

Acid-Catalyzed Hydrothermal Formation of Carbon–Carbon Bond in Glycolic Acid from a Series of Formaldehyde Producers

Saiko Morooka, Chihiro Wakai, Nobuyuki Matubayasi, and Masaru Nakahara*
Institute for Chemical Research, Kyoto University, Uji, Kyoto, 611-0011

(Received February 23, 2004; CL-040195)

The acid-catalyzed hydrothermal reaction is reported which forms a new carbon–carbon bond in the hydroxy carboxylic acid. It is found that glycolic acid is produced from formaldehyde in hot water at 225 °C with HCl. This reaction is a chemical evolution process from a C1 compound to a C2, and does not proceed in the absence of acid. A reaction of 0.3 M (mol/dm³) of formaldehyde with the double amount of HCl yielded 60% of the maximum possible amount.

Hot water dissolves a variety of organic substances, and can be used as a clean alternative to harmful organic solvents. To develop green chemistry using hot water, a systematic study of reactions in hot water is indispensable. In particular, synthetic reactions that form new bonds such as carbon–carbon or carbon–oxygen bond are of surpassing interest.^{1–5} Conventionally, the carbon–carbon bond formation is carried out under severe and delicate conditions,⁶ typically in the presence of metal catalysts or in use of a donor–acceptor pair (Diels–Alder). In stark contrast to these synthetic methods, it was demonstrated in a previous paper that a carbon–carbon bond is formed spontaneously in glycolic acid from CH₂Cl₂ in hydrothermal condition without any added catalysts.⁴ Still, the mechanism of this operationally simple reaction needs to be disclosed; the glycolic acid production is assumed to be originated in methanediol (hydrated form of formaldehyde) formation and be catalyzed by HCl which is generated in the course of the CH₂Cl₂ reaction. It is therefore crucial to identify the key reaction step and characterize its behavior. In the present work, we investigate each hydrothermal reaction step of formaldehyde. The reaction is examined separately by changing the input reactant and acidity. We show that the carbon–carbon bond formation in glycolic acid proceeds in the presence of an acid catalyst. The process is a chemical evolution process from a C1 compound to a C2 in hot water.

The reaction conditions are listed in Table 1. 1,3,5-Trioxane (a trimer of formaldehyde, called *s*-trioxane hereafter), HCl (2 M), and formic acid (99%) employed as the starting materials were obtained from Nacalai and used without further purification. CH₂Cl₂ was also purchased from Nacalai and was washed with distilled water to remove methanol contained as polymerization inhibitor. Paraformaldehyde (>95%) and ¹³C-enriched formalin (20%) were obtained from Merck and ISOTEC, respectively, and were used as received.

When CH₂Cl₂ is the starting material, it was sealed with water in a quartz NMR tube of 2.2-mm i.d. and 3.0-mm o.d. The concentration was set to 0.3 M when the reaction mixture becomes homogeneous. The filling factor of the sample (volume ratio of the solution to the total sample tube) was set to 85% at room temperature in order to make the gas phase volume negligible at the reaction temperature. When the starting material is

s-trioxane, formalin, or paraformaldehyde, it was sealed in a quartz NMR tube with aqueous HCl solution at the condition shown in Table 1. All *s*-trioxane, formalin, and paraformaldehyde produce formaldehyde, and their concentrations were adjusted to provide 0.3 M of formaldehyde at the reaction temperature. The concentration of HCl was mostly set to 0.6 M so that it matches with the condition achieved in the reaction of CH₂Cl₂; one CH₂Cl₂ molecule generates two HCl molecules upon hydrolysis.⁴ The effects of HCl and of formic acid concentration on the glycolic acid formation were examined by changing the HCl concentration and by adding formic acid, respectively.

Each sample tube was heated in a furnace kept at the reaction temperature of 225 ± 1 °C. After 2 h of reaction, the sample was removed from the furnace and cooled down to room temperature by air within a minute. After the reaction, the sample was put in a Pyrex NMR tube (5.0-mm o.d.) and the ¹H NMR spectrum was measured with ECA400 (JEOL).

To examine the necessity of HCl in glycolic acid formation, reactions of 0.1 M *s*-trioxane with and without 0.6 M HCl were studied. The product concentrations are shown in Figure 1. In both experiments, methanol and formic acid formed, which results from two formaldehyde disproportionations.⁷ One is the self-disproportionation between two formaldehydes, which generates methanol and formic acid, and the other is the cross-disproportionation between formaldehyde and formic acid, which generates methanol and CO₂. It is striking that these reactions proceed even under acidic condition in hot water, whereas the classical Cannizzaro (disproportionation) reaction needs a large amount of base catalyst at ambient condition.⁸ The formation of glycolic acid was confirmed in the experiment with HCl, while no glycolic acid was detected in the absence of HCl. Also, the yield of glycolic acid was found to be reduced by ≈60% upon the change in the HCl concentration from 0.6 to 0.3 M. Thus, it is revealed that glycolic acid forms from formaldehyde in two steps; the self-disproportionation of formaldehyde and the acid-catalyzed reaction of formaldehyde and formic acid⁹ expressed as:



From the synthetic point of view, it is of great interest to control the reaction path weight among the self-disproportionation (S), the cross-disproportionation between formaldehyde and formic acid (C), and the glycolic acid formation (G). The rates of these three reactions can be described respectively as:

$$\text{S rate} \propto [\text{HCHO}]^2 \quad (3)$$

$$\text{C rate} \propto [\text{HCHO}][\text{HCOOH}] \quad (4)$$

$$\text{G rate} \propto [\text{HCHO}][\text{HCOOH}][\text{HCl}] \quad (5)$$

In the aim of the glycolic acid production, the self- and cross-dis-

Table 1. The reaction conditions and the concentrations of the reactants

Formaldehyde Generator	Aldehyde /mM	HCl /mM	HCOOH ^a Added/mM	Filling Factor/%
dichloromethane	300	0	0	85
<i>s</i> -trioxane	100	0	0	71
<i>s</i> -trioxane	100	300	0	71
<i>s</i> -trioxane	100	600	0	71
<i>s</i> -trioxane	100	600	3000	50
formalin	300	600	0	71
paraformaldehyde ^b	300	600	0	71

^aThe hydrothermal decompositions of formic acid into CO or CO₂ were shown to occur in the present experimental condition.¹⁰

^bParaformaldehyde is in the powder form when the sample is prepared, because it requires long time to dissolve into water at room temperature.

proportionations, which produce methanol, need to be suppressed. When *s*-trioxane is treated under acidic hydrothermal conditions, the glycolic acid formation does not proceed appreciably until enough amount of formic acid is accumulated by Eq 1. Also, in the beginning of the reaction, the self-disproportionation is dominant over the glycolic acid formation due to high formaldehyde concentration; cf. the difference in the reaction order in Eqs 3 and 5. We can increase the rate and the yield of the glycolic acid formation by increasing [HCOOH] in Eq 5. As seen in Eq 4, in fact, the addition of formic acid also accelerates the cross-disproportionation, which generates methanol. According to Eq 5, on the other hand, the addition of HCl induces the glycolic acid formation only. Therefore, only when the reaction mixture is acidic enough, the reaction rate of the glycolic acid formation becomes larger than that of either self- or cross-disproportionations, and the addition of formic acid efficiently accelerates the glycolic acid formation.

To substantiate the effect of added formic acid, 0.1 M *s*-trioxane and 0.6 M HCl were reacted with and without 3.0 M formic acid, and the results were compared. When formic acid was present in excess, the yield of glycolic acid was ≈ 4 times larger than in the experiment without added formic acid. Figure 1 clearly shows our success in the selective formation of glycolic acid and the suppression of the disproportionation pathways. It is of great importance to control the reaction pathway by simply modifying reactant concentrations.

Other than *s*-trioxane, formalin and paraformaldehyde were treated with HCl in the same condition as *s*-trioxane, and they reacted similarly. Not only the product species were in accord but also their yields including glycolic acid agreed well. The difference in their yields of glycolic acid was within 10%. It is therefore clarified that the glycolic acid formation does proceed regardless of the initial form of formaldehyde.

According to the former study of glycolic acid formation from CH₂Cl₂,⁴ the mechanism of the formation was considered to consist of the following three steps; the formation of formaldehyde and HCl by the hydration of CH₂Cl₂, the formaldehyde disproportionations, and the acid-catalyzed glycolic acid formation from formaldehyde and formic acid. In this reaction scheme, HCl, which is a product in the first step, works as a catalyst. This mechanism was not conclusively demonstrated in the previous work. The present work verifies that glycolic acid does form when the reaction is initiated with formaldehyde and HCl, and does not in the absence of HCl.

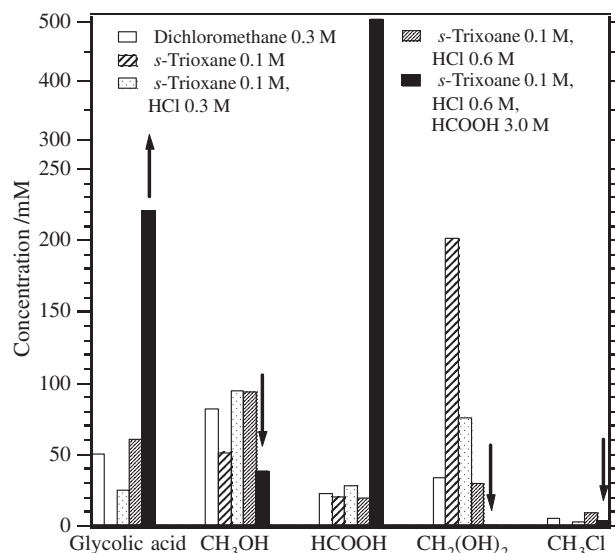


Figure 1. The product concentrations in various reaction conditions. The ordinate scale is changed at 250 mM. The arrows represent the effect of added formic acid on the product yields.

In the present work, an acidic hydrothermal reaction in which glycolic acid, a C2 compound, forms from formaldehyde, a C1 compound, is reported. The carbon-carbon bond formation in this reaction proceeds without any metal catalysts and the reaction condition is much milder than that in the conventional scheme. The selective formation of glycolic acid was achieved by the addition of formic acid under acidic hydrothermal condition. Besides the glycolic acid formation, the present work suggests a new way of producing amino acids; the amination of hydroxyl group in glycolic acid leads to the formation of glycine, the simplest amino acid.

This work is supported by the Grant-in-Aid for Scientific Research (Nos. 14540531, 15205004, and 15076205) and the Grant-in-Aid for Creative Scientific Research (No. 13NP0201) from the Japan Society for the Promotion of Science and the Ministry of Education, Culture, Sports, Science and Technology.

References and Notes

- Y. Yamasaki, H. Enomoto, N. Yamasaki, and M. Nakahara, *Bull. Chem. Soc. Jpn.*, **73**, 2687 (2000).
- Y. Tsujino, C. Wakai, N. Matubayasi, and M. Nakahara, *Chem. Lett.*, **1999**, 287.
- Y. Nagai, C. Wakai, N. Matubayasi, and M. Nakahara, *Chem. Lett.*, **32**, 310 (2003).
- C. Wakai, S. Morooka, N. Matubayasi, and M. Nakahara, *Chem. Lett.*, **33**, 302 (2004).
- Z. Zhang, Y. Dong, and G. Wang, *Chem. Lett.*, **32**, 966 (2003).
- T. Banno, Y. Hayakawa, and M. Umeno, *J. Organomet. Chem.*, **653**, 288 (2002).
- Y. Nagai, N. Matubayasi, and M. Nakahara, *Chem. Lett.*, submitted.
- J. March, "Advanced Organic Chemistry," 4th ed., John Wiley & Sons, New York (1992).
- In the time evolution of the product concentrations shown in Ref. 4, the decrease of formic acid corresponds well to the generation of glycolic acid, which indicates the direct consumption of formic acid. According to Refs. 4 and 10, furthermore, the pyrolysis of formic acid is a minor reaction, which again indicates that the glycolic acid formation does not proceed with CO; [CO] is too small compared to that required in U. S. Patent 2152852 (1939).
- C. Wakai, K. Yoshida, Y. Tsujino, N. Matubayasi, and M. Nakahara, *Chem. Lett.*, **33** (2004), in press.