November 1989 Chem. Pharm. Bull. 37(11) 3083—3087 (1989)

Acceleration of the Addition Reaction of Succinic Anhydride and *p*-Nitroaniline in Controlled-Pore Glass Solid Dispersions[1)]

Etsuo Yonemochi, Toshio Oguchi, Katsuhide Terada,[2)] Keiji Yamamoto, and Yoshinobu Nakai*

Faculty of Pharmaceutical Sciences, Chiba University, 1-33 Yayoicho, Chiba 260, Japan. *Received April 13, 1989*

The effects of controlled-pore glass (CPG) solid dispersion on the crystalline properties and solid-state reaction of succinic anhydride and *p*-nitroaniline have been investigated. From the powder X-ray diffraction and differential scanning calorimetry measurements, it was found that the mixing of organic compounds with CPG caused changes in their crystalline state. The addition reaction of succinic anhydride and *p*-nitroaniline in CPG mixtures was studied under various conditions. In the CPG mixtures, extreme acceleration of the addition reaction between succinic anhydride and *p*-nitroaniline was observed. The acceleration of the reaction can be explained in terms of the adsorption of organic molecules in the pores of CPG. In the cases of decreasing pore diameter and/or increasing CPG fraction, the reaction rate constants were significantly increased.

Keywords controlled pore glass; powder X-ray diffraction; differential scanning calorimetry; amorphous; solid state reaction; addition reaction; *p*-nitroaniline; succinic anhydride

There are many studies on the molecular interactions between medicinals and pharmaceutical adsorbents such as aluminum silicate, activated carbon and anhydrous silicic acid.[3-8)] Controlled-pore glass (CPG) was used as a model porous material in previous papers, as CPG having narrow and regulated pore size distributions is commercially available.[9,10)] We found that in CPG drug mixtures the drug molecules took three phases and showed some unusual properties.

On heating above 90 °C, succinic anhydride and *p*-nitroaniline reacted in the solid state to give the reaction product, succinic-*p*-nitroanilide. Narayan *et al.* reported the effects of compacting pressure, reaction temperature and time on the solid-state reaction between succinic anhydride and *p*-nitroaniline in mixed powder compacts.[11)]

In this study, the effects of dispersion of succinic anhydride and *p*-nitroaniline in CPGs on the drug crystalline properties were investigated by means of powder X-ray diffraction, differential scanning calorimetry (DSC) and microscopic observation. We also studied the effects of CPGs on the solid-state addition reaction of succinic anhydride and *p*-nitroaniline at below 90 °C.

Experimental

Materials CPGs were obtained from Electro-Nucleonics Ltd. and were used after drying in vacuum at 120 °C for 3 h. The CPGs were kept in a desiccator over diphosphorus pentoxide *in vacuo*. The physicochemical properties of CPGs are shown in Table I. The pore size, pore volume and specific surface area obtained by the mercury porosimeter and B.E.T. methods were quoted by the manufacturer for each sample. Succinic anhydride (Wako Pure Chemical Industries Co., Ltd., mp 393 K) and *p*-nitroaniline (Wako Pure Chemical Industries Co., Ltd., mp 419 K) were of reagent grade and were used as received from the suppliers. Succinyl-*p*-nitroanilide was synthesized by the method of Auwers.[12)]

Table I. Mean Pore Diameter, Pore Volume and Specific Surface Area of Various CPGs

	Mean pore diameter[a)] (Å)	Pore volume[a)] (ml/g)	Specific surface area[a)] (m²/g)
CPG 75	70	0.48	207
CPG 170	167	1.00	161
CPG 350	347	0.92	68.4
CPG 500	546	1.02	43.1
CPG 700	726	0.77	24.9
CPG 1000	962	1.04	26.1
CPG 3000	3002	0.76	7.20

a) Nominal.

Preparation of the Mixtures The mixtures of succinic anhydride and *p*-nitroaniline were prepared with a mortar and pestle in various mixing ratios. The mixtures of organic mixture and CPG were prepared in a similar manner.

Powder X-Ray Diffraction Powder X-ray diffraction patterns were measured by using a Rigaku Denki 2027 diffractometer. An X-ray generator (CuK_α, Ni-filtered, 30 kV, 5 mA) and scintillation counter were used.

DSC A Perkin Elmer DSC 1-B was used. The measurements were performed using liquid sample pans at a heating rate of 8 K/min under N_2 gas flow.

Measurement of Reaction Rate of Succinic Anhydride and *p*-Nitroaniline The mixed samples were stored in the desiccator at 0% relative humidity (RH), over P_2O_5. Temperatures were controlled by using an air bath at 40, 50, 60, 70, 80, and 90 °C. At regular intervals, samples were removed for analysis. To determine the amounts of the reactant and the product, the samples were dissolved in ethanol: water (50 : 50) mixture. The absorbances of the solution at 322 and 384 nm were measured with a Shimadzu double-beam spectrophotometer UV-200S, and the amounts of *p*-nitroaniline and succinyl-*p*-nitroanilide were calculated simultaneously. Succinic anhydride and succinic acid have no absorbance in this region.

Results and Discussion

Physicochemical Properties of Succinic Anhydride–*p*-Nitroaniline–CPG Mixture Figure 1 shows the DSC thermograms of the ternary mixtures at various mixing ratios. The molar ratio of succinic anhydride and *p*-nitroaniline in

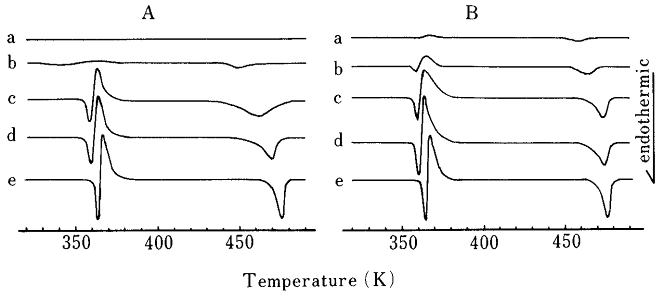

Fig. 1. DSC Curves of Succinic Anhydride–*p*-Nitroaniline–CPG Systems

A) CPG 75; B) CPG 1000, a) 10% (succinic anhydride and *p*-nitroaniline) + 90% CPG; b) 25% (succinic anhydride and *p*-nitroaniline) + 75% CPG; c) 50% (succinic anhydride and *p*-nitroaniline) + 50% CPG; d) 75% (succinic anhydride and *p*-nitroaniline) + 25% CPG; e) succinic anhydride and *p*-nitroaniline.

the mixtures was constant at 1 : 1. In the thermogram without CPG, the endothermic peak was observed at 364 K, indicating the presence of a eutectic mixture of succinic anhydride and *p*-nitroaniline. The exothermic peak at 368 K demonstrated the chemical reaction and the crystallization of the product. The endothermic peak position at 476 K was in fair agreement with the melting point of authentic succinyl-*p*-nitroanilide.

In the CPG 75 system, the two endothermic peaks observed at around 364 and 476 K shifted to lower temperature with increasing CPG content, and the peaks became small and broad. In the mixture containing 10% organic compounds, no thermal peak was observed up to 490 K. These results suggested that organic molecules were in an amorphous state in CPG, especially at low concentrations of organic compounds. For the CPG 1000 system, the thermal behavior was almost the same as that of the CPG 75 system, while the temperature shifts of the endothermic peaks were smaller than in the CPG 75 system.

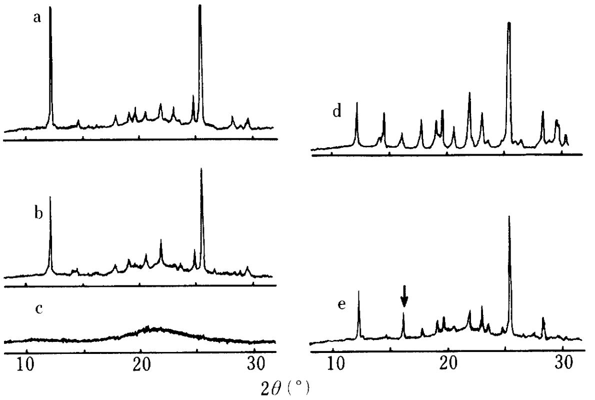

Fig. 2. X-Ray Diffraction Patterns of Mixtures of Succinic Anhydride, *p*-Nitroaniline and CPG 75

a) 50% (succinic anhydride and *p*-nitroaniline) + 50% CPG 75; b) 30% (succinic anhydride and *p*-nitroaniline) + 70% CPG 75; c) 10% (succinic anhydride and *p*-nitroaniline) + 90% CPG 75; d) succinic anhydride + *p*-nitroaniline; e) sample a) stored at 50 °C for 3.5 h.

Figure 2 shows the powder X-ray diffraction patterns of the mixtures of CPG 75 with organic compounds. In the mixture containing 10% organic compounds, no X-ray diffraction peaks were observed, and this was compatible with the formation of the amorphous state that was predicted from the DSC measurements. With increasing organic content, the X-ray diffraction peaks due to succinic anhydride at $2\theta = 17.9°$, $22.0°$ and *p*-nitroaniline at $2\theta = 12.3°$, $25.5°$ became sharp and strong. The diffraction peak intensities of succinic anhydride and *p*-nitroaniline, however, decreased after heating of the mixture at 50 °C for 3.5 h, due to the increase of addition reaction, which was confirmed by the appearance of a new X-ray diffraction peak at $2\theta = 16.7°$, shown by the arrow in Fig. 2e.

Figure 3 shows the changes of the micrographs before and after storage at 50 °C, taken with a polarizing microscope. In the freshly prepared samples, succinic anhydride and *p*-nitroaniline crystals were observed as bright particles. After storage at 50 °C for 30 min, crystalline materials were no longer detectable and the adsorption of organic compounds into CPG pores was assumed to have occured. After storage for 20 h, deposition of new crystalline materials was observed, two types of crystals (needles and prisms) being detected in the CPG 75 system, while in the CPG 1000 system only prism crystals were detected. By chemical analysis, the prism crystals were identified as anilide. The DSC, powder X-ray diffraction and microscopic observations showed that the mixing of organic crystals with CPG caused changes of the crystalline state of

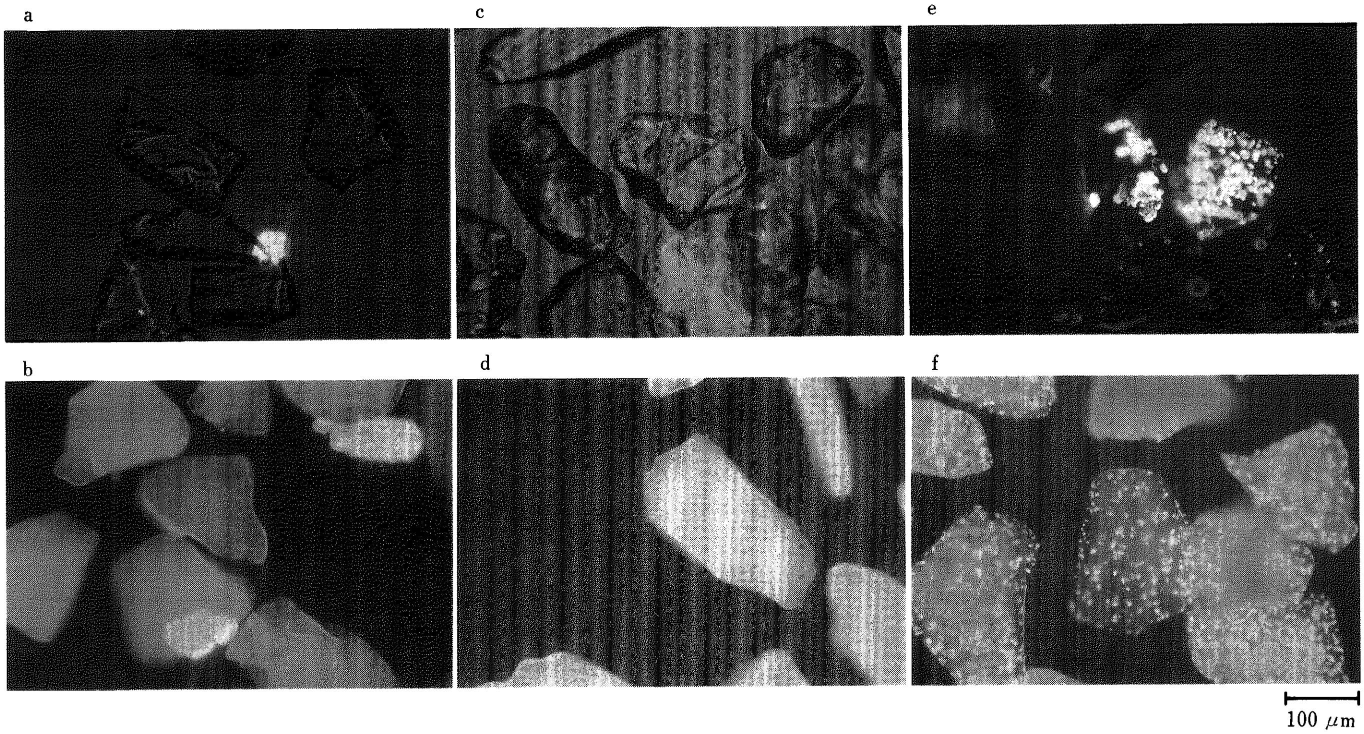

Fig. 3. Polarized Micrographs

a) 5% (succinic anhydride and *p*-nitroaniline) + 95% CPG 75; b) 5% (succinic anhydride and *p*-nitroaniline) + 95% CPG 1000; c) sample a) stored at 50 °C for 30 min; d) sample b) stored at 50 °C for 30 min; e) sample a) stored at 50 °C for 20 h; f) sample b) stored at 50 °C for 20 h.

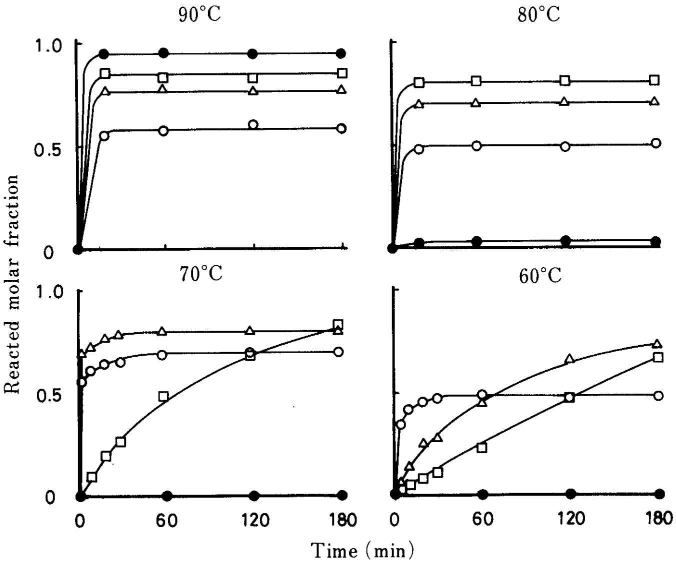

Fig. 4. Reaction Curves of *p*-Nitroaniline and Succinic Anhydride with or without Various CPGs

○, CPG 75; △, CPG 350; □, CPG 1000; ●, without CPG.

organic compounds, and accelerated the solid-state addition reaction.

Addition Reaction of Succinic Anhydride and *p*-Nitroaniline The rates of the addition reaction were measured at various temperatures for 50% organic compounds–50% CPG mixtures. An equimolar mixture of succinic anhydride and *p*-nitroaniline was used as the organic compounds. The reaction curves are shown in Fig. 4. The reaction curves at 90 °C differed markedly from the curves at the other temperatures. At 90 °C, the reactions were completed instantaneously in all mixtures. At 80 °C, the reaction took place very slowly in the absence of CPG, while the reaction proceeded in all the CPG systems. The final reacted molar fraction of succinic anhydride and *p*-nitroaniline in the CPG systems did not reach 1.0 as the hydrolysis of succinic anhydride took place simultaneously. It was observed that the formation of succinyl-*p*-nitroanilide depended on the CPG pore diameter. Decrease of the pore diameter tended to depress the amount of succinyl-*p*-nitroanilide at 80 and 90 °C. Below 70 °C, however, changes of the reaction profile were observed, especially for large pore size CPGs. It was also noted that the addition reaction proceeded sufficiently at lower temperature in the CPG systems. Further, the kinetics of the solid-state addition reaction was studied at lower temperature, below 60 °C.

Figure 5 shows the reaction curve of succinic anhydride and *p*-nitroaniline in the CPG 1000 system (5% organic compounds) at 40 °C. A first-order plot is also presented in Fig. 5. The plots of $\ln(1-\alpha)$ against time showed good linearity (α is the reacted molar fraction). The apparent first-order reaction rate constant (k) was calculated from the slope of the straight line.

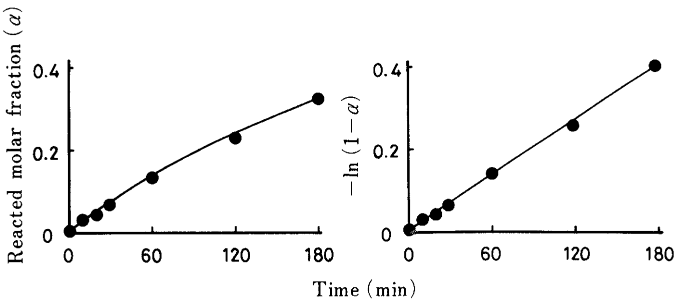

Fig. 5. Reaction Kinetics of the Mixture of 5% Succinic Anhydride–*p*-Nitroaniline and 95% CPG 1000 at 40 °C

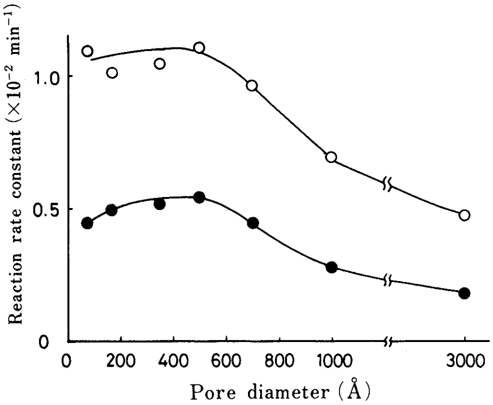

Fig. 6. Effects of Pore Diameter on the Reaction Rate Constants of Succinic Anhydride and *p*-Nitroaniline in the CPG Mixture

●, 50 °C; ○, 60 °C.

TABLE II. Thermodynamic Parameters for Reaction of Succinic Anhydride and *p*-Nitroaniline in the CPG Mixtures

	Activation energy (kJ mol^{-1})	Frequency factor (min^{-1})
CPG 170	52.2	1.20×10^6
CPG 1000	33.2	7.28×10^2

Figure 6 summarizes the effect of pore diameter on the reaction rate constant in 5% organic compounds and 95% CPGs mixtures at 50 and 60 °C. The reaction rate constants calculated for CPGs of less than 500 Å pore diameter were significantly greater than the rate constants calculated for CPGs with pore diameters larger than 500 Å. In CPG mixtures of small pore diameter, the organic compounds were present in a completely amorphous state, presumably adsorbed on the pore walls.[13] It is suggested that this caused the rapid solid-state addition reaction of succinic anhydride and *p*-nitroaniline. It is also suggested that the slow reaction rates observed at large pore diameter were a result of the presence of a residual crystalline portion of succinic anhydride and *p*-nitroaniline due to the small surface area of CPGs.

The activation energies and frequency factors for the addition reaction were calculated on the assumption of first-order kinetics as shown in Table II using the results at 40, 50 and 60 °C. The activation energy for the reaction in CPG 170 was calculated to be 52.2 kJ/mol, while that in CPG 1000 was 33.2 kJ/mol. In mixed powder compacts, Narayan *et al.* determined the activation energy of the addition reaction of succinic anhydride and *p*-nitroaniline to be 84—223 kJ/mol.[11] Comparison of the values shows that the activation energy of the addition reaction in CPG mixtures was much lower than that in powder compacts. The frequency factor of the reaction in CPG 170 was about 1000 times greater than that in CPG 1000. In the CPG 170 system, the amount of amorphous compounds was larger

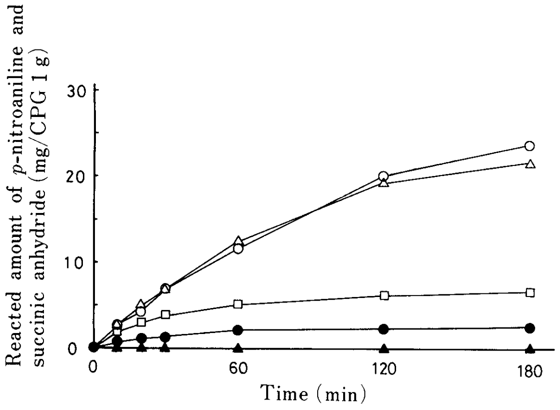

Fig. 7. Reaction Curves of Succinic Anhydride and p-Nitroaniline in the CPG 1000 Mixtures as a Function of Organic Compounds Concentration

▲, 1%; ●, 5%; □, 10%; △, 30%; ○, 50%.

than that in the CPG 1000 system. The difference in the amount of amorphous compounds between the two CPG systems seems consistent with the difference in frequency factor.

Figure 7 shows the effects of the organic compounds concentration on the reaction curves is the CPG 1000 system. The ordinate shows the amount of the product, succinic-p-nitroanilide. At 0.5% organic concentration, the reactant was not detectable. In the region of 1% to 30%, the amount of reactant increased with increasing organic concentration. No significant difference in the reacted amounts, however, was found between 30% and 50% organic concentrations.

Figure 8 shows the effect of drug concentration on the reaction rate constant in the CPG mixtures. The concentration of organic compounds was varied from 0.5 to 50%. In the CPG 170 system, between the concentration range of 0.5% to 10%, the reaction rate constant increased with increasing concentration of organic compounds. The maximum reaction rate constant was obtained at the concentration of 10%. In the range of 30 to 50%, the reaction rate constant decreased with increasing concentration. On the other hand, in the CPG 1000 system, the maximum reaction rate constant was obtained at the concentration of 5%; after that, the rate constant decreased with increase of concentration. In the CPG 170 system, at concentrations less than 10%, succinic anhydride and p-nitroaniline molecules were adsorbed in the CPG pores, and were in the amorphous state. As the organic molecules have high activity in the amorphous state, greater values of rate constant were expected. At lower concentration, however, the hydrolysis of succinic anhydride also took place as a side reaction and seemed to be very fast at 0.5 and 1% organic concentrations. Consequently, the rate of the addition reaction decreased with decrease of the organic concentration. At higher organic concentrations, the presence of a remaining crystalline portion appeared to slow down the reaction rate. In the CPG 1000 system, similar behavior was observed, although the maximum point shifted to 5% concentration due to the smaller surface area of CPG 1000.

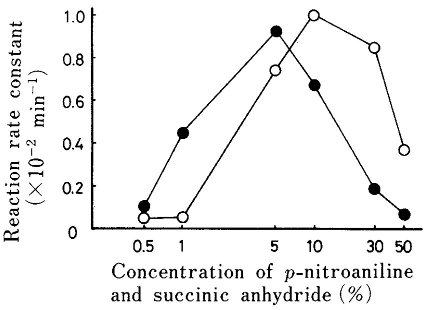

Fig. 8. Effects of p-Nitroaniline and Succinic Anhydride Concentration on the Reaction Rate Constants in the CPG Mixtures at 50 °C

○, CPG 170; ●, CPG 1000.

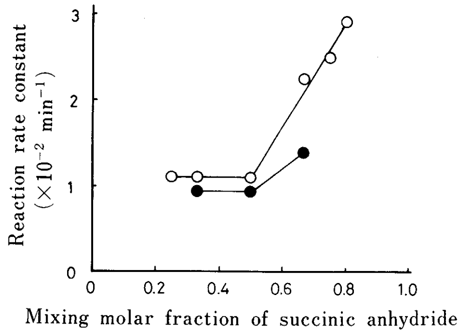

Fig. 9. Effects of Mixing Molar Fraction of Succinic Anhydride on the Reaction Rate Constant of Succinic Anhydride and p-Nitroaniline in the Mixtures of 5% Organic Compounds and CPG at 50 °C

○, CPG 170; ●, CPG 1000.

Figure 9 shows the effects of mixing molar fraction of succinic anhydride on the reaction rate constant at 50 °C. Mixing molar fraction was defined as (mol of succinic anhydride)/[(mol of succinic anhydride)+(mol of p-nitroaniline)]. The concentration of the organic compounds was constant at 5%. In the case where the mixing molar fraction was above 0.5, the rate constant increased linearly with increase of the mixing molar fraction. On the other hand, when the mixing molar fraction was less than 0.5, the reaction rate remained constant. These results indicated that the succinic anhydride concentration in the mixture determined the reaction rate constant. It is suggested that succinic anhydride changed to the amorphous state more rapidly than p-nitroaniline.

Mixing of succinic anhydride and p-nitroaniline with CPG powder accelerated the addition reaction between succinic anhydride and p-nitroaniline. In the CPG mixtures, organic molecules were adsorbed and dispersed in the CPG pores, and these dispersed and activated molecules contributed to the acceleration of the addition reaction.

Acknowledgement This investigation was supported in part by a grant from the Research Foundation for Pharmaceutical Sciences, Tokyo, Japan.

References and Notes

1) This paper is part IV of "Interaction of Medicinals and Porous Powder." The previous paper, part III: Y. Nakai, K. Yamamoto and S. Izumikawa, *Chem. Pharm. Bull.*, **34**, 301 (1986).
2) Present address: *School of Pharmaceutical Sciences, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274, Japan.*
3) K. Y. Yang, R. Glemza and C. I. Jarowski, *J. Pharm. Sci.*, **68**, 560 (1979).
4) C. Liao and C. I. Jarrowski, *J. Pharm. Sci.*, **73**, 401 (1984)
5) K. H. Kim, M. J. Frank and N. L. Henderson, *J. Pharm. Sci.*, **74**, 283 (1985).

6) T. Konno, K. Kinuno and K. Takaoka, *Chem. Pharm. Bull.*, **34**, 301 (1986).
7) Y. Nakai, K. Yamamoto, K. Terada, T. Oguchi and M. Yamamoto, *Yakugaku Zasshi*, **107**, 294 (1986).
8) Y. Nakai, K. Yamamoto, K. Terada, T. Oguchi and S. Izumikawa, *Chem. Pharm. Bull.*, **34**, 4760 (1986).
9) Y. Nakai, K. Yamamoto, K. Terada and J. Ichikawa, *Chem. Pharm. Bull.*, **32**, 4566 (1984).
10) Y. Nakai, K. Yamamoto, K. Terada and J. Ichikawa, *Yakugaku Zashi*, **105**, 296 (1985).
11) R. A. Narayan, A. Baradarajan and M. Satyanarayana, *Powder Technol.*, **33**, 187 (1982).
12) K. Auwers, *Justus Liebigs Ann. Chem.*, **292**, 188 (1896).
13) Y. Nakai, K. Yamamoto, K. Terada and T. Oguchi, *J. Pharmacobio-Dyn.*, **9**, s-9 (1986).