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# Selective Formation of 2-Hydroxy-3,3-bis(hydroxymethyl)-$\gamma$-butyrolactone from Formaldehyde on Hydrotalcite-Type Catalysts

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As a model for prebiotic sugar formation under neutral to acidic conditions, reactions of formaldehyde over hydrotalcite-type catalysts were investigated. Heating an aqueous solution of formaldehyde at 140—200 °C for 12 h over Ni–Fe hydrotalcite-type catalyst afforded 2-hydroxy-3,3-bis(hydroxymethyl)-$\gamma$-butyrolactone selectively, a 5.8% yield based on gas–liquid chromatographic analysis. The structure was identified by $^{1}$H and $^{13}$C NMR and $^{1}$H–$^{13}$C HSQC, HMBC and $^{13}$C–$^{13}$C 2D INADEQUATE NMR experiments.

Formation of carbohydrates and related compounds from a simple prebiotic molecule catalyzed by clay and other minerals$^{1)}$ or small organic molecules$^{2)}$ attracts interest owing to the possible relationship to chemical evolution. Allen$^{2)}$ pointed out that the reversible nature of the sugar formation reaction, aldol and retro-aldol reactions, should be noteworthy in terms of chemical evolution, and the study of such a system possibly leads to the development of autocatalytic system consisting of sugar-forming reactions. Therefore, investigation of a catalytic system forming sugar-like compounds would lead to understanding of chemical evolution as well as development of synthetic pathways to important carbohydrates.

The most extensively studied catalytic reactions are the formose reaction, in which formaldehyde is converted to carbohydrate derivatives under alkaline conditions.$^{3,4)}$ However, formation of carbohydrates or related compounds from formaldehyde under acidic conditions is rarely reported. Hammick et al. reported that heating of formaldehyde in concentrated sulfuric acid at 115 °C for 4.5 h yielded carbon monoxide, methyl formate, and glycolic acid.$^{5)}$ We have been interested in the sugar-forming reactions under acidic conditions, and reported the catalytic effects of H$^{+}$-mordenite$^{6)}$ and transition metal exchanged mordenite.$^{7)}$ A major product in the reaction was glycolic acid. We found that the reaction of formaldehyde over these acidic zeolite catalysts requires a higher reaction temperature and a longer reaction period than the conventional formose reactions, and the addition of transition metal salts such as Cu, Fe, and Cr salts improved the yields. In this paper, we report the formation of carbohydrate-related compounds from formaldehyde in a neutral to acidic aqueous solution on hydrotalcite-type catalysts.$^{8)}$ Hydrotalcite-type catalysts containing nickel and iron showed a high selectivity for 2-hydroxy-3,3-bis(hydroxymethyl)-$\gamma$-butyrolactone.

## Experimental

**General:** Gas–liquid chromatography was done with 5% silicone SE-30, 60—80 mesh Uniport HP, 4.2 m × 2.6 mm$\phi$, column temperature 110—270 °C (4 °C min$^{-1}$), and N$_2$ (60 mL min$^{-1}$) as carrier gas. $^{1}$H NMR spectra were acquired with either a JEOL A-500 or A-400 spectrometer in $D_2O$ or Me$_2$SO-$d_6$, and chemical shifts are reported relative to internal sodium 3-(trimethylsilyl)propanesulfonate (0 ppm) in $D_2O$ or Me$_2$SO (2.49 ppm) in Me$_2$SO-$d_6$. Mass spectra were obtained with a JEOL JMS-SX102A mass spectrometer. Powder X-ray diffraction was done on a Rigaku RAD-B diffractometer with Cu $K\alpha$ radiation.

**Preparation of Hydrotalcite-Type Catalyst: $Mg_6Al_2(OH)_{16}CO_3\cdot4H_2O$:**$^{9)}$ Magnesium nitrate hexahydrate (30.8 g) and aluminium nitrate nonahydrate (15.0 g) were dissolved in 100 mL of distilled water. The pH of the solution was adjusted to 10 by adding 2 M sodium hydroxide (1 M=1 mol dm$^{-3}$). To the suspension was added 400 mL of distilled water and the resulting suspension was stirred for 2 h at room temperature. The precipitated hydrotalcite was collected by filtration and dried overnight at 80 °C. The powder was then dispersed in 1 L of 0.1 M sodium carbonate and the suspension was stirred at room temperature for one day to exchange the interlayer nitrate ion for carbonate ion. The white powder was collected by filtration, washed with water until the pH of the washing was 7, and dried in vacuo: yield: 87%. Powder X-ray diffraction confirmed the formation of hydrotalcite: $d$(003) 7.88 Å.

Similarly $Mg_6Fe_2(OH)_{16}CO_3\cdot4H_2O$ (HT-Mg·Fe, pyroaurite,$^{10)}$ $Ni_6Al_2(OH)_{16}CO_3\cdot4H_2O$ (HT-Ni·Al, takovite), and $Ni_6Fe_2(OH)_{16}CO_3\cdot4H_2O$ (HT-Ni·Fe, reevisite) were prepared from $Mg(NO_3)_2\cdot6H_2O$–$Fe(NO_3)_3\cdot9H_2O$, $Ni(NO_3)_2\cdot6H_2O$–$Al(NO_3)_3\cdot9H_2O$, and $Ni(NO_3)_2\cdot6H_2O$–$Fe(NO_3)_3\cdot9H_2O$, respectively. Yields (%) and the values of $d$(003) (Å) were 70, 8.08 (HT-Mg·Fe); 80, 7.92 (HT-Ni·Al); and 90, 7.94 (HT-Ni·Fe), respectively.

**$Co_6Al_2(OH)_{16}CO_3\cdot 4H_2O$ (HT-Co·Al, takovite):**[11] Cobalt nitrate hexahydrate (29.1 g) and aluminium nitrate nonahydrate (12.5 g) was dissolved in 70 mL of distilled water. To this solution was slowly added a solution of sodium hydroxide (24 g) and sodium carbonate (10 g) in 100 mL of distilled water at 30 °C. The precipitates formed were aged at 60—65 °C for 18 h. The gray powder was collected by filtration and washed with distilled water until the washing was neutral. The product obtained was dried in vacuo at 125 °C overnight: yield: 79%. Powder X-ray diffraction indicated the formation of the hydrotalcite-type crystal structure: *d*(003) 7.56 Å.

The hydrotalcite HT-Mg·Al with terephthalate as an interlayer anion was prepared as follows. A solution of terephthalic acid (6.8 g) and KOH (23.1 g) in 100 mL of distilled water was slowly added to a solution of magnesium nitrate hexahydrate (20.1 g) and aluminium nitrate nonahydrate (10.0 g) in 100 mL of distilled water at room temperature. After the addition, the suspension was stirred at 70 °C for 18 h. The white powder was collected by filtration, washed with distilled water until the washing was neutral, and washed with acetone. The powder was vacuum dried, yielding 91% of hydrotalcite-type catalyst: *d*(003) 14.03 Å.

**Reaction of Formaldehyde on Hydrotalcite-Type Catalyst:** Formaldehyde aqueous solution (37%, 10 mL) and hydrotalcite-type catalyst (0.04—0.13 g[12]) were placed in a Teflon®-lined autoclave (100 mL) and the mixture was heated at 140—200 °C for 6—72 h. After the reaction mixture was cooled to room temperature, the catalyst was removed by filtration. To the filtrate was added about 200 mg of cation exchange resin (Dowex 50W-8, $H^+$ form) and the solution was stirred for 1 h at room temperature to remove the dissolving metal ions. The resin was filtered. This treatment with cation exchange resin was repeated three times. Activated charcoal 50 mg was then added to the filtrate, the suspension was stirred at room temperature for 1 h and the charcoal was filtered. The filtrate was evaporated at 40 °C in vacuo. To the residue was added water and the solution was evaporated in vacuo to remove a formaldehyde polymer, poly(oxymethylene). This was repeated until the weight of the residue becomes constant. The obtained product mixture was then dried in vacuo, and analyzed by gas–liquid chromatography, or further purified.

**Gas–Liquid Chromatography:** The product mixture was trimethylsilylated for gas–liquid chromatographic analysis and mass spectroscopic analysis.[13] The product mixture (10 mg) was dissolved in pyridine (1 mL) and the solution was cooled in an ice-water bath. Hexamethyldisilazane (0.2 mL) and chlorotrimethylsilane (0.1 mL) were then added at 0 °C. The reaction mixture was stirred for a minute and left overnight at room temperature. To the reaction mixture were added chloroform (1 mL) and distilled water (2 mL), and the suspension was vigorously stirred. After centrifugation, the water layer was discarded. This procedure was repeated until the chloroform layer became clear. The chloroform layer was analyzed by gas-liquid chromatography.

**Isolation of the Products:** The product mixture (1.6 g)[14] was taken up in water–chloroform and the chloroform layer was discarded. The water layer was concentrated to about 2 mL, and an acetonitrile–water mixture (9 : 1, 100 mL) was added. The precipitate was removed by filtration. The filtrate was concentrated in vacuo and partition-chromatographed. Celite (Hyflo-Super-Cel, Manville Sales Corp., 15 gals/sq. ft/h, 50 g) was washed with concentrated hydrochloric acid (200 mL) overnight at room temperature and then at 100 °C for 1 h. The Celite was filtered, washed with distilled water until the washing was free from chloride ion, washed with methanol, and dried at 100—110 °C for 48 h. The Celite (30 g) was then treated with the upper layer of EtOAc–propanol–water (4 : 1 : 2, 13.2 mL) and then the lower layer of the same mixed solvent. The product mixture was eluted with the lower layer of the mixed solvent. Three products detected by gas–liquid chromatogra-

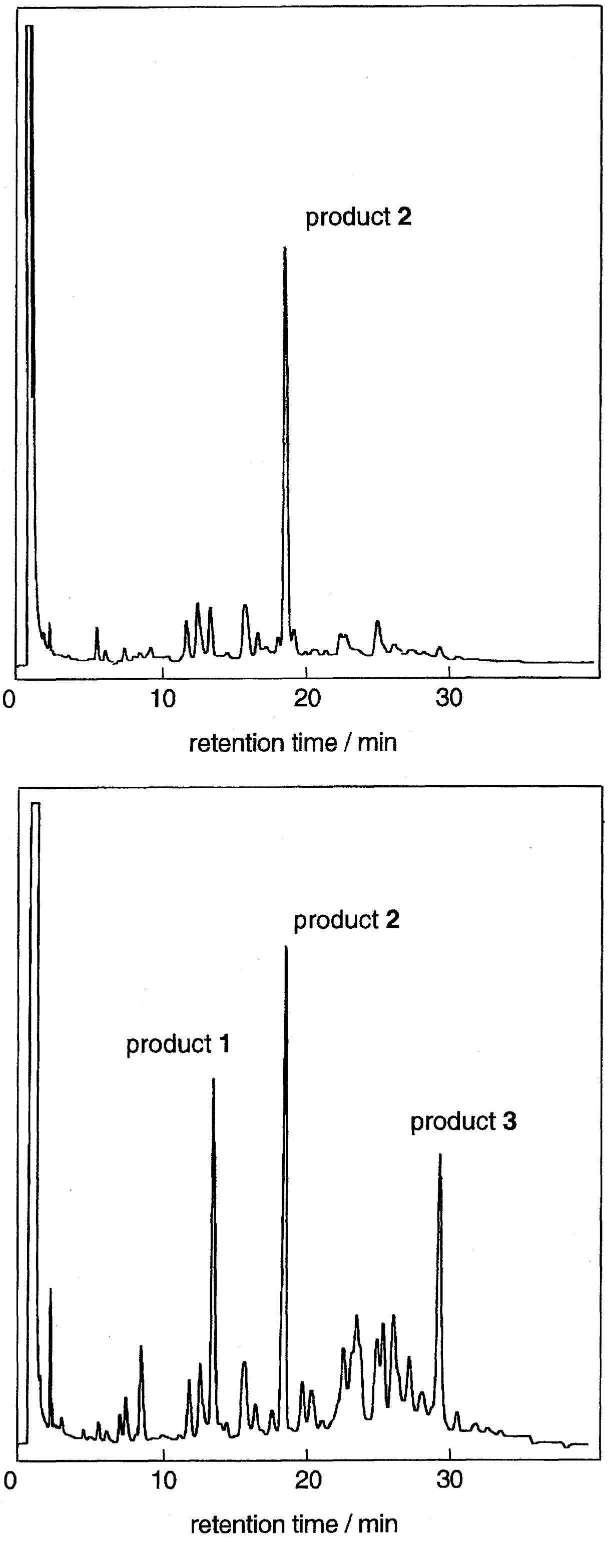


Fig. 1. Gas–liquid chromatogram of pertrimethylsilylated reaction mixture formed on top HT-Ni·Fe catalyst and bottom HT-Mg·Al catalyst at 170 °C for 12 h.

phy after trimethylsilylation were thus separated. Product **2** eluted first, followed by product **1** and then product **3** (see Fig. 1).[15)]

**2** was obtained as a hygroscopic white powder, 0.13 g: GC-MS, after trimethylsilylation, 378, $M^+$, $C_{15}H_{34}O_5Si_3$. Analysis, Calcd for $C_6H_{10}O_5 \cdot 0.2H_2O$: C, 43.48; H, 6.32%. Found: C, 43.55; H, 6.55%.

## Results and Discussion

Five hydrotalcite-type catalysts, HT-Mg•Al, HT-Mg•Fe, HT-Ni•Al, HT-Ni•Fe, HT-Co•Al were prepared and the catalytic activities on formation of carbohydrate-like compounds from formaldehyde were examined. The reaction was done in water. Reaction temperatures lower than 140 °C did not give any product except for poly(oxymethylene). Carbohydrate-like compounds were formed at 140—200 °C (Scheme 1). The pH of the solution before the reaction was 5.5—6.5 and those after the reaction were 3.0—3.3. Therefore the conversion of formaldehyde to carbohydrate-like compounds occurs under neutral to acidic conditions. This reaction differs from the formose reaction over Ca $(OH)_2$: (1) The formose reaction proceeds under alkaline conditions, while the present reaction proceeds under acidic conditions. (2) The formose reaction is complete within a few hours at 65—100 °C, but this reaction needs a higher reaction temperature and a longer reaction period.

The reaction mixture was treated with ion-exchange resin followed by activated charcoal, and poly(oxymethylene) was removed by repeated evaporation of an aqueous solution. Typical gas–liquid chromatograms of the pertrimethylsilylated product mixtures obtained in the reaction over HT-Ni•Fe catalyst and HT-Mg•Al catalyst are shown in Fig. 1. Three major products, **1**, **2**, and **3**, were formed, and their distribution depended on the catalyst used. Figure 1 indicates that all the three products were formed in nearly 1 : 1 : 1 ratio on HT-Mg•Al catalyst, but product **2** was formed predominantly on HT-Ni•Fe catalyst. Yields, and the product distribution found by gas–liquid chromatography after trimethylsilylation are listed in Table 1.

Hydrotalcite-type catalysts containing Mg (HT-Mg•Al and HT-Mg•Fe) had better yields than those containing Ni (HT-Ni•Al and HT-Ni•Fe). Among the catalysts used, HT-Ni•Fe showed a high selectivity for product **2**. HT-Mg•Al and HT-Mg•Fe are less selective and gave nearly equal amounts of products **1**—**3**.

Table 1. Product Distribution of Reaction of Formaldehyde on Hydrotalcite-Like Catalysts

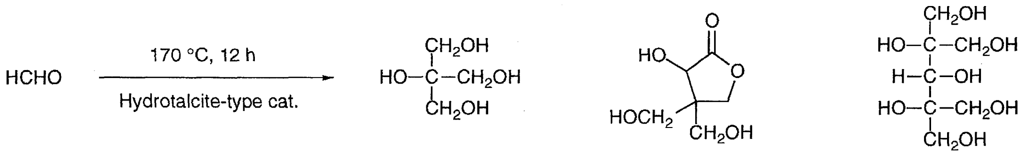
| Catalyst | Yield | Product distribution (GLC %)[b)] | | |
|---|---|---|---|---|
| | % | **1** | **2** | **3** |
| HT-Mg•Al | 17.6 | 12.4 | 17.3 | 11.7 |
| HT-Mg•Fe | 17.9 | 12.0 | 16.4 | 11.4 |
| HT-Ni•Al | 9.9 | 1.7 | 9.3 | 10.3 |
| HT-Ni•Fe | 15.3 | 4.9 | 38.0 | 1.7 |
| HT-Co•Al | 20.9 | 7.6 | 19.1 | 10.2 |
| HT-Mg•Al[a)] | 19.7 | 7.1 | 15.2 | 3.4 |

a) The interlayer anion was terephthalate, while the interlayer anion of the other HT was carbonate. b) The product distribution of **2** determined by GLC for HT-Ni•Fe catalyst was 38% while the isolated yield of **2** was 8%. This discrepancy is ascribed to the loss during the isolation process and to the presence of any higher molecular compounds which cannot be detected by GLC.

Two products, **1** and **2**, were isolated and the structures were identified. Isolation of product **3** was unsuccessful. The products were isolated by reprecipitation from water–acetonitrile followed by partition chromatography on Celite. The purity of the isolated products was checked by gas–liquid chromatography after converting the products to pertrimethylsilyl derivatives. The purity of isolated **2** was 90—95% and that of isolated **1** was 70—80%.

The structure of product **2** was identified by mass spectroscopy, $^1$H, $^{13}$C NMR, $^1$H–$^{13}$C HSQC,[16)] HMBC,[17)] and INADEQUATE[18)] experiments. The $^1$H NMR spectrum in $D_2O$ has one singlet at $\delta = 4.62$ (1H), two doublets at $\delta = 4.41$, and 4.32 ($J = 9.5$ Hz, 2H), two doublets at $\delta = 3.77$, 3.69 ($J = 11.3$ Hz, 2H), and one singlet at $\delta = 3.67$ (2H). When NaOD was added, the spectrum became quite simple, two singlets at $\delta = 4.06$ (1H) and 3.68 (6H). The $^1$H NMR spectrum in $Me_2SO$-$d_6$ had one doublet at $\delta = 5.81$ ($J = 6.5$ Hz, 1H) and two triplets at $\delta = 4.94$ and 4.69 ($J = 5.2$, 5.2 Hz, 1H each) at 20 °C. These signals moved to a higher field by 0.12—0.14 ppm when the temperature was raised to 50 °C, suggesting that these are OH protons. The CH protons appear at $\delta = 4.33$ (doublet, $J = 5.8$ Hz, 1H), 4.17, 4.05 (two doublets, $J = 8.9$ Hz, 1H each), and 3.31—3.40 (multiplets, 2H), and these signals did not move (<0.01 ppm) when the temperature was raised to 50 °C. In $^{13}$C NMR in $D_2O$, signals appeared at $\delta = 180.33$ (s), 71.48 (t), 69.90 (d), 62.00 (t), 61.57 (t), and 50.41 (s). The signal multiplicity of the off-resonance spectrum is shown in parentheses.

The $^{13}$C NMR spectrum indicates that **2** has six carbons; one carbonyl carbon, three methylene carbons, one methine carbon, and one quaternary carbon. Simplified $^1$H NMR spectrum in NaOD suggests that **2** has a cyclic structure, possibly a lactone ring. The $^1$H NMR spectrum in $Me_2SO$-$d_6$ and mass spectra indicate that three hydroxyl groups exist, one secondary hydroxyl and two primary hydroxyl groups.



**1** **2** **3**

Scheme 1.

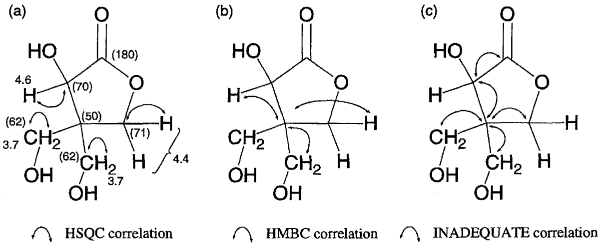


Fig. 2. (a) $^1$H and $^{13}$C NMR signal assignment of product **2** recorded in $D_2O$, and $^1$H–$^{13}$C HSQC correlations. Chemical shifts of each $^1$H (ppm) are shown. In the parentheses are shown chemical shifts of $^{13}$C (ppm). (b) $^1$H–$^{13}$C HMBC correlations. (c) $^{13}$C–$^{13}$C INADEQUATE correlations.

All these spectral results indicate the structure and the assignments shown in Fig. 2. This structure and the assignment were further supported by the two-dimensional NMR studies: HSQC, HMBC, and INADEQUATE. $^1$H–$^{13}$C HSQC correlation, $^1$H–$^{13}$C HMBC correlation, and $^{13}$C–$^{13}$C INADEQUATE (see Fig. 3) correlation are shown in Fig. 2. On the basis of these NMR results the structure of **2** was identified as shown in Fig. 2. These spectral data are consistent with those reported for the product obtained in a formose reaction in methanolic sodium hydroxide.[19)]

Product **1** isolated by partition chromatography on Celite showed one singlet at $\delta = 3.58$ in the $^1$H NMR spectrum in $D_2O$, and two signals at $\delta = 64.94$ (triplet) and 77.58 (singlet) in the $^{13}$C NMR spectrum. Comparison of the retention time of gas–liquid chromatography and the mass spectrum with the reported ones[16)] indicates that **1** is 2-hydroxymethyl-1,2,3-propanetriol. Product **3** was not isolated as a pure form. The gas–liquid chromatography and mass spectroscopy[20)] suggest that it is 2,4-bis(hydroxymethyl)-1,2,3,4,5-pentanepentaol.[19)] These products were also found in the formose reaction in methanolic sodium hydroxide.

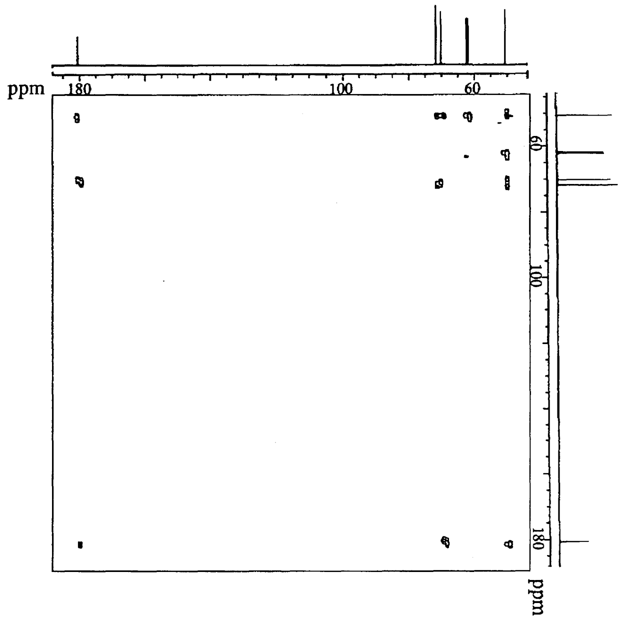


Fig. 3. $^{13}$C–$^{13}$C INADEQUATE spectrum of **2** in $D_2O$ (ca. 300 mg in 0.4 mL). The experimental conditions were optimized for $J_{cc} = 55$ Hz.

The mechanism of the formation of these products is unknown. The fact that both the conventional formose reaction and this reaction yielded the same products **1**—**3** may suggest that the intrinsic thermodynamic stability of these compounds or a facile kinetic pathway to these compounds accounts for the selectivity of these reactions.

In conclusion, this work demonstrates that (1) polyhydroxy compounds **1**—**3** were formed on hydrotalcite-type catalysts, (2) the selectivity of the product **2** was highest for Ni•Fe hydrotalcite, and (3) the structure of **2** was identified by NMR and mass spectroscopy.

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20) EI-MS after trimethyl silylation: $m/z$ (relative intensity) 307 (26), 217 (100), 205 (5), 103 (98). $^{13}$C NMR ($D_2O$) $\delta$/ppm 79.48 (s), 74.47 (d), 66.41 (t), 64.85 (t).