Kinetics and Mechanism of the Additive Reaction of Aniline with Dicyandiamide[1]

L.-P. Guo, X.-D. Du, and J.-H. Lei

Department of Applied Chemistry, School of Science, Wuhan University of Technology,
Wuhan, Hubei, 430070, People's Republic of China
e-mail: yhx2000@263.net
Received December 18, 2007

Abstract—Kinetics of the additive reaction of aniline with dicyandiamide resulting in phenylbiguanide production was studied based on the analysis of reaction rate by high performance liquid chromatography. It is a second-order reaction on the condition of the constant temperature and acidity. It is first-order for both aniline and dicyandiamide. The reaction rate is influenced evidently by acidity. It reaches its maximum at pH 2.6. The mechanism for this reaction was suggested that aniline is nucleophilic reagents additive with the protonated cyano-group in dicyandiamide. The rate equation derived from the mechanism can describe the experimental results well. The reaction rate calculated from the rate equation reaches its maximum at pH 2.5, which is close to the experimental result. For different aromatic amine adding to dicyandiamide have the same reaction order, the mechanism ought to be the same.

DOI: 10.1134/S0023158409030045

1. INTRODUCTION

The general class of compounds called biguanides has been known for a long time [1–5]. The ability of biguanides to chelate metals has been widely used in coordination chemistry [6, 7]. In recent years, biguanides have proved to be broadly useful. For example, metformin [8] has important applications in curing diabetes, and chlorhexidine [9] is widely used as antiseptics. Moreover, biguanides are strong organic bases, and they are also valuable catalysts for some organic synthesis [10, 11]. In addition, can be used as curing agent for epikote with better latency and solidification [12, 13]. Their applications in electron device, chip capsulation and special covering have better applied prospect. Thereby, in recent years, the synthesis and structure research of biguanides and their derivates gain people's attention again [14–17].

Phenylbiguanide and its derivates were mainly prepared by the additive reaction of aniline with dicyandiamide in acidic condition [2, 14, 16]. The fundamental reaction formula is shown as Scheme 1.

However, the kinetics of this reaction has not been further studied, and its mechanism has not been clear, either. For a more in-depth understanding of this reaction, thus effectively supervise the synthesis of phenylbiguanide and its derivates, it is necessary to study the mechanism of this reaction.

In this paper, the reaction rate of the additive reaction was determined by high performance liquid chromatography (HPLC). The reaction kinetics and mechanism were studied, which provided theoretical basis for the synthesis of arylbiguanides and should be useful to improve the synthesis method.

2. EXPERIMENTAL

2.1. Reagents and Equipment

Aniline ($PhNH_2$) and its derivates were on A.R. and purified by distilling under reduced pressure before use. Dicyandiamide (DICY) was on A.R. All the other reagents undeclaration were on A.R. Experimental water was distilled water.

HPLC analysis used AGILENT-1100 chromatography system of the American AGILENT Company. IR spectrum analysis used AVATAR-370 fourier transform infrared spectroscopy of American Thermo Nicolet Company. UV spectrum analysis used Lambda-35 UV spectrometer of the American PerkinElmer Company.

2.2. Synthesis of Phenylbiguanide

Aniline (9.30 g, 0.100 mol) and DICY (8.40 g, 0.100 mol) were added to 80 ml water, the mixture was stirred. Drop HCl (6.0 mol/l) to adjust the pH to a certain value, and then add water until the total volume was 100 ml. The mixture was heated to 373 K at reflux, with continuous addition of HCl (6.0 mol/l) to maintain the pH. After 3 h, stop heating the mixture and pour in 30 ml NaOH solution (5.0 mol/l) with adequate stirring. Cool the mixture to crystallize. Then the precipitate was separated by filtration, washed with water, and dried under reduced pressure. Further purification

---

[1] The article is published in the original.

X = alkyl, aryl, or halogen
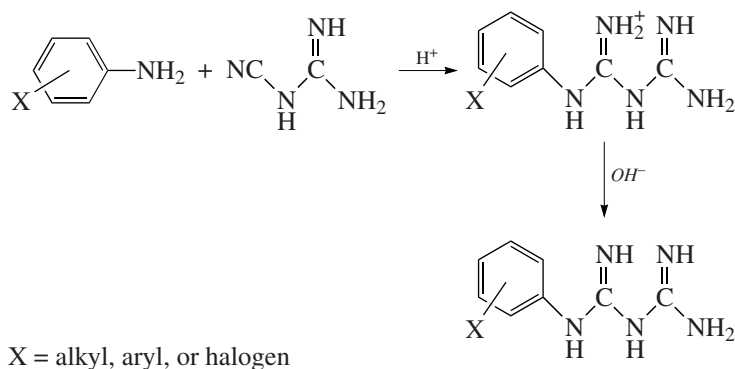
Scheme 1. Synthesis of arylbiguanides by the additive reaction of aromatic amine with dicyandiamide.

could be achieved by recrystallization from ethanol-water solution (10%, volume fraction), and then dry the mixture under reduced pressure. This yielded pure phenylbiguanide as a colorless powder, mp: 411.5 to 413.0 K, IR (KBr, cm^{-1}): 3341, 3178, 1608, 1533, 1488, 1367, 1250, 915, 840, 759, 670, accordant with documentation [14].

2.3. Determination of the Reaction Rate

In the process of synthesis of phenylbiguanide, a certain amount of the sample was sucked with a microaeroscope at a certain interval period, then quickly diluted with water, cooling. Adjust the mixture to neutral with 1.0 mol/l sodium acetate solution. The concentration of reactants were determined by HPLC method. Chromatographic conditions: 298 K; methanol-water solution (70%, volume fraction) as the mobile phase; chromatographic column of SinoChrom ODS-BP 5μ, 4.6 × 200 mm; UV detector at 230 nm. Plot the concentration of the reactants against reaction time, then the reaction rate can be determined by differential method.

Table 1. The concentrations of aniline varying with the reaction time

Time, 10^3 s	Concentration of aniline, mol/l
0.00	0.300
0.60	0.213
1.20	0.151
1.80	0.104
2.40	0.077
3.00	0.051
3.60	0.037
4.20	0.030
4.80	0.024

Note: $C_{0,\,aniline} = 0.300\,mol/l$, $C_{0,\,DICY} = 10C_{0,\,aniline}$, pH 3.5, 373 K.

The synthesis and determination of the reaction rate of other derivates of phenylbiguanide is carried out in the same way described above.

3. RESULTS AND DISCUSSION

3.1. Reaction Kinetics of the Synthesis of Phenylbiguanide

3.1.1. Determination of reaction order. Let the initial concentration of aniline $C_{0,\,aniline} = 0.300$ mol/l, and initial concentration of dicyandiamide $C_{0,\,DICY} = 10C_{0,\,aniline}$. As the reactant dicyandiamide was in large excess, the concentration was considered constant through the reaction. Reaction was carried out at 373 K and pH 3.5. Determine the concentration of aniline, $C_{aniline}$, which varies with the reaction time. The results are shown in Table 1. Plot the logarithm of concentration against time, then a straight line through the origin is obtained (Fig. 1a). It follows the integral form of the first-order reaction rate equation, which is $-kt = \ln C/C_0$. So, the reaction is confirmed to be first-order for aniline. According to the general formula of reaction rate equation $w = kC^n$, $\log w = n\log C + \log k$ available, the reaction rate corresponding to diverse concentration can be obtained by differential method. Plot $\log w$, against $\log C$, and then a straight line is obtained, which shows that the reaction order for aniline $n = 1.03 \approx 1$ (Fig. 1b).

Let the initial concentration of dicyandiamide $C_{0,\,DICY} = 0.200$ mol/l, and concentration of aniline $C_{0,\,aniline} = 10C_{0,\,DICY}$. Reaction was carried out at 373 K and pH 3.5. Determine the concentration of dicyandiamide, $C_{0,\,DICY}$, which varies with the reaction time. The results are shown in Table 2. In the same way described above, the reaction is proved to be first-order for dicyandiamide (Figs. 2a and 2b).

3.1.2. Influence of pH on the reaction rate. Let the initial concentrations of both aniline and dicyandiamide are 1.00 mol/l, controlling the reaction carry out at different pH, and measure the corresponding reaction
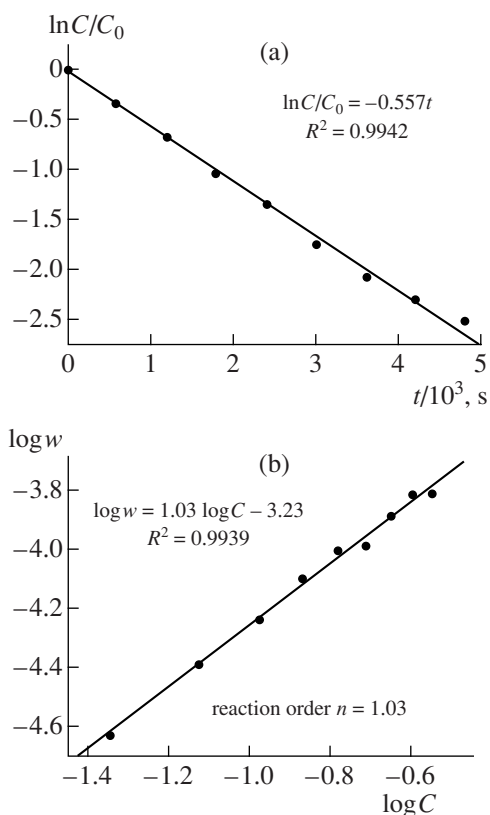
Fig. 1. The determination of reaction order for aniline. (a) Plot the logarithm of concentration against time, then a straight line through the origin is obtained. It shows the reaction is first-order for aniline. (b) Plot $\log w$, against $\log C$, and then a straight line is obtained, which is $\log w = 1.03\log C - 3.23$. It means the reaction order for aniline $n = 1.03 \pm 1$.
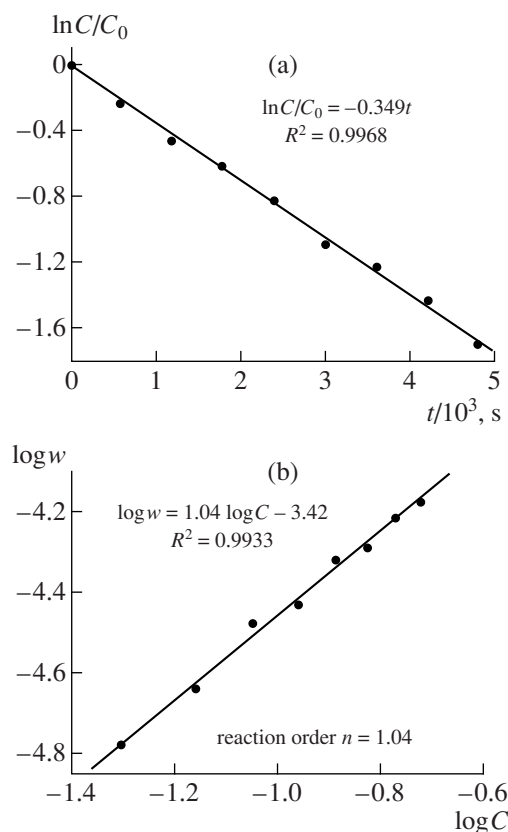

Fig. 2. The determination of reaction order for dicyandiamide. (a) Plot the logarithm of concentration against time, then a straight line through the origin is obtained. It shows the reaction is first-order for dicyandiamide. (b) Plot $\log w$, against $\log C$, and then a straight line is obtained, which is $\log w = 1.04\log C - 3.42$. It means the reaction order for dicyandiamide $n = 1.04 \pm 1$.

rate. To avoid the influence of side reaction, extrapolate the date to $t = 0$, and the initial rate is gotten (Fig. 3). The results show that the reaction rate is influenced apparently by acidity. Under near-neutral conditions, the reaction occurs so slowly that it almost impossible for it to happen. By adding an appropriate amount of acid, the reaction is accelerated obviously. When under low acidity conditions, the reaction rate increases significantly with the increase in acidity, and reaches its maximum at pH 2.6. Continue to increase acidity, the reaction rate decreases gradually with the increasing acidity.

According to the data of reaction rate, the reaction rate constant at different pH has been worked out (Table 3).

3.1.3. Rate equation. The results above indicate that, the reaction rate is determined by the concentration of aniline and dicyandiamide and the acidity. The reaction is first-order for both aniline and dicyandiamide. So, the reaction rate equation has the form as

$$w = k([H^+])C_{DICY}C_{aniline}, \qquad (1)$$

where $k([H^+])$ is the function of concentration of hydrogen ion.

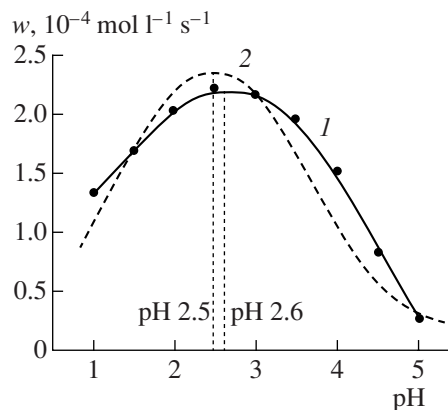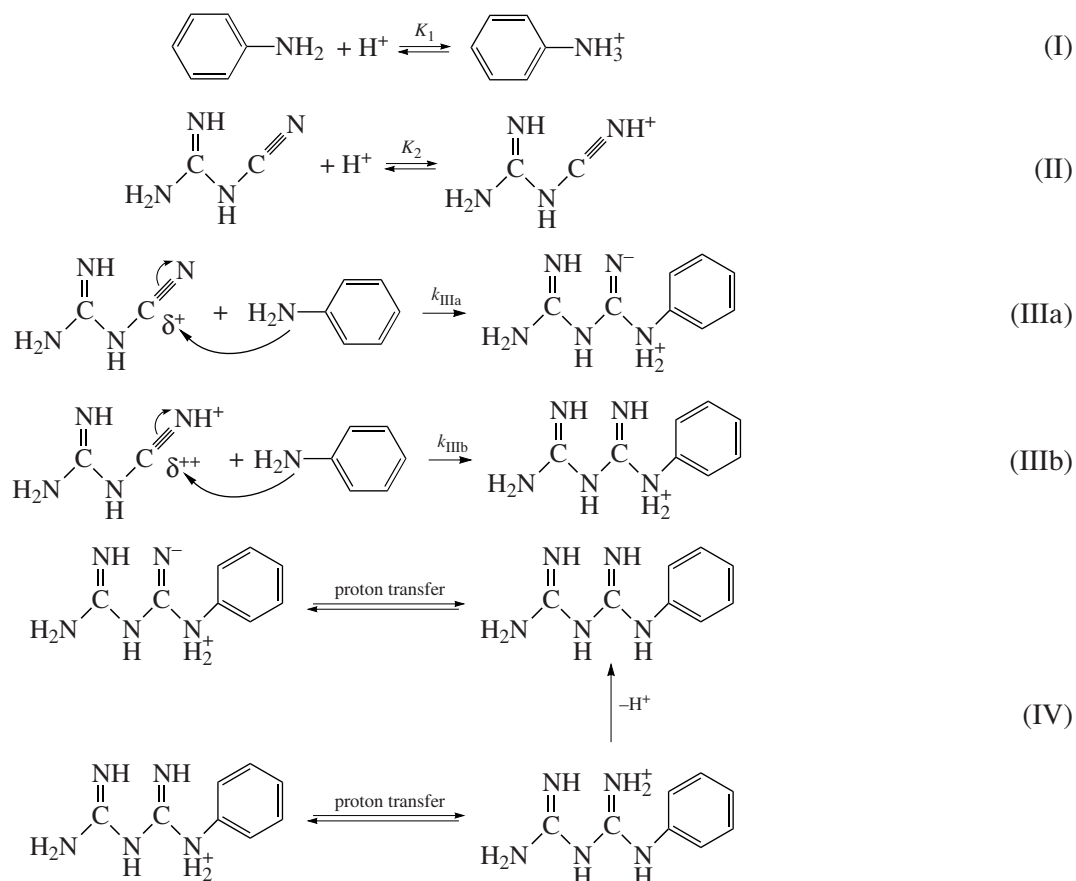**Fig. 3.** The reaction rate varying with the pH. (*1*) Determined value, (*2*) calculated according to Eq. (10).

Scheme 2.

3.2. Reaction Mechanism of the Synthesis of Phenylbiguanide

3.2.1. Reaction mechanism. Aniline, with an unshared electron pair of amino nitrogen atom, is a typical nucleophile; In the dicyandiamide molecule, the carbon atom of the cyano-group, with a partial positive charge, is vulnerable to be attacked by the nucleophile. Therefore, it ought to be a nucleophilic addition reaction. According to the results shown above, as well as the basic property of cyano-group, the mechanism of the additive reaction of aniline with dicyandiamide is suggested as Scheme 2.

Table 2. The concentrations of dicyandiamide varying with the reaction time

Time, 10^3 s	Concentration of DICY, mol/l
0.00	0.200
0.60	0.158
1.20	0.125
1.80	0.108
2.40	0.088
3.00	0.067
3.60	0.058
4.20	0.048
4.80	0.036

Note: $C_{0, \text{DICY}} = 0.200$ mol/l, $C_{0, \text{aniline}} = 10 C_{0, \text{DICY}}$, pH 3.5, 373 K.

Table 3. Reaction rate constant at different pH

pH	Reaction rate constant, 10^{-4} mol^{-1} l s^{-1}
1.0	1.33
1.5	1.70
2.0	2.03
2.5	2.22
3.0	2.17
3.5	1.96
4.0	1.52
4.5	0.83
5.0	0.28

Note: 373 K.

Aniline is an organic weak base and couples with the hydrogen ion to form anilinium ion. Reaction (I) can quickly reaches the equilibrium. In the dicyandiamide molecule, the nitrogen atom of the cyano-group, with an unshared electron pair, can accouple with the hydrogen ion, displaying alkalinity to a certain extent. UV spectrum (Fig. 4) shows, adding excessive strong acid to dicyandiamide solution, the transition peak at 194 nm that corresponds to the excitation of p electron disappears. After adjusting the solution to be neutral, its absorption curve comes back immediately. This indicates that, dicyandiamide can quickly establish equilibrium (II) in acidic condition. The dissociation constant of dicyandiamide, $K_{b, DICY}$, is determined by the potentiometric titration method (see APPENDIX A) at 373 K, $K_{b, DICY} = 10^{-10.84}$.

In the dicyandiamide molecule, the nitrogen atom of the cyano-group, with its greater electronegativity than that of the carbon atom, pulls the electron cloud of the triple bonds close to it. This makes the carbon atom somewhat electron deficient and gives it a partial positive charge. Aniline, with an unshared electron pair of amino nitrogen atom, attacks the carbon atom of the cyano-group as a nucleophile. Then, the addition reactions (IIIa) and (IIIb) occur. Affected by the positive charge of the nitrogen atom in the protonated cyano-group, the electron cloud of the triple bonds is pulled close to the nitrogen atom intensely. It makes the carbon atom much more positive and more vulnerable to be attacked by the nucleophile. So reaction (IIIb) is much faster than reaction (IIIa).

After the addition reaction finished, the intermediates undergo the transfer of the protons and the final product phenylbiguanide is obtained.

3.2.2. Kinetic analysis of the mechanism. During the process above, reactions (IIIa) and (IIIb) are additive reaction, and take place slower. All the other steps are proton transfer reactions, which can reach the balance immediately. So reactions (IIIa) and (IIIb) are the rate-determining steps. Reactions (IIIa) and (IIIb) are parallel reactions. Then the expression for the overall reaction rate w is:

$$w = w_{IIIa} + w_{IIIb}, \qquad (2)$$

where w_{IIIa} is the reaction rate of (IIIa), w_{IIIb} is the reaction rate of (IIIb).

From equilibrium (I), it solve to

$$[PhNH_2] = \frac{K_w}{K_{b, aniline}[H^+] + K_w} C_{aniline}, \qquad (3)$$

where K_w is the ion-product constant of water (at 373 K, $K_w = 10^{-12.26}$ [17]). $K_{b, aniline}$ is the dissociation constant of aniline (obtained by the experiment, at 373 K, $K_{b, aniline} = 10^{-8.70}$, see APPENDIX A), $C_{aniline}$ denotes the total concentration of aniline in the system, $[PhNH_2]$ denotes the equilibrium concentrations of aniline molecule.
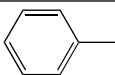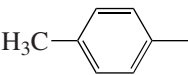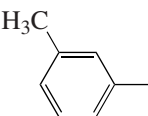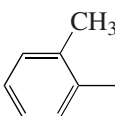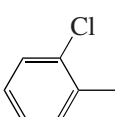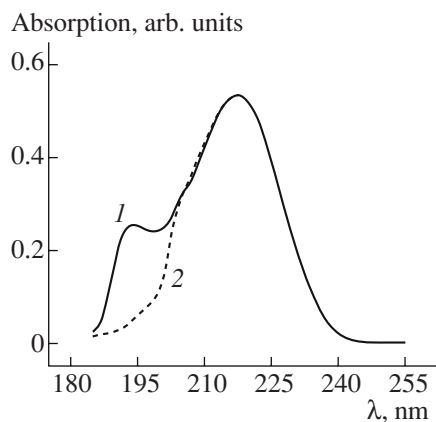
From equilibrium (II), it solve to

Fig. 4. UV spectrum of dicyandiamide (*1*) in neutral aqueous solution, (*2*) in acidic aqueous solution.

$$[DICY] = \frac{K_w}{K_{b, DICY}[H^+] + K_w} C_{DICY}, \qquad (4)$$

$$[DICYH^+] = \frac{K_{b, DICY}[H^+]}{K_{b, DICY}[H^+] + K_w} C_{DICY}, \qquad (5)$$

where $K_{b, DICY}$ is the dissociation constant of dicyandiamide (obtained by the experiment, at 373 K, $K_{b, DICY} = 10^{-10.84}$, see Section APPENDIX A), C_{DICY} denotes the total concentration of aniline in the system, $[DICY]$ and $[DICYH^+]$ denote the equilibrium concentrations of

Table 4. Reaction orders of $Ar-NH_2 + DICY \longrightarrow$ Arylbiguanide

Ar=	Reaction order	
	for aromatic amine	for dicyandiamide
⬡	1.03	1.04
H₃C—⬡	1.00	1.03
H₃C ⬡	1.02	0.98
⬡ CH₃	1.03	1.05
Cl ⬡	0.97	1.02

Note: pH 3.5, 373 K.

dicyandiamide molecule and protonated dicyandiamide ion.

According to the law of mass action, reaction (IIIa) follows that

$$w_{IIIa} = k_{IIIa}[PhNH_2][DICY]. \qquad (6)$$

Reaction (IIIb) follows that

$$w_{IIIb} = k_{IIIb}[PhNH_2][DICY^+]. \qquad (7)$$

When we substitute Eqs. (3), (4), and (5) into Eqs. (6) and (7), then substitute these into Eq. (2), the expression for the overall reaction rate can be rearranged to

$$w = \frac{K_w(k_{IIIa}K_w + k_{IIIb}K_{b,DICY}[H^+])}{(K_{b,aniline}[H^+] + K_w)(K_{b,DICY}[H^+] + K_w)} \qquad (8)$$
$$\times C_{DICY}C_{aniline}.$$

Equation (8) is the rate equation of additive reaction of aniline with dicyandiamide.

In Eq. (8), K_w, $K_{b,aniline}$, $K_{b,DICY}$ as well as k_{IIIa}, k_{IIIb} are constants and only depend on the temperature. Let the function

$$f([H^+]) = \frac{K_w(k_{IIIa}K_w + k_{IIIb}K_{b,DICY}[H^+])}{(K_{b,aniline}[H^+] + K_w)(K_{b,DICY}[H^+] + K_w)}.$$

Hence, Eq. (8) can be expressed as

$$w = f([H^+])C_{DICY}C_{aniline}, \qquad (9)$$

which has the same form as the experimental result shown in Eq. (1).

According information above, reaction (IIIb) occurs much faster than reaction (IIIa), and that's to say, $k_{IIIb} \gg k_{IIIa}$. Equation [9] can be simplified to

$$w = \frac{K_w k_{IIIb} K_{b,DICY}}{(K_{b,aniline}[H^+] + K_w)(K_{b,DICY}[H^+] + K_w)} \qquad (10)$$
$$\times C_{DICY}C_{aniline}.$$

The tendency of the reaction rate varying with pH is calculated according to Eq. (10) (Fig. 3). This tendency is well consistent with the experimental result shown in Fig. 1. And it can be obtained that the reaction rate reaches its maximum at

$$pH = -\log\frac{K_w}{\sqrt{K_{b,aniline}K_{b,DICY}}} = 2.5,$$

which is close to the experimental result shown in Fig. 3.

Discussions above show that the reaction mechanism can be used to the experimental phenomenon well and its deduction is consistent with the experimental results. So the reaction mechanism is reasonable.

3.3. Reaction Kinetics and Mechanism of the Synthesis of Arylbiguanides

Under constant temperature and acidity conditions, the addition reaction orders of dicyandiamide with several kinds of aromatic amine has been determined (Table 4).

The results show that the addition reaction orders of aromatic amine with dicyandiamide are in agreement. It is second-order for the overall reaction and is first-order for both aromatic amine and dicyandiamide. This suggests that diverse substitutional groups of the benzene ring have not essential effect on the reaction mechanism. That is to say, different aromatic amine carry out the addition reaction with dicyandiamide following the same mechanism.

4. CONCLUSIONS

(1) Under constant temperature and acidity conditions, the additive reaction of aniline with dicyandiamide is a second-order reaction, and it is first-order for both aniline and dicyandiamide. The reaction rate is influenced evidently by acidity. It reaches its maximum at pH 2.6, and when the acidity is lower or higher, the reaction rate decreases. The reaction rate equation has the form that

$$w = k([H^+])C_{DICY}C_{anililne},$$

where $k([H^+])$ is the function of concentration of hydrogen ion.

(2) The mechanism of the synthesis is suggested as follows: As a nucleophile, the aniline attacks the carbon atom of cyano-group in the dicyandiamide, then the nucleophilic addition occurs. The cyano-group protonizes in acidic conditions, which leads the addition easier. And the concentration of nucleophile varying with acidity because aniline can couples with hydrogen ion. The rate equation derives from the preceding mechanism is

$$w = \frac{K_w(k_{IIIa}K_w + k_{IIIb}K_{b,DICY}[H^+])}{(K_{b,aniline}[H^+] + K_w)(K_{b,DICY}[H^+] + K_w)}$$
$$\times C_{DICY}C_{aniline},$$

which has the same form with the experimental result, and can fit the experimental results well.

(3) For different aromatic amine additiving with dicyandiamide have the same reaction order, the mechanism ought to be the same.

APPENDIX A

THE DETERMINATION OF PROTONATION CONSTANT OF DICY

Transfer 150.0 ml solution of DICY (c_{DICY} = 0.1001 mol/l) to a four-mouth flask equipped with a

stirrer, a pH glass electrode, a reflux-condenser and a buret. Isolated with air and then placed at 100°C oil bath. The potentiometric titration was implemented after the temperature steady. Drop a certain amount of HCl solution (c_{HCl} = 0.4637 mol/l) and stirred sufficiently, and then recorded the pH of the system and the total volume of HCl.

Calculation formula is as Eq. (A1) [17]:

$$pH = pK_a - \log \frac{c_a - [H^+] + [OH^-]}{c_b + [H^+] - [OH^-]}, \qquad (A1)$$

where c_a, c_b is the concentration of protonic acid and base in the system, respectively.

The result is shown in table. Hence, $K_{b,DICY}$ = $10^{-10.84}$ at 100°C is obtained.

The determination of protonation constant of DICY at 100°C

V_{HCl}, ml	1.00	5.00	10.00	15.05	20.03	25.04	30.00
pH	3.07	2.32	2.01	1.78	1.64	1.53	1.47
c_a, mol/l	0.0031	0.0150	0.0280	0.0423	0.0546	0.0663	0.0773
c_b, mol/l	0.0964	0.0819	0.0649	0.0487	0.0337	0.0194	0.0061
$\log \dfrac{c_a - [H^+] + [OH^-]}{c_b + [H^+] - [OH^-]}$	−1.641	−0.929	−0.589	−0.406	−0.248	−0.118	0.029
$pK_{a,DICY}$	1.43	1.39	1.42	1.37	1.39	1.41	1.50
Average of $pK_{a,DICY}$				1.42			

$pK_{b,DICY} = pK_w - pK_{a,DICY} = 10.84$

APPENDIX B

THE DETERMINATION OF PROTONATION CONSTANT OF ANILINE

Transfer 150.0 mL solution of aniline ($c_{aniline}$ = 0.1009 mol l^{-1}). The potentiometric titration was implemented according to the same method in Appendix A (c_{HCl} = 0.4637 mol/l), and the result was calculated according to Eq. (A1).

The result is shown in table. Hence, $K_{b,aniline}$ = $10^{-8.70}$ at 100°C is obtained.

The determination of protonation constant of aniline at 100°C

V_{HCl}, ml	1.00	5.02	10.04	15.03	20.04	25.02	30.04
pH	4.99	4.32	3.95	3.65	3.40	3.07	2.62
c_a, mol/l	0.0031	0.0150	0.0291	0.0422	0.0546	0.0663	0.0774
c_b, mol/l	0.0972	0.0826	0.0655	0.0495	0.0344	0.0202	0.0067
$\log \dfrac{c_a - [H^+] + [OH^-]}{c_b + [H^+] - [OH^-]}$	−1.502	−0.742	−0.355	−0.073	0.193	0.493	0.917
$pK_{a,aniline}$	3.49	3.58	3.60	3.58	3.59	3.56	3.54
Average of $pK_{a,aniline}$				2.56			

$pK_{a,aniline} = pK_w - pK_{a,aniline} = 8.70$

REFERENCES

1. Bamberger, E. and Dieckmann, W., *Ber. Dtsch. Chem. Ges.*, 1892, vol. 25, p. 543.
2. UK Patent 581346.
3. Overberger, C.G., Michelotti, F.W., and Carabateas, P.M., *J. Am. Chem. Soc.*, 1957, vol. 79, p. 941.
4. Shirai, K. and Sugino, K., *J. Org. Chem.*, 1960, vol. 25, p. 1045.

5. Shapiro, S.L., Parrino, V.A., Rogow, E., and Freedman, L., *J. Am. Chem. Soc.*, 1959, vol. 81, p. 3725.

6. Ray, P., *Chem. Rev.*, 1961, vol. 61, p. 313.

7. Hubberstey, P. and Suksangpanya, U., *Struct. Bond*, 2004, vol. 111, p. 33.

8. Campbell, R.K., White, J.R., and Saulie, B.A., *Clin. Ther.*, 1996, vol. 18, no. 3, p. 360.

9. Thomas, L., Russell, A.D., and Maillard, J.Y., *J. Appl. Microbiol.*, 2005, vol. 98, p. 533.

10. Gelbard, G. and Vieffaure-Joly, F., *Tetrahedron Lett.*, 1998, vol. 39, p. 2743.

11. Gelbard, G. and Vielfaure-Joly, F., *React. Funct. Polym.*, 2001, vol. 48, p. 65.

12. JP-Kokai-49-93498.

13. JP-Kokai-52-5899.

14. LeBel, O., Maris, T., and Duval, H., *Can. J. Chem.*, 2005, vol. 83, p. 615.

15. Bharatam, P.V., Patel, D.S., and Iqbal, P., *J. Med. Chem.*, 2005, vol. 48, p. 7615.

16. Mayer, S., Daigle, D.M., Brown, E.D., et al., *J. Comb. Chem.*, 2004, vol. 6, p. 776.

17. Lebel, O., Maris, T., and Wuest, J.D., *Can. J. Chem.*, 2006, vol. 84, p. 1426.