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The Prediction of the Optical Resolution Process by the Use of the Preferential Crystallization Procedure

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In the optical resolution of DL-serine *m*-xylene-4-sulfonate dihydrate by the preferential crystallization procedure, the prediction of the resolution process was studied. The solution saturated with the DL-form at 20 °C was cooled under a programmed cooling pattern and was seeded with the L-isomer. The decrease in the concentration of the L-isomer during the process was predicted by a conventional calculation method. Then, the waiting time for the spontaneous crystallization of the D-isomer was predicted by using the limiting values of the first and the second metastable regions, which were discussed in a previous report. As a result, a good agreement was obtained between the predicted results and the experimental results.

In the previous report,[1] the waiting time for the spontaneous crystallization of the unseeded isomer was investigated in an attempt to perform successfully the optical resolution DL-serine *m*-xylene-4-sulfonate dihydrate (DL-Ser·mXS·$2H_2O$) by the preferential crystallization procedure. As a result, it was found that the spontaneous crystallization of the unseeded isomer did not occur until the value of S_{II} expressed by the equation of $S_{II}=\int_0^{\theta n} f(C_D-C_S-S_I)\mathrm{d}\theta$ reached a constant value independent of the cooling speed and the lowest arrival temperature. Here, S_I and S_{II} are the limiting values of the first and the second metastable regions for the unseeded D-isomer respectively: C_D, the concentration of the D-isomer; C_S, the solubility of the D-isomer; f, the correction factor approximated by C_D/C_L; θ, the cooling time; and θn, the waiting time for the spontaneous crystallization of the unseeded D-isomer. Therefore, the waiting time for the spontaneous crystallization of the unseeded D-isomer might be predicted if the increase in the supersaturation degree due to cooling and the decrease in the concentration of the seeded L-isomer due to preferential crystallization were previously known.

In the present paper, the decrease in the concentration of the seeded L-isomer in the optical resolution process of DL-Ser·mXS·$2H_2O$ under given cooling conditions was predicted according to the usual methods.[2–4] Then, the waiting time for the unseeded D-isomer, θn, was predicted from the above equation by using the values of S_I and S_{II} determined in the previous report. As a result, a good agreement was obtained between the predicted results and the experimental results.

Materials and Methods

Materials, Apparatus, and Analytical Methods. The materials, experimental apparatus, analytical methods, expression of the supersaturation degree, and operation of the preferential crystallization procedure were described in the previous report.[1]

Cooling Methods. The solution for preferential crystallization was cooled under cooling patterns previously programmed. Two cooling patterns were used. One was cooled at the rate of 1/8 °C per min and maintained at 12.0 °C. The other was cooled at the rate of 1/2 °C per min and maintained at 14.5 °C.

Prediction of the Decrease in the Concentration of the Seeded L-*Isomer*, C_L. The crystal growth rate of the seeded L-isomer in the process of preferential crystallization can be expressed as the following general equation:[2–4]

$$-\frac{\mathrm{d}C_L}{\mathrm{d}\theta}=aK(C_L-C_S)^n, \tag{1}$$

where C_L is the concentration of the L-isomer; K, the overall crystal-growth coefficient; a, the surface area of the crystals; n, the crystal-growth rate order; and C_S, the solubility of the L-isomer as a function of the temperature, t. The value of a increases with the growth of the seed crystals. In this report, it was assumed that a increased in proportion to $(W/W_0)^{2/3}$,[2] namely:

$$a=(W/W_0)^{2/3}\cdot a_0, \tag{2}$$

where W_0 is the initial weight of the seed crystals, W is the weight of the crystals at time θ, and a_0 is the initial surface area corresponding to W_0.

Substituting Eq. 2 into Eq. 1 gives:

$$-\frac{\mathrm{d}C_L}{\mathrm{d}\theta}=\left(\frac{W}{W_0}\right)^{2/3}\cdot a_0K\cdot(C_L-C_S)^n. \tag{3}$$

Taking logarithms, Eq. 3 gives:

$$\log\left\{\left(-\frac{\mathrm{d}C_L}{\mathrm{d}\theta}\right)\Big/\left(\frac{W}{W_0}\right)^{2/3}\right\}=n\log(C_L-C_S)+\log a_0K. \tag{4}$$

Equation 4 means that the plot of $\log\{(-\mathrm{d}C_L/\mathrm{d}\theta)/(W/W_0)^{2/3}\}$ against $\log(C_L-C_S)$ is a straight line, and that the values of n and a_0K can be evaluated from the slope and the intercept of the straight line respectively. In order to determine the values of a_0K and n, the time course of the decrease in C_L was obtained under the following conditions. The supersaturated solution of DL-Ser·mXS·$2H_2O$ (936 g) and water (1300 g) was maintained at a constant temperature of 14.5 °C or 12.0 °C, seeded with 2 g of L-Ser·mXS·$2H_2O$ (100—200 meshes), and allowed to crystallize. From the slope of the tangent on the time course of the decrease in C_L, the value of $(-\mathrm{d}C_L/\mathrm{d}\theta)$ was determined. The value of W was calculated from the decrease of C_L. A plot of $\log\{(-\mathrm{d}C_L/\mathrm{d}\theta)/(W/W_0)^{2/3}\}$ against $\log(C_L-C_S)$ gave a straight line, as is shown in Fig. 1. Then, the values of n and a_0K could be

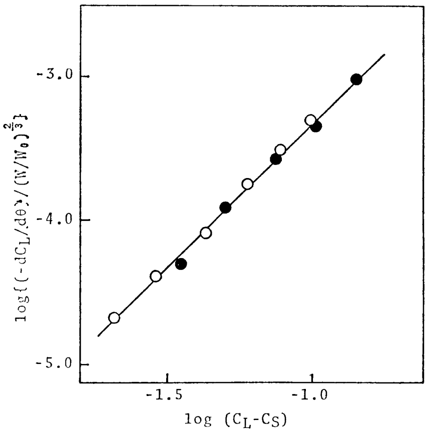

Fig. 1. Plots of $\log\{(-dC_L/d\theta)/(W/W_0)^{2/3}\}$ against $\log(C_L-C_S)$.
○: 14.5 °C, ●: 12.0 °C.

determined from the straight line; they were $n=2$[—] and $a_0K=6.49\times10^{-2}$ [min^{-1}].

On the other hand, the relationship between C_S in Eq. 3 and t was already obtained in the previous report at the following empirical equation:

$$\log C_S = 2.34 \times 10^{-2}t - 9.12 \times 10^{-1}. \tag{5}$$

Since the solution is cooled under a programmed pattern, t is already given. Therefore, C_S is known.

Consequently, the decrease in C_L due to preferential crystallization can be predicted by means of calculations based on Eq. 3 on the assumption that the n and K obtained above are constant during the preferential crystallization procedure.

Prediction of Waiting Time for the Spontaneous Crystallization of the D*-Isomer, θn.* The previous report showed that the supersaturation state of the unseeded D-isomer in the actual resolution process on the solution saturated with DL-Ser·mXS·2H$_2$O at 20 °C was stable until the value of S_{II} in Eq. 6 reached 4.49 [g·min/g(water)].

$$S_{II} = \int_0^{\theta n} f(C_D - C_S - S_I)\,d\theta, \tag{6}$$

where the integration is restricted to cases of $C_D - C_S \geqq S_I$; f is the correction factor against the change in the ratio of C_L/C_D, which may be empirically approximated by $f=C_D/C_L$, judging from the result of our previous report.

The values of S_I and S_{II} are known to be 6.6×10^{-2} [g/g(water)] and 4.49 [g·min/g(water)] respectively; C_D is the initial concentration until the spontaneous crystallization takes place, C_S is obtainable from Eq. 5, and f is also obtainable because C_L is obtained from Eq. 3. Therefore, the waiting time for the spontaneous crystallization of the D-isomer can be predicted by calculating θn from Eq. 6.

Results and Discussion

As an example, it was assumed that the optical resolution of DL-Ser·mXS·2H$_2$O was carried out as follows. DL-Ser·mXS·2H$_2$O (936 g) was dissolved in water (1300 g) by heating it at 35 °C for one hour in a 2*l*-cylindrical glass vessel. The solution was then stirred at a constant speed (210 rpm), subsequently cooled at the rate of 1/8 °C per min, and thereafter maintained at 12.0 °C. Two grams of L-Ser·mXS·2H$_2$O (100—200 meshes) was seeded at 20 °C in the course of cooling, and only the L-isomer was preferentially crystallized.

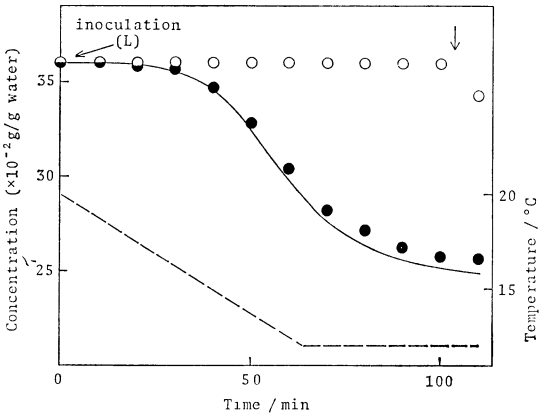

Fig. 2. Comparison between calculated results and experimental data in the optical resolution process of DL-Ser·mXS·2H$_2$O.
——: Calculated curve, ○, ●: experimental data of concentrations of D-isomer (○) and L-isomer (●), ↓: predicted point of spontaneous crystallization of D-isomer, — — — —: temperature curve programmed so as to cool at the rate of 1/8 °C per min to 12 °C.

In order to calculate the decrease in the concentration of the L-isomer according to Eqs. 3 and 5, the numerical values of the constants in those equations were obtained as has been described in the section on Materials and Methods. The product of the overall crystal-growth coefficient and the surface area of the seed crystals, a_0K, was 6.49×10^{-2} [min^{-1}]; the crystal-growth rate order was $n=2$ [—].

Under the present experimental conditions, the initial values of C_L, C_D, and W were 0.360 [g/g (water)], 0.360 [g/g(water)], and 0.00154 [g/g(water)] respectively. Using these values and according to Eqs. 3 and 5, the decrease in C_L due to the preferential crystallization of the L-isomer under the programmed cooling pattern described above was calculated. The calculated result for the decrease of C_L is shown in Fig. 2.

To predict the waiting time for spontaneous crystallization, θn, the value of S_{II} was caluclated according to Eq. 6. The waiting time, θn, at which the value of S_{II} reached 4.49 [g·min/g(water)] was 104 [min]. That is, it was predicted that the spontaneous crystallization of the unseeded D-isomer would occur 104 min after the time of inoculation of the L-isomer, as is shown in Fig. 2.

On the other hand, the actual resolution was carried out under the same conditions as have been described in the above illustrative example. The experimental data are also plotted, together with the predicted results, in Fig. 2, indicating that these were in good agreement.

As another example, the prediction of the preferential crystallization process was carried out on the assumption that the solution was cooled at the rate

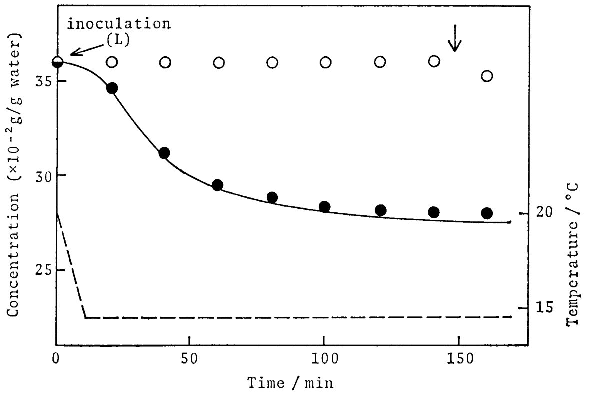

Fig. 3. Comparison between calculated results and experimental data in the optical resolution process of DL-Ser·mXS·$2H_2O$.

——: Calculated curve, ○, ●: experimental data of concentrations of D-isomer (○) and L-isomer (●), ↓ : predicted point of spontaneous crystallization of D-isomer, — — —: temperature curve programmed so as to cool at the rate of 1/2 °C per min to 14.5 °C.

of 1/2 °C per min and thereafter maintained at 14.5 °C. The results ($\theta n = 148$ [min]), predicted in the manner described above, and the experimental data are shown in Fig. 3, indicating that these were also in good agreement.

These results show that the our quantitative approach to ascertaining the limit of the metastable region in the preferential crystallization process is proper and that the waiting time for the spontaneous crystallization of the unseeded isomer can be successfully predicted. Although we did not study the optimization of the optical resolution process of DL-Ser·mXS·$2H_2O$, it seems to be possible to do so by the method presented here. It would also be interesting to learn whether such a prediction method can be applied for the optical resolution processes of other racemic mixtures.

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