NOTES

Homogeneous Catalytic Condensation of Methylene Glycol (the Formose Reaction)

Volume Changes

Liquid volume changes during formose reaction in the presence of excess calcium hydroxide catalyst were first observed by Balezin (*1, 2*). A dilatometric analysis indicated that the volume of the solution fell sharply as Ca(OH)$_2$ was dissolved and that the volume rose again during both the induction period and the period of the formose reaction. Although apparently important as an indication of reaction mechanism, only polemic comments (*3, 4*) were made and the phenomenon was not investigated further. We now show that the phenomenon is important as an indicator of reaction mechanism.

The formose reaction is generally conducted in either water or a dilute aqueous solution of an alcohol (*5*). Effective catalysts for the formose reaction are inorganic cations with an ionic radius of 0.95 to 1.07 Å, preferably calcium hydroxide (*6*) or unhindered tertiary amines (*5–8*).

Water is structured (*9, 10*). Solutes affect the entropy of water (*11*), and the restructuring of water can be a driving force for a chemical reaction. Dissolved ions become solvated, and association shells are formed. In protic solvents, the energy of solvation of ionic ligands able to form hydrogen bonds may be quite large, leading to high solvation enthalpies (*12*). Complex formation between a metal ion and a ligand in solution involves competition between the ligand and the solvent for the coordination site on the metal ion (*13*). Consequently, ligand substitution reaction (*14*) are often indicated by changes in the volume of the solution (*15*).

Calcium ion, a strong disrupter of water

structure, causes a contraction in the volume of aqueous solutions. Alkaline earth hydroxides also form complexes with many carbohydrates (*16–21*), so it seems reasonable that alkaline earth hydroxides would form complexes with the sugars formed in the formose reaction, effecting a second volume contraction. Prior to sugar formation, there is an induction period that also involves complex formation and decomplexation of the primary reaction products (*22*). A complexation/decomplexation model has been used to derive kinetic parameters for the formose reaction (*23*).

The apparatus and general procedures used to effect the formose reaction have been described (*22, 24, 25*). The dilatometer used consisted of a 500-ml, three-necked reaction flask equipped with a magnetic stirring bar, a calibrated 5-ml buret, a supply/storage vessel, and a thermometer. Insulation was used to prevent heat transfer from the motor to the monitored liquid. The formose reaction mixture was prepared in separate equipment and transferred into the reaction vessel by way of the supply/storage vessel. A blank solution containing CaCl$_2$ and HCHO was observed in a second dilatometer for a determination of room-temperature variations on dilatometer readings. The measurements on the dilatometer containing the formose reaction mixture were corrected for volume changes observed for the blank.

A quantity of the same formose reaction mixture was kept in a separate flask under the same environmental conditions and frequently sampled for analysis of residual formaldehyde, Cannizzaro products, and sug-

474

ars formed during the reaction. These results were compared to those of the following standard, room-temperature formose reaction: to a 500-ml volumetric flask was added 125 ml of 1 M CaCl$_2$, followed by 9.1 ml of 13.76 M HCHO. The resulting solution was diluted to 200 ml. Then 62.5 ml of 1 M NaOH were added slowly with continued agitation. After thorough mixing, a solution of D-glucose was added as a co-catalyst to a final concentration of 10^{-2} M, and the time of initiation of the reaction was recorded. Water was added to a volume of 500 ml, and a 25-ml sample (blank) was withdrawn for analysis of HCHO content, pH, titratable acids, and appearance. At 20-min intervals, additional 25-ml samples are withdrawn and analyzed in the same way.

Formation of the formaldehyde–calcium monohydroxide ion complex was studied in two ways: (1) Buret Method. A calibrated 50-ml buret was filled to various levels with aqueous solutions of calcium chloride (0.5 to 4 M). An aqueous solution of formaldehyde was added from a 10-ml buret in small increments and with thorough mixing. Readings of the combined liquid volume were taken until they were constant, i.e., until all temperature effects were dissipated. The mole ratio of reagents was plotted against the volume change. (2) Jobs Method (26). Density measurements were used for the determination of the apparent coordination numbers in complexes of the calcium ion with formaldehyde and with sugars. As a control, solutions of calcium chloride were blended with water in the same proportions, and corrections were derived for volume contraction owing to dilution.

The volume change during the formose reaction depended on the concentration and ratio of the reactants and amounted to 0.1–0.5% of the liquid volume, i.e., a change of 0.5–2.5 ml in a 500-ml dilatometer. A 500-ml flask changes 0.01 ml in volume for each degree deviation from 20°C, while water contained in the flask varies by 0.09 ml/°C. The volume change in a normal solution of base is about 40% higher. As an approximation, a change of 0.1 ml volume was assumed for each degree of temperature variation.

Conversion of formaldehyde to sugars was required for maximum liquid volume expansion. Most expansion (a maximum of 0.5%) was observed at the optimal HCHO : Ca(OH)$_2$ mole ratio of about 3. There was little change in the amount of expansion at a mole ratio of 2, but the percentage expansion was reduced at mole ratios less than 2 and greater than 3. This indicated that methylene glycol complexes with calcium hydroxide in an exact ratio prior to the formose reaction and that the magnitude of volume expansion during the formose reaction depends on the quantity of complexed species formed in the reaction mixture. (A HCHO : Ca(OH)$_2$ mole ratio of 2–3 also maintained an optimal pH for sugar formation.)

The relation between volume expansion and formaldehyde consumption during the formose reaction is qualitatively illustrated in Fig. 1. During the reaction, there was an initial temperature increase in the reaction mixture (22.5 to 24.5°C). This was followed by a temperature increase in the reaction mixture from 24.5 to 25.9°C during the sugar formation stage, and a subsequent temperature drop back to 22.5°C (ambient conditions). (In Fig. 2, expansion data were not converted to normalized temperature conditions, and this is reflected in the shape of the expansion curve.) Figure 2 indicates that (a) there was volume expansion in the reaction mixture as soon as the reagents were combined for reaction, (b) there was further volume expansion during the induction period (Cannizzaro product generation) and again during the sugar formation period (the onset of sugar formation is clearly indicated by a change of slope), and (c) the endpoint of the formose reaction coincided with a maximum of volume expansion followed by a contraction owing to equilibration of the reaction mixture with the lower temperature of the environment.
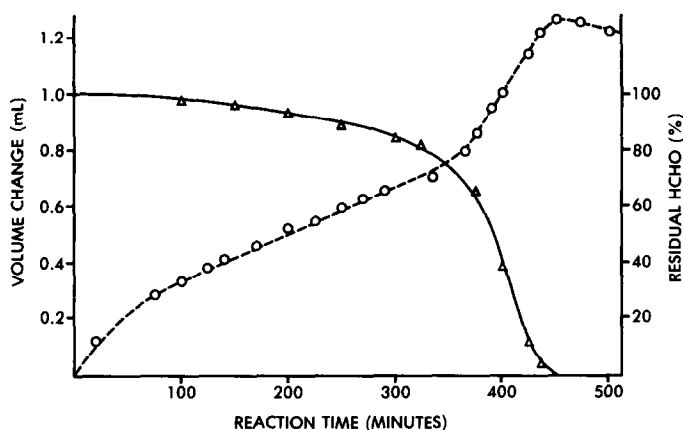
FIG. 1. Relationship of formaldehyde consumption and liquid volume expansion. Reaction conditions: 125 ml 1 M CaCl$_2$, 9.1 ml 13.76 M HCHO, 62.5 ml 1 M NaOH, water to 500 ml; room temperature. (○) Volume change, ml; (△) remaining formaldehyde, %.

Data were then normalized to a standard temperature of 20°C (Fig. 2). The volume expansion consisted of two linear sections; an expansion of about 0.067 ml/h during the induction period, and an expansion of 0.133 ml/h during the sugar formation period. The change of slope coincides with the change from the induction period to the sugar formation period. Maximum expansion was reached and maintained at the time of completion of the formose reaction.

The experiments, the results of which are presented in Figs. 1 and 2, were conducted with reaction mixtures which contained residual, uncomplexed calcium hydroxide and were, in the initial stage of the reaction, heterogeneous. The plot for volumetric ex-

pansion of a homogeneous formose reaction mixture (25) also consists of two linear portions (Fig. 3). The slopes are 0.096 ml/h for the induction period and 0.24 ml/h for the sugar formation period. The slope ratio is 0.4. The change of slope of the plot for volume expansion coincides with the onset of sugar formation. The volume expansion relative to formaldehyde consumption during the sugar formation period was about one sixth of the volume expansion during the induction period. Differences in the rate and degree of volume expansion (Fig. 2 vs Fig. 3) can be related to differences in the number of reacting molecules and ions versus product molecules and ions.

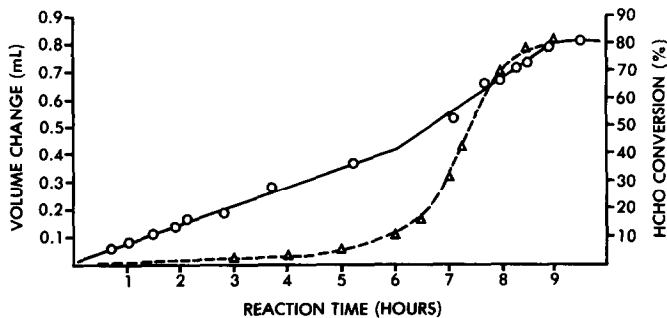Combining into one plot, the data for

FIG. 2. Normalization of liquid volume expansion data (Fig. 2) to standard temperature (20°C). (○) Volume change, ml; (△) formaldehyde conversion, %.
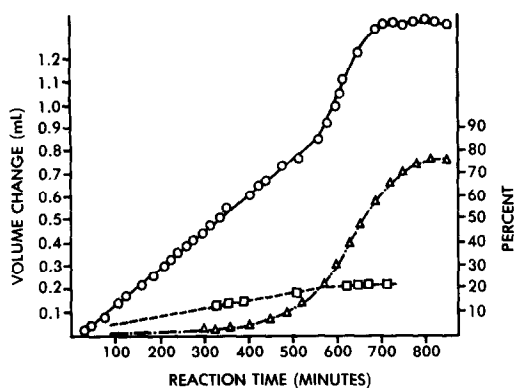
FIG. 3. Conversion of formaldehyde to sugars and Cannizzaro products and liquid volume expansion during a homogeneous formose reaction. (O) Volume change, ml; ($\triangle$) reducing sugars generated, %; ($\square$) Cannizzaro reaction products, %.

sugar formation from formaldehyde, for volume expansion during the reaction, for pressure change in the head space above the reaction mixture (24), and for the temperature of the reaction mixture (Fig. 4) reveals the coincidence of maximum expansion with the onset of pressure loss above the reaction mixture and the reaction temperature maximum. All three signal completion of the formose reaction, even though the requirement of different vessels

for gas pressure measurements, expansion readings, and sugar analysis results in some shift in the curves.

Because a volume contraction was observed when the various reagents required for the formose reaction were combined into a homogeneous reaction mixture and a similar effect was observed when formaldehyde was added to a solution of calcium chloride, a quantitative determination of the latter was undertaken in order to correlate it with the apparent coordination number of calcium monohydroxide ions relative to HCHO (Fig. 5). The volume reached a minimum at a $HCHO : CaCl_2$ mole ratio of about 3 and thereafter remained constant. The data indicates formation of a complex at a $HCHO : CaCl_2$ mole ratio of 3. This ratio agrees with the previously derived active complex ratio of $HCHO : Ca(OH)^+$ of 3 based on the turbidometric titration with sodium hydroxide of blends of $CaCl_2$ and HCHO in aqueous solutions (27).

The detection of weak complexes in solution is based on the blending of two (or more) equimolar solutions of reagents in various ratios and measuring properties which indicate the existence of a complex (26). The concentration of the complex will
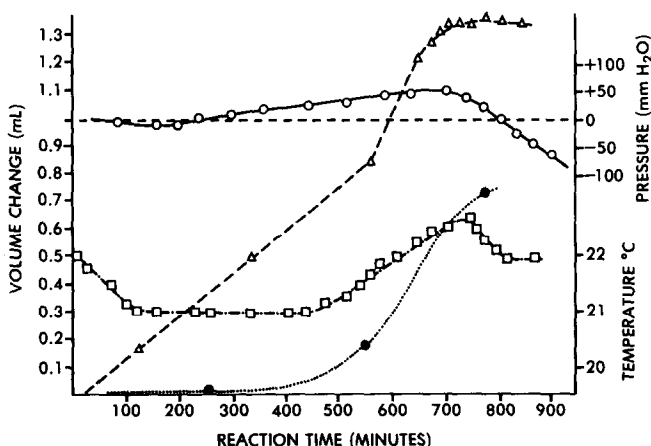

FIG. 4. Relationship of gas pressure changes above the reaction mixture and liquid volume expansion normalized to standard temperature (20°C) to the progress of the formose reaction. For reaction conditions, see legend to Fig. 2. (O) Gas pressure, mm H_2O; ($\triangle$) volume change, ml; ($\square$), temperature, °C; (●) reducing sugars generated. (No ordinate. Included to show the relationship of the other parameters to the progress of the reaction. Actual progress of the reaction is plotted in Fig. 3.)
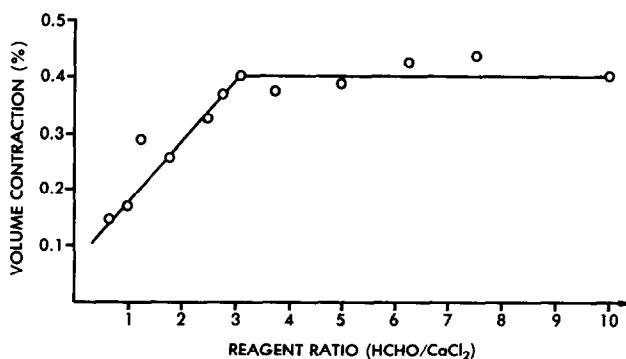
FIG. 5. Volume contraction in binary solutions of calcium chloride and formaldehyde as a function of reagent ratio.

be at a maximum when the solutions are blended in the same proportion as that in which the solutes are present in the complex. Data obtained in this way exhibited considerable scatter because of problems associated with measuring accurately such large volumes of liquids and because of the small contractions. Nevertheless, a plot of the data had a maximum at a HCHO : CaCl$_2$ ratio of 3–3.5, in agreement with the results of the buret method (plot not included).

In summary, the formose reaction is accompanied by a volume contraction during formation of a complex between calcium monohydroxide and methylene glycol, followed by two stages of volume expansion, which are linear with time, during the induction period (Cannizzaro reaction) and the sugar formation period. The transition between the two reaction periods is indicated by a change in the rate of liquid volume expansion. Expansion of the formose reaction mixture concurrent with the formation of Cannizzaro products and sugars is believed to be the result of (1) the release of water of hydration from methylene glycol during the disproportionation and condensation reactions, (2) the partial or total decomplexation of products, (3) the restructing of the water matrix, (4) the generation of a charged species (formate ion), and (5) the hydration of linear-chain and branched chain sugars. The observation of volume change allows direct monitoring of the progress of the formose reaction.

REFERENCES

1. Balezin, S. A., *Zh. Obshch. Khim.* **7**, 2099 (1937).
2. Balezin, S. A., *Izv. Akad. Nauk SSSR, Ser. Khim.*, 355 (1946).
3. Kuzin, A., *Zh. Obshch. Khim.* **8**, 759 (1938).
4. Balezin, S. A., *Zh. Obshch. Khim.* **17**, 2288 (1947).
5. Shigemasa, Y., Taji, T., Sakezawa, Ch., Nakashima, R., and Matsuura, T., *J. Catal.* **58**, 296 (1979).
6. Krylov, O. V., Sinyak, Yu. E., Berlin, An. A., and Shul'gina, I. L., *Dokl. Akad. Nauk SSSR* **199**, 643 (1971).
7. Runge, K., and Mayer, R., *Ann.* **707**, 161 (1967).
8. Gutsche, C. D., Redmore, D., Buriks, R. S., Nowotny, K., Grassner, H., and Armbruster, C. W., *J. Amer. Chem. Soc.* **89**, 1235 (1967).
9. Krindel, P., and Eliezer, I., *Coord. Chem. Rev.* **6**, 217 (1971).
10. Stillinger, F. H., *Science* **209**, 451 (1980).
11. Ben-Naim, A., and Vaslow, F., *in* "Water and Aqueous Solutions" (R. A. Horne, Ed.), pp. 425, 465. Wiley–Interscience, New York 1972.
12. Baran, V., *Coord. Chem. Rev.* **6**, 65 (1971).
13. Ahrland, S., and Bjoerk, N. O., *Coord. Chem. Rev.* **16**, 115 (1975).
14. Bennetto, H. P., and Caldin, E. F., *J. Chem. Soc. A*, 2198 (1971).
15. Spiro, T. G., Revesz, A., and Lee, J., *J. Amer. Chem. Soc.* **90**, 4000 (1968).
16. Bemiller, J. N., *in* "Starch: Chemistry and Technology" (R. L. Whistler and E. F. Paschall, Eds.), Vol. I, p. 309. Academic Press, New York, 1965.
17. Rendleman, J. A., Jr., *Adv. Carbohydr. Chem.* **21**, 209 (1966).

18. Angyal, S. J., and Davis, K. P., *Chem. Commun.*, 500 (1971).
19. Angyal, S. J., *Aust. J. Chem.* **25**, 1957 (1972).
20. Roy, N., and Mitra, A. K., *Carbohydr. Res.* **24**, 175, 180 (1972).
21. Monlik, S. P., and Khan, D. B., *Carbohydr. Res.* **41**, 93 (1975).
22. Maurer, H. W., Bemiller, J. N., and Smith, G. V., *J. Catal.* in press.
23. Weiss, A. H., La Pierre, R. B., and Shapira, J., *J. Catal.* **16**, 332 (1970).
24. Maurer, H. W., Bemiller, J. N., and Smith, G. V., *J. Catal.* **103**, 239 (1987).
25. Maurer, H. W., Bemiller, J. N., and Smith, G. V., *J. Catal.* in press.
26. Job, P., *Ann. Chim.* **9**, 113 (1928).
27. Suggett, A., *J. Solution Chem.* **5**, 33 (1976).

HANS W. MAURER*,[1]
JAMES N. BEMILLER*,[2]
GERARD V. SMITH*,‡

*Department of Chemistry and Biochemistry
and ‡Molecular Science Program,
Southern Illinois University at Carbondale,
Carbondale, Illinois 62901

[1] Current address: Laurel Research Laboratory, Westvaco Corporation, Johns Hopkins Road, Laurel, Md. 20707.
[2] Current address: Whistler Center for Carbohydrate Research, Purdue University, West Lafayette, Ind. 47907.