyst, the first step of the reaction of bromination was the control step, k_1 was much smaller than k_2.

The bromination reaction of 1,ω-diols accorded with mechanism of S_N2, which could be certified by the fact that k_1 was much smaller than k_2 from the rate equation and the solvent effects.

The model of the kinetics of the synthesis of 1,7-dibromoheptane was established and its kinetics equation of chemical reaction could be expressed as follows:

$$c_A = \frac{f/2}{\exp\left(FA\exp\left(\frac{34.01m - 96.64}{8.3145T}\right)t - \ln\left(\frac{2c_{A,0}}{F + 2c_{A,0}}\right)\right) - 1}$$

The mass fraction 'm' of sulphuric acid had a good linear relationship with the activate energy 'E_a' in the reaction system, it could low the activation energy while the acid strength increased. It told the direction for the reaction under mild, clean and energy saving condition for replacing the traditional liquid catalysts with solid acid catalysts.

The reaction activation energy E_a of this system was about 90 KJ/mol, it was between the general chemical reaction activation energy of 40-200 kJ mol^{-1} and belonged to the chemical reaction control process.

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