3566 © 1983 The Chemical Society of Japan Bull. Chem. Soc. Jpn., 56, 3566—3570 (1983) [Vol. 56, No. 12

Mechanochemical Change in the Solid State of Hexobarbital

Akiko IKEKAWA* and Sohachiro HAYAKAWA†
Faculty of Pharmaceutical Sciences, Showa University, Hatanodai, Shinagawa-ku, Tokyo 142
†*Department of Applied Physics, Faculty of Science, Tokyo Institute of Technology, Oh-okayama, Meguro-ku, Tokyo 152*

(Received April 26, 1983)

The effect of ball-milling on X-ray diffraction diagrams, IR spectra, DTA and DSC thermograms of hexobarbital was investigated. It was found that the regularity at the crystal part changed upon ball-milling without any diluent. In addition to this change, an amorphous part increased upon ball-milling with microcrystalline cellulose (MCC). The solubility in a KH_2PO_4–Na_2HPO_4 buffer solution (pH 6.0) also increased upon ball-milling with MCC, though the solubility did not change without MCC. The analysis of IR spectra indicated that hydrogen bonds were formed between the C=O group of hexobarbital and the OH group of MCC upon ball-milling. Both the increase in the amorphous part and solubilization of hexobarbital upon ball-milling were attributed to the stabilization of the amorphous state caused by the interaction with MCC.

Previously, the change in the solid state of amobarbital upon ball-milling, both with and without any diluent, was investigated.[1–3] In this paper, the change in the solid state of hexobarbital upon ball-milling was discussed.

Experimental

The materials used were microcrystalline cellulose (MCC) described in a previous paper[4] and hexobarbital [5-(1-cyclohexenyl)-1,5-dimethyl-2,4,6(1*H*, 2*H*, 3*H*)-pyrimidinetrione] supplied from Teikoku Kagaku Sangyo Co.

A sample was inserted in a stainless-steel mill (in diameter of 10 cm and in capacity of 900 cm^3) containing 30 stainless-steel balls (with true density of 8.2 g/cm^3 and in diameter of 1.9 cm) and 10 balls of diameter of 2.5 cm. The mill was rotated at the velocity of 120 min^{-1}. The ball-milled samples are 10 g of MCC, 10 g of hexobarbital, a mixture of 1 g of hexobarbital and 9 g of MCC, and a mixture of 3 g of hexobarbital and 7 g of MCC.

The following measurements were carried out in the way reported previously; X-ray diffraction diagrams, DTA and DSC thermograms, IR spectra by the use of Nujol method, and particle size distribution of hexobarbital.[4] Solubility of hexobarbital in various samples in KH_2PO_4–Na_2HPO_4 buffer solution (pH 6.0, ionic strength 0.08) at 30 °C was obtained from the absorbance at 219 nm as described in the previous paper.[4]

Results and Discussion

Ball-milling without Any Diluent. *X-Ray Diffraction*: Figure 1 shows the effect of ball-milling without any diluent on X-ray diffraction diagrams of hexobarbital. The diffraction intensities of the lines at 8.4°, 11.1, 15.8, and 23.2° of 2θ decreased and those of the lines at 14.5 and 17.3° of 2θ increased by ball-milling. Fine powders were obtained on evaporation of an ethanol solution or a chloroform solution of hexobarbital under reduced pressure. The differaction diagram of the powders obtained from an ethanol solution was similar to the diagram for original hexobarbital, and the diagram for the powders obtained from a chloroform solution was similar to the diagram for ball-milled hexobarbital. It is clear from this fact that the change in the diffraction intensities in Fig. 1 is not attributed to the decrease in particle size. The locations of the lines were little influenced by ball-milling. The presence of polymorphs for hexobarbital has not been reported yet. These facts suggest that the regularity at the crystal part of hexobarbital changes by ball-milling.

The mean values of the lattice disturbance amplitude, $\overline{U_x''}$, were obtained, using all the combinations of the two of the diffraction intensities of the lines at 8.4, 11.1, 14.3, 15.8, 17.3, and 23.2—23.5° of 2θ.[5] As is shown in Fig. 2, $\overline{U_x''}$ was at a minimum at the ball-milling time around 1—5 h. Each line was indexed as is shown in Fig. 1, on the basis of the crystal structure reported by

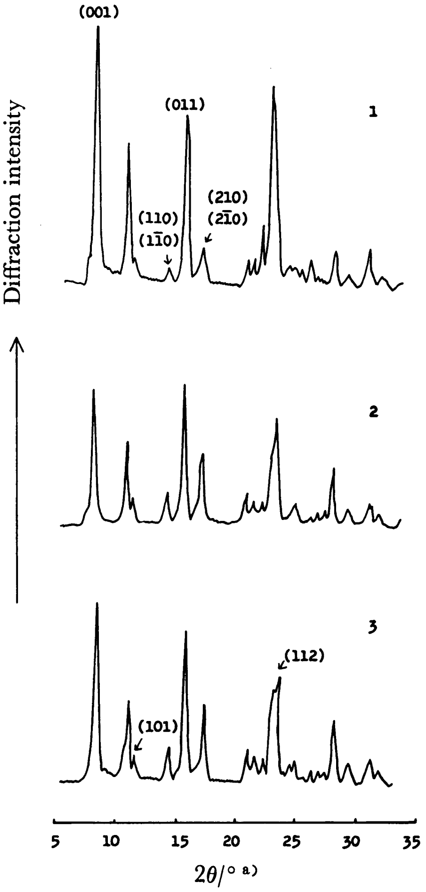

Fig. 1. Effect of ball-milling without any diluent on a X-ray diffraction diagram of hexobarbital.
Ball-milling time/h: 1 ; 0, 2 ; 0.5, 3 ; 60.
a) 2θ is the angle between the incident X-ray and the scattering X-ray.

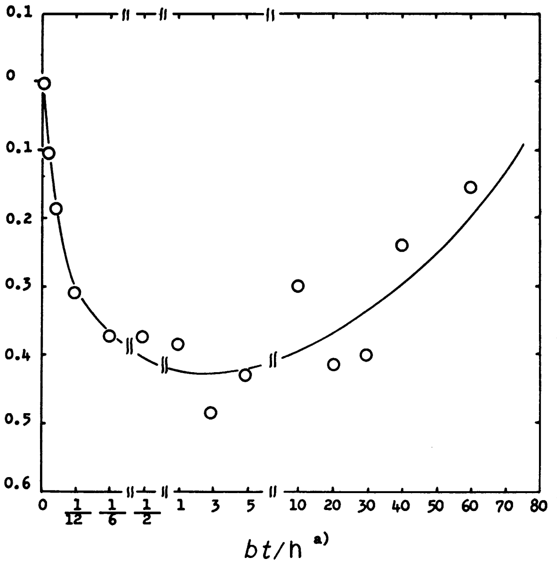

Fig. 2. Variation in $\overline{U_x}''$ with ball-milling in the absence of any diluent.
a) *bt* is the ball-milling time.

Jean-Pierre Bideau *et al.* ($P2_1/c$, a=16.79 Å, b=6.65 Å, c=11.02 Å, β=108° 17′).[6] These results suggest that the regularity at the crystal part increases in the first stage of ball-milling and that the regularities in (110), $(1\bar{1}0)$, $(2\bar{1}0)$, and (210) planes increase more remarkably than those in the other planes. It is also shown that the regularity decreases upon ball-milling for more than 10 h.

The crystallinity obtained by the Ruland's method[7] was little influenced by ball-milling.

IR Spectra: Figure 3 shows the effect of ball-milling without any diluent on IR spectra of hexobarbital. The absorbances at 3240 and 1720 cm^{-1} regions increased upon ball-milling. The absorbance at each of the wave number, ν, was determined, assuming the transmittance on the straight line, passing through 3400 and 1900 cm^{-1} or 1900 and 900 cm^{-1}, to be 100%. In Fig. 4, $R_{\nu,\nu'}$ is the ratio of the absorbance at the wave number of ν to the absorbance at ν'. The $R_{3240,3210}$ and $R_{1720,1660}$ values increased and the $R_{\nu,1660}$ values (ν/cm^{-1}=1670—1705, 1730—1740) decreased upon ball-milling.

In the IR spectra of barbituric acid derivatives, the band at 3000—3600 cm^{-1} region is assigned to be due to the NH stretching vibration. The absorption of free NH in the solid state of phenobarbital is observed at 3310 cm^{-1}, and this band shifts to lower frequency by hydrogen bonding. The three bands at 1600—1800 cm^{-1} region is assigned to the stretching vibrations of the C=O groups. In the spectra of hexobarbital, the highest frequency band at 1740—1750 cm^{-1} is assigned to the C=O group at the 2-position, the middle frequency band to the C=O group at the 4-position, and the lowest frequency band to the C=O at the 6-position. The absorption band due to the free C=O at the 4-position is around 1730 cm^{-1}, and the band due to the free C=O in the 6-position is around 1700 cm^{-1}. These bands shift to lower frequency by hydrogen bonding. It is also reported that the C=O group in the 6-position of hexobarbital forms hydrogen bonds with the NH group in the solid state.[8]

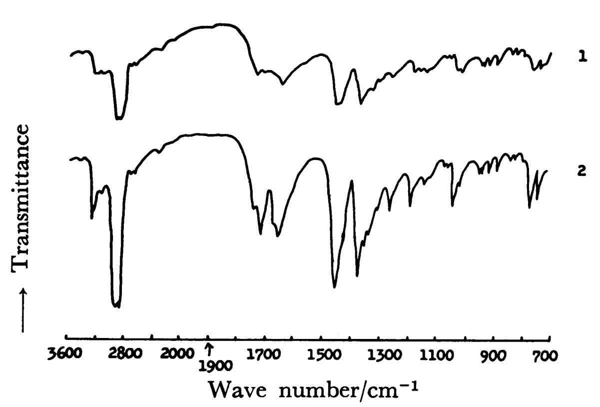

Fig. 3. Effect of ball-milling without any diluent on IR spectra of hexobarbital.
1: Original hexobarbital, 2: hexobarbital ball-milled for 60 h without any diluent.

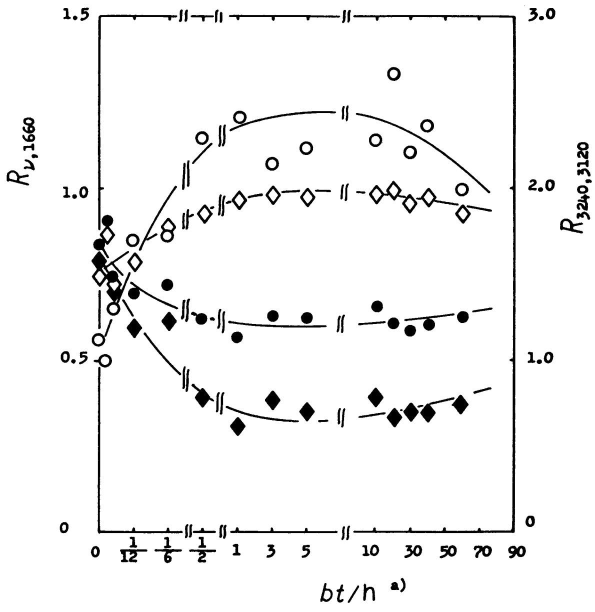

Fig. 4. Variation in $R_{\nu,\nu'}$ for hexobaribital with ball-milling in the absence of any diluent.
(ν/cm^{-1})/(ν'/cm^{-1}): 1740/1660(●), 1720/1660 (◇), 1690/1660(◆), 3240/3120(○).
a) *bt* is the ball-milling time.

It is suggested from the above results that the 4-carbonyl groups free from hydrogen bonding with the NH groups increased by ball-milling. The bands at 1020—1060 cm^{-1} due to the skeletal vibration[8] also changed upon ball-milling; this is also considered to be due to the change in hydrogen bonding. As is shown in Figs. 2 and 4, the variation in $\overline{U_x}''$ with ball-milling is parallel to the variation in $R_{\nu,\nu'}$; this fact suggests that the variation in hydrogen bonding due to ball-milling is related to the variation in the regularity at the crystal part.

No difference was observed before and after ball-milling in the melting point, the heat of fusion, and the solubility of hexobarbital in KH_2PO_4–Na_2HPO_4 buffer solution (pH 6.0) at 30 °C.

Particle Size: In Fig. 5, D_{50} is a median diameter by

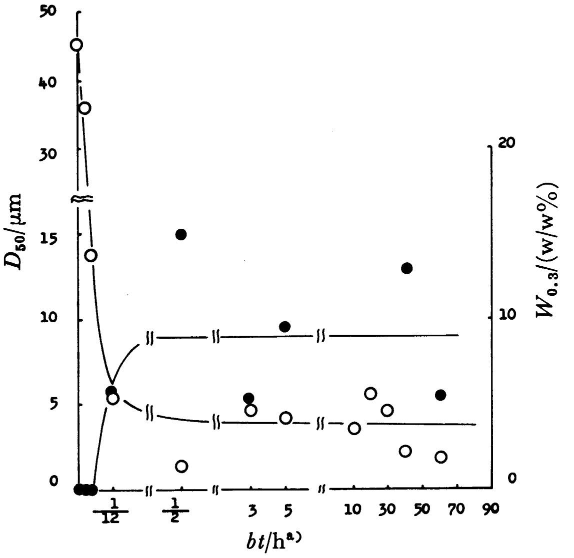

Fig. 5. Variation in particle size of hexobarbital with ball-milling in the absence of any diluent.
○: D_{50}, ●: $W_{0.3}$.
a) *bt* is the ball-milling time.

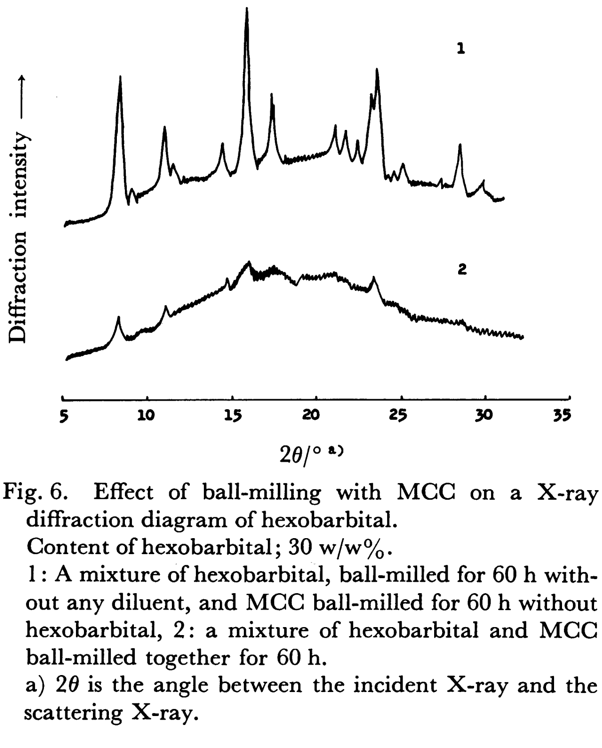

Fig. 6. Effect of ball-milling with MCC on a X-ray diffraction diagram of hexobarbital.
Content of hexobarbital; 30 w/w%.
1: A mixture of hexobarbital, ball-milled for 60 h without any diluent, and MCC ball-milled for 60 h without hexobarbital, 2: a mixture of hexobarbital and MCC ball-milled together for 60 h.
a) 2*θ* is the angle between the incident X-ray and the scattering X-ray.

weight base and $W_{0.3}$ is the weight fraction of the particles smaller than 0.3 μm in diameter. The D_{50} and $W_{0.3}$ values of hexobarbital varied in the first stage, and they stayed nearly constant after ball-milling for more than 30 min. The variations in D_{50} and $W_{0.3}$ with ball-milling were parallel to the variation in $\overline{U_x}''$ and $R_{\nu,\nu}'$ in the first stage. Probably, the change in the regularity at the crystal part becomes remarkable when the particles are broken.

Ball-milling with MCC. *X-Ray Diffraction*: The ratio of the diffraction intensity at 17.3° of 2*θ* to the intensity at 15.8° of 2*θ* increased at the first stage of ball-milling. As is shown in Fig. 6, the diffraction intensities for hexobarbital decreased gradually upon ball-milling with MCC. The crystallinity, x_{cr}, for hexobarbital ball-milled for 60 h without any diluent, was 0.92 as determined by the Ruland's method.[7] The x_{cr} values of hexobarbital in the ball-milled mixture with MCC were determined from the ratio of the intensity of the diffraction lines in the range of 10—20° of 2*θ* to the intensity for the mixture of hexobarbital (ball-milled for 60 h without any diluent) and MCC, for the diffraction lines were overlapped with those of MCC in the range of 20—30° of 2*θ* in the first stage of ball-milling. The x_{cr} value decreased upon ball-milling and the rate in the first stage was larger for the mixture containing larger amount of MCC. (Fig. 7)

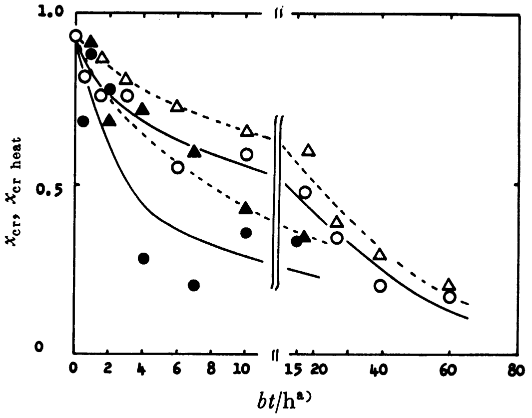

Fig. 7. Effect of ball-milling with MCC on the solid state of hexobarbital.

Content of hexobarbital/(w/w%)	x_{cr}	$x_{cr\ heat}$
10	●	▲
30	○	△

a) *bt* is the ball-milling time.

Heat of Fusion: The heat of fusion, ΔH_{obsd}, for hexobarbital decreased from 27.6 kJ/mol to 6.7 kJ/mol upon ball-milling the mixture with MCC containing 30 w/w% of hexobarbital for 60 h. The peak of fusion of hexobarbital disappeared upon ball-milling the mixture containing 10 w/w% of hexobarbital for more than 30 h. The ΔH_{obsd} value did not change upon ball-milling without any diluent, though the regularity at the crystal part slightly changed. Assuming that ΔH_{obsd} for the amorphous part is zero, the crystallinity of hexobarbital ($x_{cr\ heat}$) is obtained from Eq. 1.

$$x_{cr\ heat} = (\Delta H_{obsd}/27.6) \times 0.93 \qquad (1)$$

As is shown in Fig. 8, the $x_{cr\ obsd}$ values were nearly identical with the x_{cr} values.

Melting Point: In Fig. 8, T_1 is the temperature at which the peak of fusion starts, T_2 is the melting point, and T_3 is the temperature at the intersecting point of the base line and the extension of the line behind the peak. The peak of fusion of hexobarbital was broadened, and T_1, T_2, and T_3 were lowered by ball-milling with MCC, though the peak was not influenced upon ball-milling without any diluent. In Figs. 7 and 9, parallel relationship is seen between the lowering of these temperatures and the decrease in x_{cr} by ball-milling; this

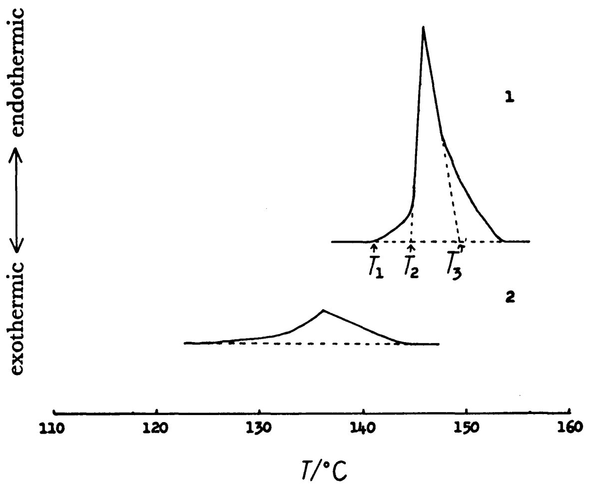

Fig. 8. DTA thermograms of hexobarbital ball-milled with MCC.

Content of hexobarbital/30 (w/w%)	Ball-milling time/h
1	0
2	40

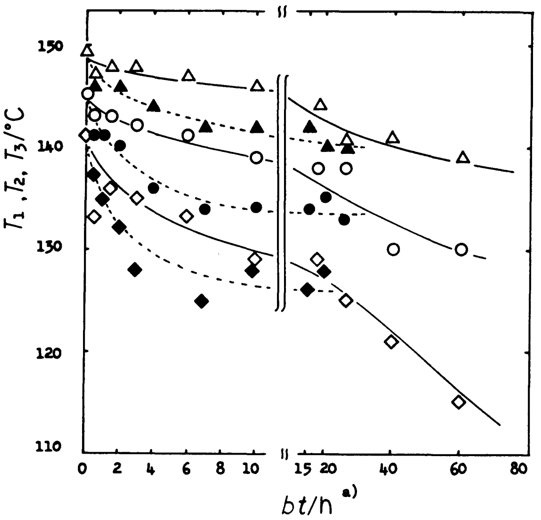

Fig. 9. Influence of ball-milling with MCC on T_1, T_2, and T_3.

Content of hexobarbital/(w/w%)	T_1	T_2	T_3
10	◆	●	▲
30	◇	○	△

a) *bt* is the ball-milling time.

result shows that the lowering of the temperatures is attributable to the increase in the amorphous part.

IR Spectra: Figure 10 shows the effect of ball-milling on IR spectra of the mixtures of hexobarbital and MCC. The absorbances around 1670—1730 and 1110 cm^{-1} regions increased upon ball-milling. The absorbance at 3400 cm^{-1} region also increased for the mixture containing 30 w/w% of hexobarbital. The band around 1670—1730 cm^{-1} corresponds to the stretching vibration of the C=O groups of hexobarbital.[8] In the IR spectra of the cellulose derivatives, the band around 3400 cm^{-1} region was assigned to the stretching mode of hydrogen-bonded OH groups.[9] The intensities and

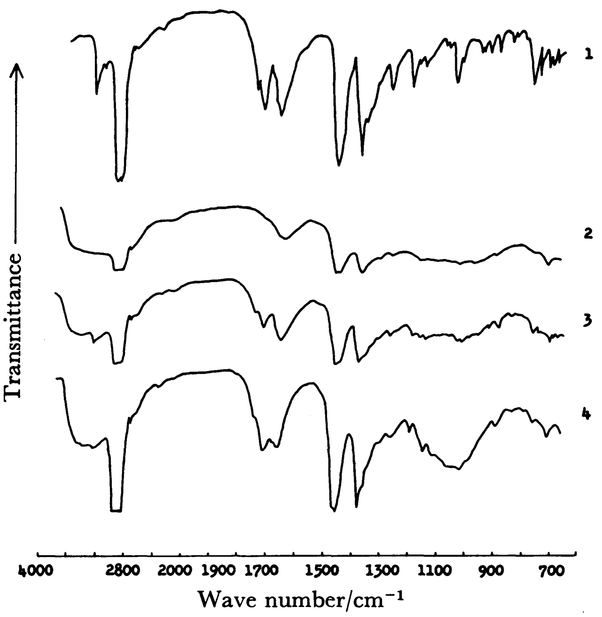

Fig. 10. Influence of ball-milling on IR spectra of a mixture of hexobarbital and MCC.

1: Hexobarbital ball-milled for 60 h without any diluent, 2: MCC ball-milled for 60 h without hexobarbital, 3: a mixture of "1" and "2" in the ration of 3 : 7 by weight, 4: a mixture of 3 g of hexobarbital and 7 g of MCC ball-milled together for 60 h.

frequencies of this band was reported to be affected by the difference in a hydrogen-bonding system.[10] The band at 1110 cm^{-1} was assigned to the C–O stretching mode, perphaps coupled to the C–C frequency. This band was also reported to change with the variation in the hydrogen-bonding system.[9–11] These facts indicate that hydrogen bonds are formed between the C=O groups of hexobarbital and the OH group of MCC. The variation in the skeletal vibration of hexobarbital around 1045 cm^{-1} is probably due to the change in the hydrogen bonds of the C=O groups.[8]

The absorbance at each of the wave numbers, ν, was determined, assuming that the transmittance on the straight line passing through 1850 and 800 cm^{-1} was 100%. In Fig. 11, $R_{1740,1660}$ was little influenced by ball-milling. $R_{\nu,1660}$ values (ν/cm^{-1}=1675—1735) were affected slightly in the first stage, and they increased after ball-milling for more than 10 h. This tendency was remarkable at the range of 1690—1700 cm^{-1}. These results show that the 4-carbonyl group of hexobarbital forms hydrogen bonds with MCC upon ball-milling and that the absorbance of hexobarbital at 1730 cm^{-1} shifts to the lower frequency.

Solubility: A suspension of the ball-milled mixture in KH_2PO_4–Na_2HPO_4 buffer solution (pH 6.0) was shaken at 30 °C, and the concentration of hexobarbital in the filtrate of the suspension was measured. The concentration stayed nearly constant after shaken for more than 15 min. In Fig. 12, $c_{20\mathrm{min}}$ is the concentration for the suspension shaken for 20 min. The $c_{20\mathrm{min}}$ value was little influenced in the first stage of ball-milling, and the value increased after ball-milling for more than 10 h. The variation in $c_{20\mathrm{min}}$ with ball-milling was parallel to the variation in $R_{\nu,1660}$ (ν/cm^{-1}=1665—1735)

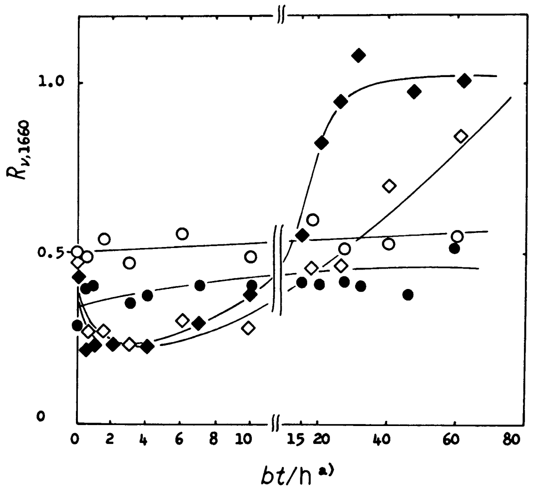

Fig. 11. Variation in $R_{\nu,1660}$ with ball-milling.

	ν/cm^{-1}	
Content of hexobarbital/(w/w%)	1740	1690
10	●	◆
30	○	◇

a) *bt* is the ball-milling time.

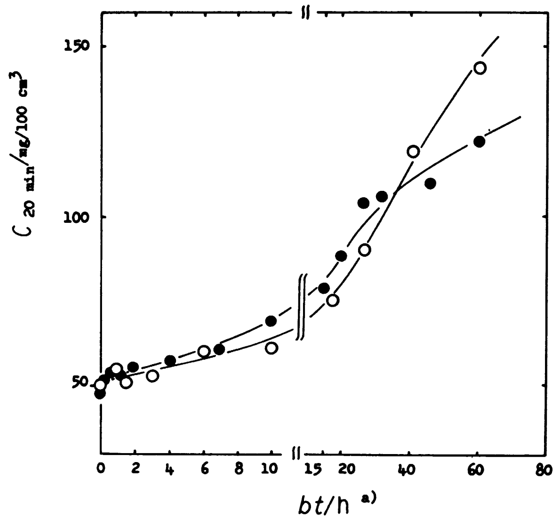

Fig. 12. Variation in $c_{20\mathrm{min}}$ upon ball-milling with MCC. Content of hexobarbital/w/w%: ○; 10, ●; 30.
a) *bt* is the ball-milling time.

The increase in the solubility of hexobarbital upon ball-milling is probably due to the interaction with MCC.

In the previous paper, amobarbital was ball-milled with such diluents as methylcellulose (MC) and dextran. Solubility of amobarbital in distilled water increased upon ball-milling with diluents, though it increased only slightly in the absence of any diluent. The analysis of the IR spectra indicated that hydrogen bonds were formed between the C=O groups of amobarbital and the OH groups of the diluents by ball-milling. MC and dextran are both soluble in distilled water. After the suspension of the mixture with MC or dextran in distilled water had been set aside for a week after the time of preparation, the solid state of amobarbital undissolved in the suspension was compared with the state before dissolution. From this comparison, it was shown that the presence of diluent in the ball-milled mixture prevented the amorphous part to be crystallized. It was concluded from the above results that the increase in the solubility of amobarbital upon ball-milling was attributed to the stabilization of the amorphous state caused by the interaction with diluents.[3] It is analogized from these results in the previous paper[3] that the increase in the amorphous part and in the solubility of hexobarbital upon ball-milling are both due to the stabilization of the amorphous state caused by the interaction with MCC, though these could not be confirmed experimentally because of poor solubility of MCC in distilled water.

The authors are grateful to Mrs. Mayumi Tobe, one of the members of the Analytical Center of Showa University, for the measurement of IR spectra.

References

1) A. Ikekawa and S. Hayakawa, *Bull. Chem. Soc. Jpn.*, **54**, 2587 (1981).

2) A. Ikekawa and S. Hayakawa, *Bull. Chem. Soc. Jpn.*, **55**, 1261 (1982).

3) A. Ikekawa and S. Hayakawa, *Bull. Chem. Soc. Jpn.*, **55**, 3123 (1982).

4) N. Kaneniwa, A. Ikekawa, and M. Sumi, *Chem. Pharm. Bull. (Tokyo)*, **26**, 2734, 2744 (1978).

5) T. Kubo, "Mekanokemisutori Gairon," Tokyo Kagaku Dojin, Tokyo (1978), p. 18.

6) Jean-Pierre Bideau, F. Leroy, and J. Housty, *C. R. Acad. Sci. Paris*, *t.* **271**, 500 (1970).

7) W. Ruland, *Acta Crystallogr.*, **14**, 1180 (1961).

8) R. J. Mesley, *Spectrochim. Acta, Part A*, **26**, 1427 (1970).

9) H. G. Higgins, G. M. Stewart, and K. J. Harrington, *J. Polym. Sci.*, **51**, 59 (1961).

10) J. H. Keighley and S. N. Pandey, *J. Text. Inst.*, **1**, 23 (1976), R. H. Marchessault and C. Y. Liang, *J. Polym. Sci.*, **43**, 71 (1960).

11) M. L. Nelson and R. T. O'Connor, *J. Appl. Polym. Sci.*, **8**, 1311 (1964).