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Stability of Solid Dosage Forms. I. Hydrolysis of Meclofenoxate Hydrochloride in the Solid State

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The kinetics of hydrolysis of mechlofenoxate hydrochloride (MF-HCl) into *p*-chlorophenoxyacetic acid (CPA) and dimethylaminoethanol hydrochloride (DMAE-HCl) in the solid state were studied with respect to the effect of temperature (50 to 80°C) and humidity (20 to 80%RH).

The degradation ratio, x at the initial stage could be correlated to time by the equation

$$x = kt^n$$

where k and n are parameters. The degradation at the later stage was found to conform to first-order kinetics. The following mechanism is proposed: at a humidity below the CRH of MF-HCl, water vapor initiates the hydrolysis of MF-HCl into CPA and DMAE-HCl on the surface of the solid by a gas-solid reaction. Once DMAE-HCl is produced, water starts to be adsorbed and forms a sorbed moisture layer, in which intact MF-HCl dissolves, diffuses and decomposes. After being completely dissolved, MF-HCl decomposes in an apparent first-order reaction. At a humidity above CRH, on the other hand, water is adsorbed rapidly on the surface of the solid and MF-HCl appears to decompose in solution from the beginning. The decomposition is not a first-order reaction because of the incompleteness of the dissolution and diffusion at the initial stage, but becomes first-order at the later stage.

Keywords——meclofenoxate hydrochloride; stability; hydrolysis in solid state; kinetics; mechanism; water vapor pressure

Difficulties in predicting the drug stability in solid dosage forms have often been experienced because the reaction in the solid state is affected by many variables, and the mechanisms involved are not fully understood at present.

Many attempts have been reported to interpret the mechanisms involved in the degradation of pharmaceutical solids on the basis of the theoretical models proposed by Prout and Tompkins[1] and Jandar[2] (contracting sphere model), or by Prout and Tompkins,[3] Carstensen,[4] and Kawakita[5] (nucleation model). However, the degradation mechanisms for most pharmaceutical solids are still obscure.

Regarding the effect of water on the degradation of pharmaceutical solids, many interpretations have been attempted on the basis of theories such as the sorbed moisture layer model proposed by Leeson and Mattocks.[6] For the decomposition of water-soluble drugs, however, most of these studies have been carried out with solid dosage forms containing various excipients, and not with pure solid drugs. Therefore the conclusions may not be of general validity.

On the other hand, much recent research has been devoted to predicting the stability of practical drug products by statistical methods such as the application of Weibull probability paper,[7] regardless of the mechanisms involved. However, it also seems important to make further efforts to clarify the mechanisms throughout the degradation process and to establish the principles of the degradation of pure solid drugs, which might also be applicable to solid dosage forms.

In the present study, the solid state degradation of meclofenoxate hydrochloride (MF-HCl), which is known to hydrolyze easily, was studied, especially in relation to the effect of temperature and humidity, in order to gain a better insight into the degradation mechanism of a water-soluble pure solid.

Experimental

Materials——MF-HCl (Toyama Kagaku Co.) was recrystallized from acetone, ground in a mortar, sieved (149—177 μm) and kept over P_2O_5 under reduced pressure (mp 141°C).

Other chemicals used were of reagent grade.

Kinetic Studies——Twenty-five mg of MF-HCl powder was weighed into polyvinylchloride dishes (20 × 5 mm, about 70 mg), which were each placed in a reaction vessel containing a saturated solution of an inorganic salt (KCl, $NaNO_3$, NaBr, NH_4NO_3 or KF) as shown in Fig. 1. The reaction vessels were placed in a thermostated bath (50, 60, 70 or 80°C) regulated within ±0.1°C precision. The whole amount of sample in a dish was removed when required, and analyzed to determine the extents of decomposition and water adsorption. The kinetic run was repeated twice at each controlled temperature-humidity condition.

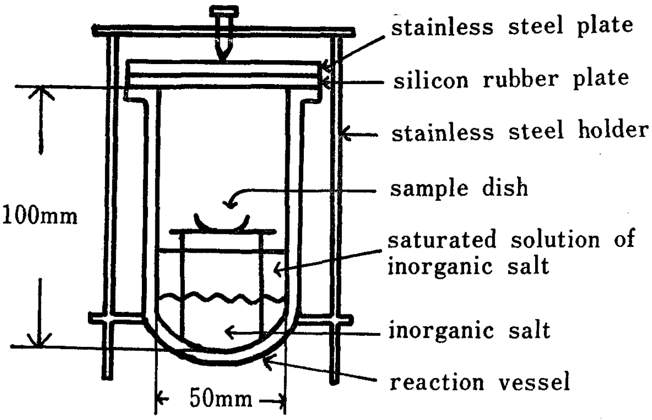

Fig. 1. Apparatus for Kinetics Study

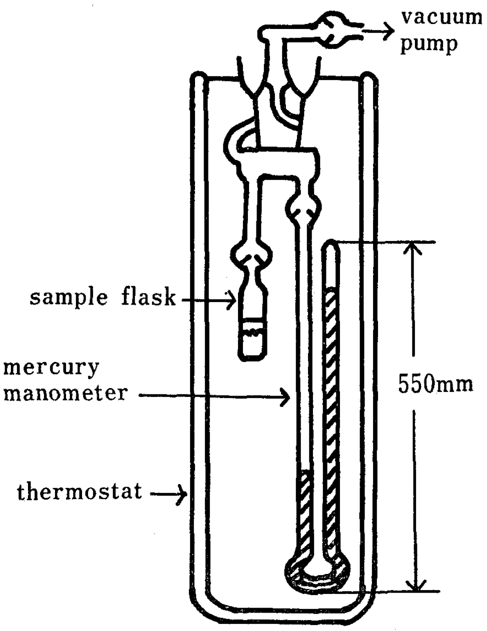

Fig. 2. Apparatus for Vapor Pressure Measurement

Water Vapor Pressure Measurement——The water vapor pressure over the saturated solution of inorganic salt used to achieve constant humidity was determined by the apparatus shown in Fig. 2. A flask containing a saturated solution of an inorganic salt with excess crystals was connected to the apparatus, and then, with cooling of the flask, air was evacuated from the entire apparatus. The apparatus was placed in a thermostat set at a desired temperature and the pressure was measured with a manometer. Figure 3 shows the relative humidities (RH) calculated from the vapor pressures observed with the saturated solutions of inorganic salts, at which kinetic studies were carried out.

The water vapor pressures over the saturated solutions of MF-HCl and its decomposed products···*p*-chlorophenoxyacetic acid (CPA) and dimethylaminoethanol hydrochloride (DMAE-HCl)···were also determined and the calculated critical relative humidities (CRH) are shown in Fig. 3.

Estimation of Water Content——The sample in the dish was weighed immediately after being removed from the reaction vessel. Since the increase in the weight was due to the water consumed for chemical reaction (hydrolysis) and the water adsorbed (or condensed) on the solid, the amount of adsorbed water was calculated by subtracting the amount of water corresponding to the decomposition of MF-HCl from that corresponding to the increase in the weight.

No change in the weight of the dish without samples was observed under any of the conditions studied. Furthermore, the fact that the total amounts of MF-HCl plus CPA, and of chloride ion were found to be constant throughout the reaction suggests that no compound was liberated from the dish.

Determination of MF-HCl and Its Decomposed Product by High Performance Liquid Chromatography (HPLC)——The whole of the powder sample in a dish, which had been removed from the reaction vessel and weighed, was dissolved in CH_3CN in a 50 ml volumetric flask containing 5 ml of 3-methylsalicylic acid solution

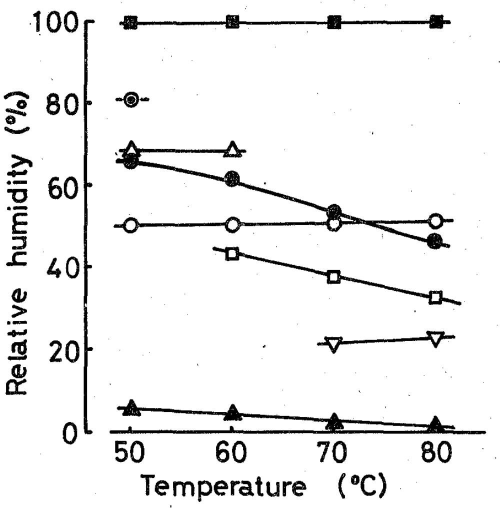

Fig. 3. Relative Humidity over Saturated Solutions of Various Inorganic Salts, MF–HCl and Its Decomposition Products at Various Temperatures

◎, KCl; △, NaNO$_3$; ○, NaBr; □, NH$_4$NO$_3$; ▽, KF; ●, MF–HCl; ▲, DMAE–HCl; ■, CPA.

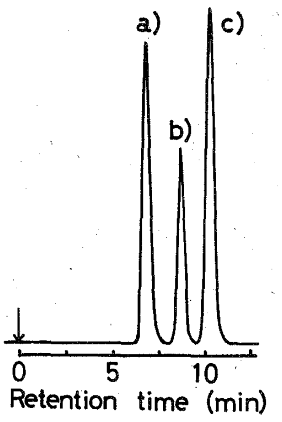

Fig. 4. HPLC Chromatogram of partially Decomposed MF–HCl

a) MF–HCl, b) CPA, c) 3-methylsalicylic acid (internal standard).

(0.3% in CH_3CN) as an internal standard. The solution was brought up to 50 ml with CH_3CN and 5 μl of the solution was subjected to HPLC.

The HPLC conditions were as follows; column, Hitachi gel 3011 (3 mm i.d. × 50 cm); mobile phase, 5%(v/v) acetic acid and 95%(v/v) CH_3CN; flow rate, 0.3 ml/min; detector, ultraviolet (UV) 280 nm. A chromatogram of partially decomposed MF-HCl is shown in Fig. 4. The amounts of MF-HCl and CPA were calculated from the peak area and the peak height ratio, respectively.

Results and Discussion

Degradation of Meclofenoxate–HCl Powder

Figures 5 and 6 show the typical time courses of degradation and water adsorption of MF–HCl powder stored at 50, 60, 70 and 80°C with 21 to 81%RH (See Fig. 3). In all instances, MF–HCl was found to hydrolyze into a water-soluble product, DMAE–HCl and a water-insoluble product, CPA, as shown in Chart 1, and the total amount of MF–HCl and CPA was found to be constant over the period of degradation. This suggests that no reaction other than hydrolysis occurred under any of the conditions studied.

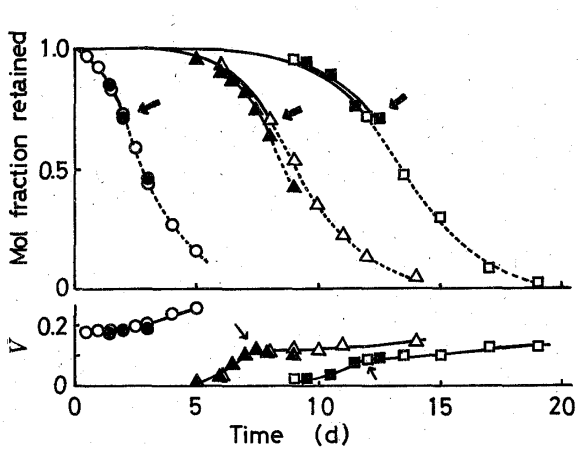

Fig. 5. Degradation of MF–HCl and Water Adsorption at 60°C at Various Humidities

○●, 68%; △▲, 50%; □■, 43% RH.
○△□, the first run; ●▲■, the second run; ——, the values calculated by a non-linear least-squares method.

All the decompositions followed sigmoid-shaped curves, while the pattern of water adsorption depended on the RH. When the RH was above the critical relative humidity (CRH) of MF–HCl (See Fig. 3), the water adsorption occurred rapidly, so that MF–HCl appeared to be dissolved from the beginning of the reaction. On the other hand, when the RH was below CRH, the water adsorption took place slowly and showed a concave curve until an equilibrium seemed to be

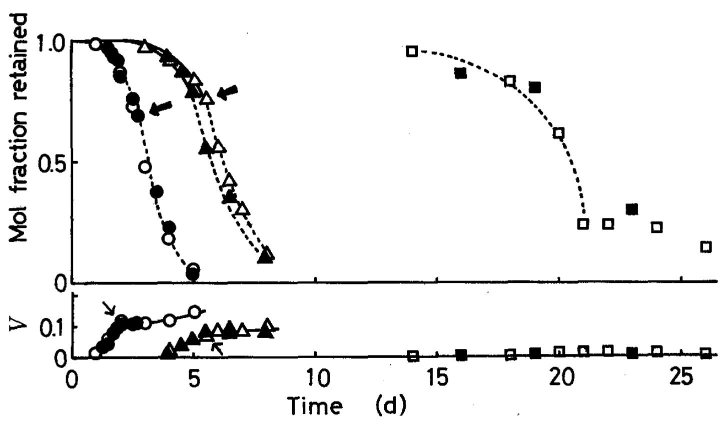

Fig. 6. Degradation of MF–HCl and Water Adsorption at 70°C at Various Humidities

○●, 51%; △▲, 38%; □■, 21% RH.
○△□, the first run; ●▲■, the second run; ——, the values calculated by a non-linear least-squares method.

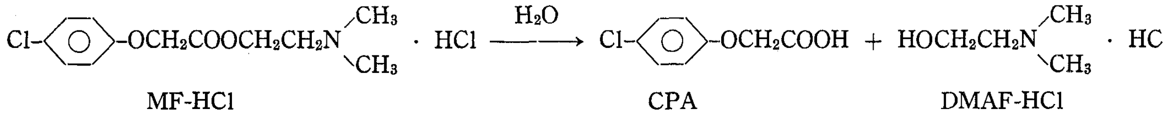

Chart 1

achieved. No water adsorption, however, was observed throughout the period of decomposition at 80°C, 23% RH and 70°C, 21% RH.

All the decompositions followed sigmoid curves under all conditions studied. Those curves could be divided into two parts, marked off by arrows in Figs. 5 and 6, except for the degradations which are not accompanied by any water adsorption. At the later stage (after the arrows), the apparent concentration of MF–HCl, which was calculated from the percent retained and the amount of adsorbed water, decreased in an apparent first-order manner. Figure 7 shows Arrhenius plots of the apparent rate constants, from which ΔH was estimated to be 11.5 kcal/mol.

At the early stage (before the arrows), on the other hand, the percent decomposed, x, could be approximated by equation 1

$$x = kt^n \tag{1}$$

where k and n are constants, as can be seen in Figs. 8 and 9, which show plots of the logarithm of the percent decomposed against that of the time at the RH above and below CRH, respectively. At RH above CRH, n, calculated from the slope, ranged from 1.5 to 1.8. At RH below CRH, on the other hand, n ranged from 4.3 to 6.0 except for the decompositions at 80°C, 33%RH and 70°C, 51%RH, which showed large scatters. Assuming that n is independent of temperature and humidity, and is constant at each RH range, the decompositions were simulated by the non-linear least-squares method. The solid lines in Figs. 5 and 6 represent the calculated values, which agree well with the observed values. The value of n was estimated to be 1.6 and 5.2 at RH above and below CRH, respectively. The dependence of k calculated according to equation 1 on the water vapor pressure is shown in Fig. 10. A linear relationship was observed between the logarithm of k and the vapor pressure at RH above and below CRH, respectively.

The decompositions at 80°C, 23%RH and 70°C, 21%RH, where no water adsorption was observed, showed large scatters, though the percent decomposed could be approximated yb

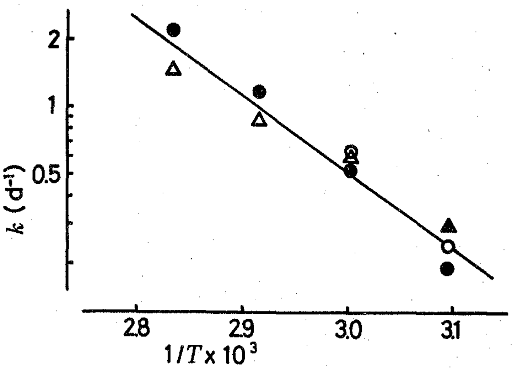

Fig. 7. Arrhenius Plot for Degradation at the Later Stage

●, 50% (50, 60°C), 51% (70, 80°C); △, 43% (60°C), 38% (70°C), 33% (80°); ○, 68% (50, 60°C); ▲, 81% RH (50°C).

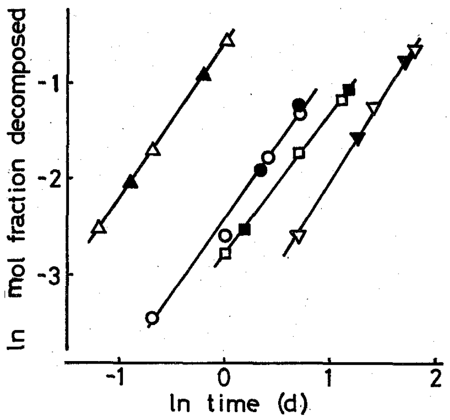

Fig. 8. Degradation at the Early Stage at Humidities above CRH

△▲, 80°C, 51%; ○●, 60°C, 68%; □■, 50°C, 81%; ▽▼, 50°C, 68%RH.

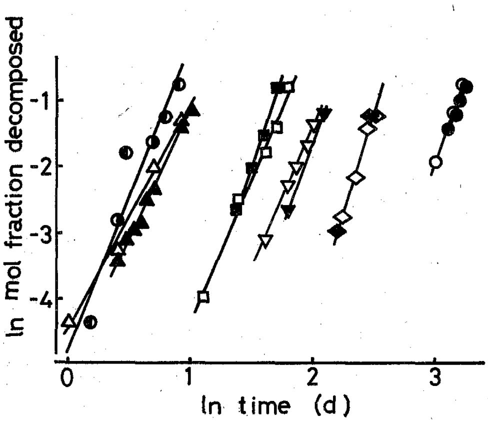

Fig. 9. Degradation at the Early Stage at Humidities below CRH

◐◑, 80°C, 33%; △▲, 70°C, 51%; □■, 70°C, 38%; ▽▼, 60°C, 50%; ◇◆, 60°C, 43%; ○●, 50°C, 50%RH.

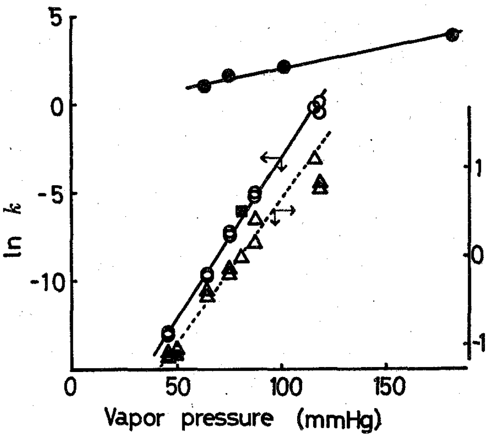

Fig. 10. Relationship between Vapor Pressure and Rate Constant of Degradation at the Early Stage

●, at humidities above CRH; ○, below CRH; ■, at 80°C, 23% and 70°C, 21%RH; △, k calculated by means of Prout and Tompkins' equation.

equation 1 and n was calculated to be 4.8 to 6.0. The logarithm of k in this case could also be correlated to the vapor pressure by the same straight line as shown in Fig. 10.

Since all the initial decompositions can be approximated by equation 1 and the constant k can be estimated on the basis of the relationship between k and vapor pressure shown in Fig. 10, it is possible to predict the initial decomposition under any conditions of temperature and humidity.

Degradation Mechanism for Meclofenoxate–HCl Powder

The degradation mechanism for ME–HCl powder will be discussed in three cases.

(1) **Degradation at RH above CRH**——The water adsorption is so fast that MF–HCl appears to be homogeneously dissolved from the beginning of the reaction. However, the decomposition at the initial stage is not a first-order process as in the later stage, and it can be represented by equation 1, where $n=1.6$ (Fig. 8). This suggests that MF–HCl is not dissolved to form a completely homogeneous solution at this stage. Furthermore, the fact that the decom-

position is not zero-order suggests that the apparent decomposition rate depends on the dissolution and diffusion rates as well as on the reaction rate of MF–HCl. As can be seen in Fig. 11, which shows the decompositions in various concentrated solutions, decomposition even under conditions where MF–HCl appears to be dissolved (at the initial concentration of 2.5 mg/mg H_2O, represented by solid circles in Fig. 11), is not first-order at the initial stage and shows a lag time, like the solid state decomposition at higher RH (at 68%RH, represented by triangles in Fig. 11). This suggests that the lag time observed in the solid state decomposition is due to the dependence of the apparent decomposition rate on the dissolution and diffusion rate, as well as on the water adsorption rate.

The decomposition at the later stage (after the arrows in Figs. 5 and 6) can be considered as a reaction in solution because the apparent first-order rate constant is approximately in accord with that in dilute solutions (Fig. 11) and gives a straight line with $\Delta H = 11.5$ kcal/mol in the Arrhenius plot (Fig. 7). The amount of adsorbed water at this stage depends on the RH, and slightly on the percent of MF–HCl decomposed, as shown in Fig. 12. This may be interpreted by considering that the mol fraction of MF–HCl in the solution, namely the concentration of MF–HCl, depends on the RH, and sufficient water to get this concentration is adsorbed corresponding to the total amount of MF–HCl and the water-soluble product, DMAE–HCl, which is constant during the decomposition. The slight increase in the amount of adsorbed water with the decomposition may be ascribed to the small effect of the slightly water-soluble product, CPA, on the vapor pressure.

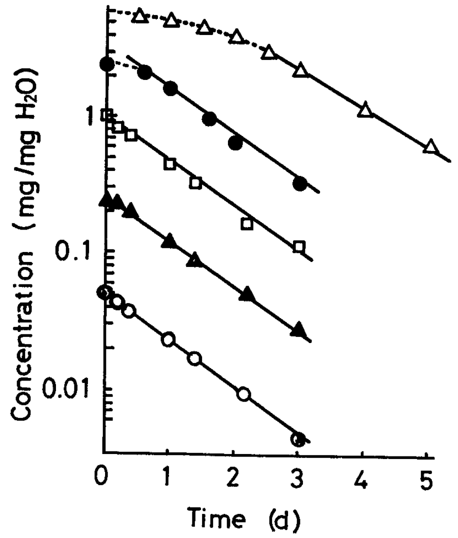

Fig. 11. Degradation in Solution at 60°C at Various Concentrations

○▲□ and ●, 500, 100, 25 and 10 mg of water, respectively, was added to 25 mg of MF–HCl in a 10 ml volume test tube.

△, 25 mg of MF–HCl was stored at 68%RH (the concentration was calculated from percent retained and amount of water adsorbed).

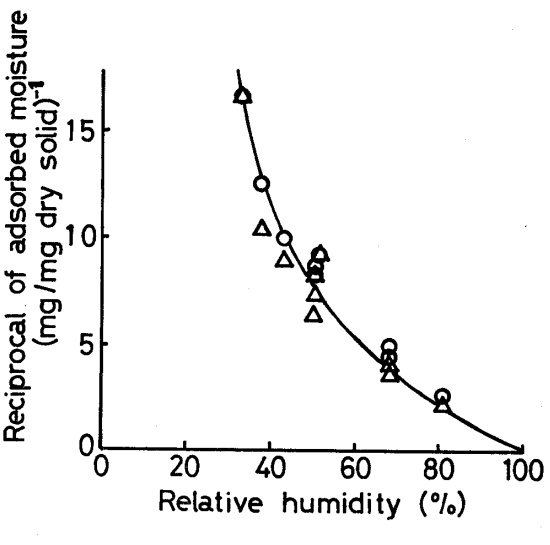

Fig. 12. Relationship between Adsorbed Moisture and Relative Humidity

At 50% (○) and 80% (△) decomposition.

(2) **Degradation at RH below CRH**——At the initial stage, water is adsorbed slowly on the surface of the solid and the decomposition can be represented by equation 1 (Fig. 9). In many autocatalytic reactions,[8] equation 2 has been quoted to represent the reaction rate

$$\frac{dx}{dt} = kx^l(1-x)^m t^q \qquad (2)$$

where k, l, m and q are constants. Prout and Tompkins'equation[3] (equation 3), which has frequently been quoted for autocatalytic reactions governed by nucleation, is obtained by integrating equation 2 when $l=0$ and $n=m=1$,

$$\ln\frac{x}{1-x}=kt+c \qquad (3)$$

where k and c are constants. The initial decomposition of MF–HCl at RH below CRH apparently conforms to this equation under each condition ($r>0.98$), though k calculated by means of equation 3 does not show such a good correlation with water vapor pressure as that calculated by means of equation 1 (Fig. 10). Equation 1 is derived from equation 2 by substituting zero for l and m ($n=q+1$). Since n was estimated to be 5.2 by the non-linear least-squares method, *i.e.*, much bigger than that generally reported for gas-solid reactions ($n=1.5$),[9] a gas-solid reaction does not seem to be predominant in the decomposition at this stage. The amount of adsorbed water is plotted against the fraction of decomposed MF–HCl in Fig. 13, which shows that adsorbed water increases proportionally to the decomposition, namely to the amount of DMAE–HCl formed, at this stage. This can be ascribed to the small CRH and high hygroscopicity of DMAE–HCl (Fig. 3), and suggests that the water adsorption rate is much larger than the reaction rate. Furthermore, the dependence of k on temperature and humidity is much larger than that observed at RH above CRH, as shown in Fig. 10. These results suggest that MF–HCl powder decomposes in the following way. Water vapor initiates the hydrolysis of MF–HCl into CPA and DMAE–HCl on the surface of the powder by a gas-solid reaction. Once DMAE–HCl is produced, water starts to be adsorbed on the surface and forms a sorbed moisture layer, in which intact MF–HCl dissolves, diffuses and then decomposes. In other words, the decomposition of MF–HCl is induced by a gas-solid reaction and accelerated by the formation of DMAE–HCl which apparently serves to provide reaction nuclei.

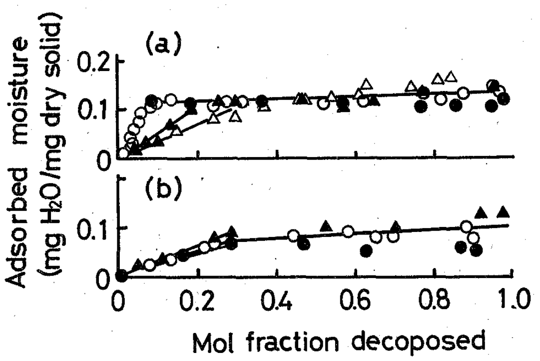

Fig. 13. Relationship between Moisture Uptake and Mol Fraction Decomposed of MF–HCl at Various Temperatures and Humidities

(a), 50% (50, 60°C), 51% (70, 80°C); (b), 43% (60°C), 38% (70°C), 33%RH (80°C) △, 50°C; ▲, 60°C; ○, 70°C; ●, 80°C.

The decomposition at the later stage (after the arrows in Figs. 5 and 6) may be regarded as a first-order reaction in homogeneous solution, as in case (1). When MF–HCl is apparently dissolved (at the small arrow), a lag time is observed before the decomposition starts to conform to first-order kinetics (at the big arrow). This may indicate that MF–HCl is not completely dissolved and diffused at this stage, as mentioned in case (1).

The pH value of the adsorbed water may be considered to be constant during the decomposition, because the basicity of DMAE is similar to that of MF, because HCl was found not to be liberated from the system, and because CPA is not soluble in water.

(3) **Degradation at Low RH Where No Water Adsorption Occurs**——Though the decomposition showed a larger scatter compared to cases (1) and (2), the initial decomposition (until 30% decomposition) can be represented by equation 1, and n was estimated to be 4.8 to 6.0, as in case (2). However, the dependence of k on water vapor pressure seems larger than that in case (2) (Fig. 10). Furthermore, the absence of water adsorption and the slow decomposition at the later stage suggest that the decomposition mechanism under these conditions differs from that in case (2). Further studies to find the reason for the poor reproducibility of the data are required in order to clarify the mechanism in this case.

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