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Mechanochemical Considerations on the Maximal Numbers of Radicals Generated in Binary Powders of Glycolic Acid and Silica-Alumina

Hiroshi KASHIWAGI,* Saburo ENOMOTO, and Masami INOUE

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-01, Japan.

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The number of radicals generated in a binary powder of glycolic acid and silica-alumina was determined by means of electron spin resonance (ESR) spectroscopy. The maximal number of spins/g and the duration of the maximal number of spins/g were dependent on the calcination temperature of silica-alumina, on conditions of storage such as atmosphere or temperature of storage, and on the particle size of silica-alumina. Each of the above values was found to be influenced significantly by mechanical force induced by shaking or compressing. Techniques for decreasing the number of radicals induced by mechanical force are discussed.

Keywords ESR; radical number; maximal spin number duration; binary powder; glycolic acid; silica-alumina; mechanochemistry; mechanical force; particle size; storage condition

In the field of engineering, the effects of sintering, lubrication, wear, adsorption, wetting, or cracking on structure or on reactivity have recently been studied mechanochemically by using a relatively complicated system containing a polymer.[1,2] In the field of pharmaceutical sciences, however, only a few investigations have so far dealt with mechanochemistry.[1,3]

Aluminosilicates, utilized as antacids, cause contact reactions when mixed with organic compounds.[1] The strength of the bond between an organic molecule and an aluminosilicate may vary widely. For instance, the presence of strongly bonded molecules and almost free molecules was observed simultaneously by the use of nuclear magnetic resonance (NMR) spectroscopy.[4,5] As another example, an acid-base indicator adsorbed on solid-acid sites on the surface of an aluminosilicate was colored corresponding to its acidity and its acid strength.[6] However, it usually took 2—3 d, as estimated visually, to establish equilibrium.[7] Consequently, we thought that electron spin resonance (ESR) spectroscopic data for a non-equilibrium state or for the attainment or decay process of an equilibrium state might be obtainable by using a binary powder containing an aluminosilicate and a general organic compound. This approach could be used to examine the effect of mechanical force.

We previously observed the formation of radicals in binary powders of a saccharide and a metal oxide,[8,9] and of a metal oxide and an organic compound[10] upon stirring in a glass vessel by means of ESR spectroscopy. Furthermore, we presented the effect of mechanical energy on the number of radicals generated in a binary powder of glycolic acid (GA) and silica-alumina (SA).[1] Recently, we reported the time-course of the number of radicals in a binary powder of GA and SA up to 5 years after mixing.[11] We showed, though qualitatively, that an initial increase in the number of radicals occurred, followed by a plateau at the maximal amount of radicals, and finally a decrease in the number of radicals from its maximal value.

Then, we found that the maximal number of spins/g (MNS) and the duration of the maximal number of spins/g (DMNS) were affected by mechanical force applied by shaking or compressing. In the present paper, we present some numerical values for the effect of mechanical energy on MNS or on DMNS using a binary powder of GA and SA. The effect of particle size of SA or that of temperature of storage on MNS or on DMNS is also described. Finally, a technique for decreasing the number of radicals induced mechanically during the manufacture or storage of drugs is presented.

Results and Discussion

Characterization of Radicals As described in the preceding paper,[11] the ESR signals obtained with a binary mixture of GA and SA may be made up of two components. The stronger component, which accounts for more than 90% of the total number of spins, was attributed to electrons or holes trapped in SA because the spectrum of the mixture was similar to that of a mixed system of SA with ascorbic acid or with glycerol, but was different from that of a mixture of GA with silica gel or with zeolite. The weaker component, which varied synchronously with the stronger one, was attributed to diglycolic acid radicals based on the resemblance of the spectrum to that obtained with a binary mixture of SA and diglycolic acid upon heating.

Mechanochemical Considerations on the Maximal Numbers of Spins/g and on the Duration of the Maximal Numbers of Spins/g In the preceding paper,[11] we described qualitatively the effects of calcination temperature of SA (T_{ca}) and of atmosphere for the storage of a binary powder of GA and SA on MNS and on DMNS. MNS, DMNS,

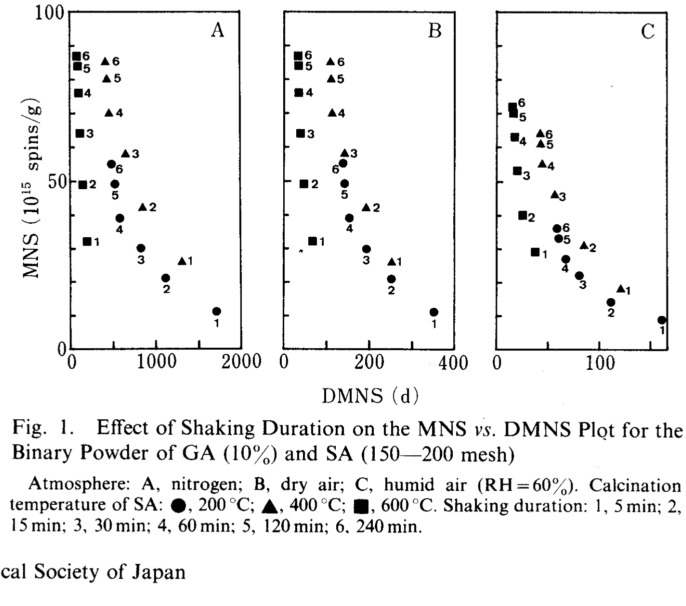

Fig. 1. Effect of Shaking Duration on the MNS *vs.* DMNS Plot for the Binary Powder of GA (10%) and SA (150—200 mesh)

Atmosphere: A, nitrogen; B, dry air; C, humid air (RH = 60%). Calcination temperature of SA: ●, 200 °C; ▲, 400 °C; ■, 600 °C. Shaking duration: 1, 5 min; 2, 15 min; 3, 30 min; 4, 60 min; 5, 120 min; 6, 240 min.

and the length of time required to attain MNS (t_{MNS}) were found to be influenced by mechanical force induced by shaking or compressing in the manner described below.

1) Effect of Shaking Duration Figure 1 shows the effect of shaking duration on the MNS (ordinate) *vs.* DMNS (abscissa) plot. It can be seen that MNS increased with increase in shaking duration and with increase in T_{ca}. Furthermore, the increase in MNS became smaller with increase in shaking duration and finally MNS reached an almost constant value (*e.g.*, the constant values of MNS for a binary powder containing SA calcined at 600 °C (SA_{600}) in nitrogen, dry air, and humid air were found to be 87×10^{15}, 87×10^{15}, and 72×10^{15} spins/g, respectively).

The t_{MNS} tended to decrease with increase in shaking duration or with increase in T_{ca}. For example, t_{MNS} in a binary powder of GA (10%) and SA calcined at 200 °C (SA_{200}) in nitrogen after shaking for 15 min was 100 h, and this dropped to 75 h after shaking for 240 min.

In contrast to MNS, DMNS decreased with increase in shaking duration and with increase in T_{ca}. Moreover, the decrease in DMNS became smaller with increase in shaking duration and reached an almost constant value. At constant shaking duration and a constant T_{ca}, MNS in dry air was almost identical with that in nitrogen, while MNS in humid air (RH = 60%) was 50—80% of that in dry air. However, DMNS at constant shaking duration and a constant T_{ca} can differ by a factor of 10 or more.

MNS for a binary powder containing SA calcined at 400 °C (SA_{400}) increased with increase in shaking duration and tended to reach almost the same constant value as that for a binary powder of GA and SA_{600}. At a shaking duration of 5 min, MNS for an SA_{400}-containing powder in humid air was almost intermediate between that for an SA_{600}-containing powder and that for an SA_{200}-containing powder. On the other hand, MNS for a binary powder containing SA_{400} in dry air or in nitrogen at a shaking duration of 5 min was similar to that for a binary powder containing SA_{600}. DMNS in nitrogen tended to vary remarkably at a T_{ca} of around 600 °C. The same tendency was observed in dry air or humid air. However, the decrement of DMNS in the region of 200—400 °C was not so small as that in the region of 400—600 °C. As discussed in the preceding paper,[11] contact reaction depends on the atmosphere and the nature of the active sites on the surface of SA, which may be correlated to the formation of Lewis acid sites from Brönsted acid sites at a T_{ca} of around 600 °C.[12]

2) Effect of Compressive Stress Figure 2 shows the effect of compressive stress on MNS and on DMNS. MNS increased and DMNS decreased with increase in the compressive stress and with increase in T_{ca}. The increase in MNS and the decrease in DMNS gradually became smaller with increase in compressive stress and tended to reach plateaus at a given compressive stress (250—500 kg/cm²). At a constant compressive stress and a constant T_{ca}, MNS in dry air was almost the same as that in nitrogen, while MNS in humid air was 50—80% of that in dry air. However, DMNS at a constant compressive stress and a constant T_{ca} can differ from one another sometimes by a factor of more than 10.

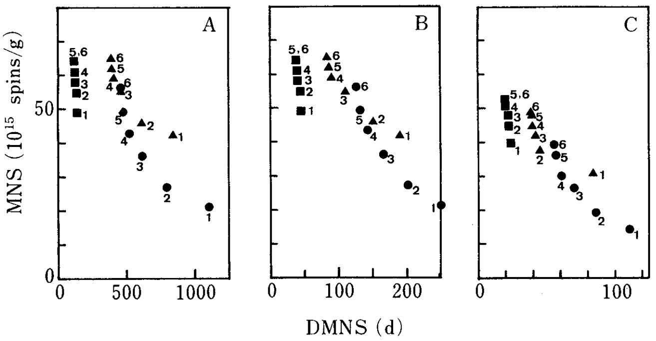

Fig. 2. Effect of Compressive Stress on the Plot of MNS against DMNS for the Binary System of GA (10%) and SA (150—200 mesh) at Constant Shaking Duration (15 min)

Compressive stress: 1, 1 kg/cm²; 2, 10 kg/cm²; 3, 50 kg/cm²; 4, 100 kg/cm²; 5, 250 kg/cm²; 6, 500 kg/cm². Other symbols are the same as those in Fig. 1. The values of MNS and DMNS at $T_{\mathrm{ca}} = 600$ °C became constant at a compressive stress greater than 250 kg/cm² (5 and 6).

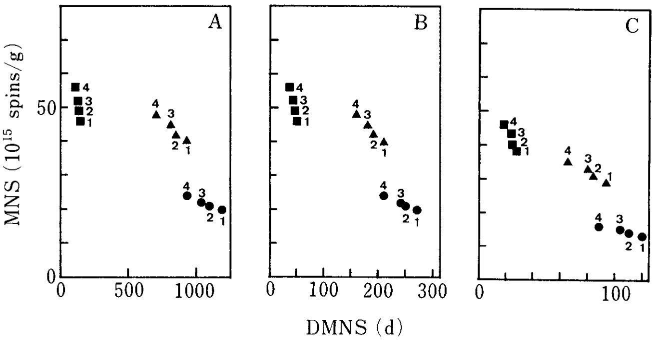

Fig. 3. Effect of Particle Size on the MNS *vs.* DMNS Plot for the Binary System of GA (10%) and SA at Constant Shaking Duration (15 min)

Particle size: 1, 100—150 mesh; 2, 150—200 mesh; 3, 200—250 mesh; 4, 250—325 mesh. Other symbols are the same as those in Fig. 1.

3) Effect of the Particle Size of SA MNS, DMNS, and t_{MNS} were also found to be dependent on the particle size of SA. The effect of particle size on MNS and on DMNS is illustrated in Fig. 3. MNS increased and DMNS decreased with decrease in the size of SA particles. For a constant particle size of SA (100—150, 200—250, or 250—325 mesh), MNS, DMNS, or t_{MNS} showed almost the same dependence on T_{ca} or on atmosphere for storage as that for a mixture containing GA and SA (150—200 mesh) described before.[11] In every case, the increment of MNS and the decrement of DMNS with T_{ca} and so forth became greatest when SA having the smallest particle size (250—325 mesh) was used.

MNS, DMNS, and t_{MNS} in a binary powder of GA (10%) and SA (100—150, 200—250, or 250—325 mesh) were affected by mechanical energy such as shaking duration or compressive stess in a similar manner to that shown in Figs. 1 and 2 for a binary powder of GA and SA (150—200 mesh).

4) Effect of Storage Temperature of the Mixed Powders MNS and DMNS were also found to be dependent on the storage temperature (T_{st}) of mixed powders. Figure 4 presents the effect of T_{st} on the plot of MNS against log DMNS for the binary powder of GA (10%) and SA (150—200 mesh). Increase in MNS and decrease in DMNS were observed with a rise in T_{st}. The dependences of MNS and DMNS on T_{ca}, on atmosphere of storage, and on particle size of SA at a constant T_{st} (40 °C or 80 °C) were similar to those obtained at T_{st} of 25 °C, as shown in Figs. 1—3. Increment of MNS and decrement of DMNS were

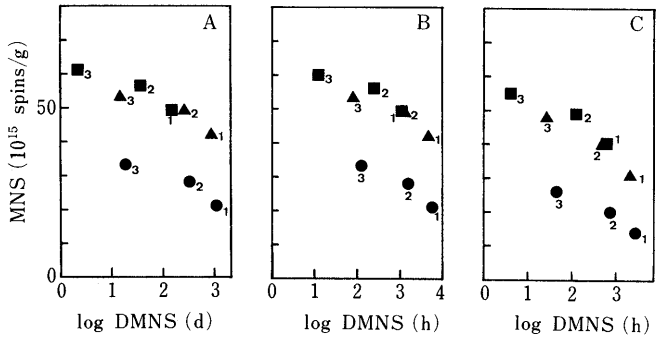

Fig. 4. Effect of Storage Temperature on the Plot of MNS against log DMNS for the Binary Mixture of GA (10%) and SA (150—200 mesh) at Constant Shaking Duration (15 min)

Temperature of storage: 1, 25 °C; 2, 40 °C; 3, 80 °C. Other symbols are the same as those in Fig. 1.

considerable when an SA_{600}-containing powder was stored at a high temperature (80 °C). A decrease of DMNS at 80 °C was prominent in a humid atmosphere.

MNS, DMNS, and t_{MNS} for a binary powder of GA (10%) and SA (150—200 mesh) stored at a constant temperature (40°C or 80°C) were affected by mechanical force induced by shaking or compressing in a similar manner to that shown in Figs. 1 and 2 for the binary powder stored at 25 °C.

A binary powder of GA (0.1%) and SA_{600} (150—200 mesh) at constant shaking duration (15 min) was allowed to stand for 2 h at 80 °C, then 10% of GA was mixed into this powder at 25 °C, shaken for 15 min, and then stored at 25 °C in nitrogen. MNS for this powder was determined to be 55×10^{15} spins/g, which was intermediate between the values at T_{st} of 25 °C (49×10^{15} spins/g) and 80 °C (61×10^{15} spins/g). DMNS of this powder was found to be 95 d, which was less than the value at a T_{st} of 25 °C (140 d) and greater than the value at a T_{st} of 80 °C (51 h). This suggests that a mixed powder of GA and SA once allowed to stand at an elevated temperature can increase the number of radicals, which may accelerate the contact reaction of GA on SA. The induction of active sites on the surface of SA on exposure to a high temperature may suggest the need for activation energy for the generation of active sites. Further details will be reported in a subsequent publication.

Application to the Manufacture and Storage of Drugs As described above, MNS and DMNS were found to be dependent on T_{ca} and on conditions of storage of the powders, such as atmosphere or temperature. DMNS decreased remarkably in oxygen or a humid atmosphere. As described in previous papers,[1,11] the formation of radicals may be one of the main courses of contact reactions in drugs and the reduction of DMNS suggests an increase in the rates of contact reactions. That is to say, mechanical energy can induce radicals and the radicals can accelerate contact reactions during the manufacture or storage of drugs. In addition, conditions of storage such as temperature and atmosphere significantly affect the rates of contact reactions. Even if powders are not mixed until immediately before use, mechanical energy applied during the manufacture of powders may increase the radical-generating abilities of mixed powders and then may increase the rates of contact reactions upon mixing.

We consider that it is important to minimize the number of radicals in a mixed powder during the manufacture and storage of drugs. For example, when GA (10%) and SA_{600} was mixed under stirring (15 min) at −72 °C (dry ice in ethanol) and stored in a freezer (around −5 °C) in an atmosphere of nitrogen, the number of spins/g at 24 h, 7 d, or 5 years after mixing was determined to be 2×10^{15}, 9×10^{15}, or 12×10^{15} spins/g, respectively. Moreover, much of the GA showed an unaltered infrared (IR) spectrum even 5 years after mixing. Thus, we should like to propose that a powdery drug should be stored at a temperature as low as possible, in an oxygen-free and moisture-free atmosphere, and should be mixed just before its use. It should be worthwhile to examine the effects of other types of mechanical forces as well. Proper consideration of mechanochemical effects could lead to improvements in the methods of manufacturing or storing drugs.

Experimental

Materials Commercial GR grade GA was used after being recrystallized from water and dried under a vacuum. Nikki Kagaku N631-L Type SA was calcined for 5 h at 200, 400, or 600 °C.

ESR Measurement The spectrometer, instrumental settings, and the method for the determination of the number of radicals were described in previous papers.[1,11] The number of radicals was expressed in spins per gram of SA. Experimental errors in the numbers of spins/g were found to be less than 3.5%.[1,11]

Procedure GA (0.1—10%) was mixed with SA (100—150, 150—200, 200—250, or 250—325 mesh) in nitrogen, dry air, or humid air and was shaken vigorously in a glass vessel for 5—240 min. A mixed powder of GA and SA was placed between two stainless steel plates after having been shaken for 15 min in a glass vessel. Compressive stress in the region of 1—500 kg/cm² was applied for 5 min by the use of a tabulating machine. This mixed powder was stored in a desiccator, a glass vessel, or an ESR cell in an atmosphere of nitrogen, of dried air, or of humid air at 25—80 °C in the dark. Powders thus prepared were shaken at 10- to 12-h intervals. Dried air or humid air was obtained using a desiccator by the usual method.[13] The T_{st} of a mixed powder was adjusted by the use of a thermostat.

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