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Stable Free Radical Formation in the Binary Powders of Silicates and Organic Compounds

Stable free radical formation was observed in the binary powders of silicates and general organic compounds by the use of ESR at room temperature in the air. A large amount of free radicals was formed, if an OH or COOH group containing organic molecule was used. Free radicals were stable not only in the air but also in the suspension of benzene. However, they disappeared immediately upon contact with proton donating liquid molecules. Increase in spectral intensities with time and variation of spectral shapes with moisture were observed.

Keywords——electron spin resonance; mixed powder of two components; free radical; chemical interaction; incompatibility; silicate; solid acid

Chemical incompatibilities are usually undesirable for drugs, but it is necessary to investigate them widely for improving the methods of preparation and preservation of drugs. To our regret, it is difficult to study in detail on chemical changes in drugs, even in the case that the occurence of them are obvious at first glance. So, comparatively small number of reports were known relating to the analyses of chemical reactions in powder drugs. For example, spectroscopic and chromatographic techniques were applied to the analysis of isomerization of vitamine D_2 in inorganic powders containing solid acid sites.(1)

In our opinion, chemical interactions may be included in all drugs, if weak intra- and intermolecular interactions are taken into account. Now we imagine that there are many kinds of interactions necessary for the study of incompatibilities, and that some of interactions have not yet been thought much of, or have not yet been tried to be observed in the study of chemical incompatibilities.

We reported previously the free radical formation in the binary powders of saccharides and metaloxides.(2) Analogous to this observation, we succeeded in observing the stable free radical formation in the binary powders of silicates and general organic compounds by means of electron spin resonance (ESR).

Silicates used here were silica alumina, aluminum silicate, magnesium aluminosilicate, Y type zeolite, and aerosil 200 (hydrophilic silica gel). All these silicates were used after calcining for 5 hours at 110—600°. Organic molecules used here were amino acids, vitamines, pyridine carboxylic acids, aliphatic and aromatic carboxylic acids, nitrogen ring containing aromatic acids and bases, hydrocarbons, and so on.

Prescribed ratios (0.1—50 wt%) of organic compounds were mixed directly with silicates in the air at a time and stirred vigorously for 15 minutes. ESR spectra (X band, 100 kHz modulation) of these mixed powders were measured at room temperature (23°) from immediately after mixing up to 50 days. Amounts of free radicals were determined by using DPPH and were converted to the number of spins per gram of anhydrous silicates.

Fig. 1 depicts the typical ESR spectra of the stable free radicals generated in the binary powders of silica alumina and (a) glycolic acid, (b) ascorbic acid, (c) salicylic acid, and (d) quinoline. These spectra offer corroborating evidence for the stable free radical formation in these binary powders. Furthermore, ESR spectra were measured for the binary systems of silicates and organic molecules having a variety of combinations and compositions. Consequently, stable free radical formation was generally observed in the air at room temperature. Amounts of free radicals were 1×10^{12}—6×10^{13} spins/g for the binary powders containing

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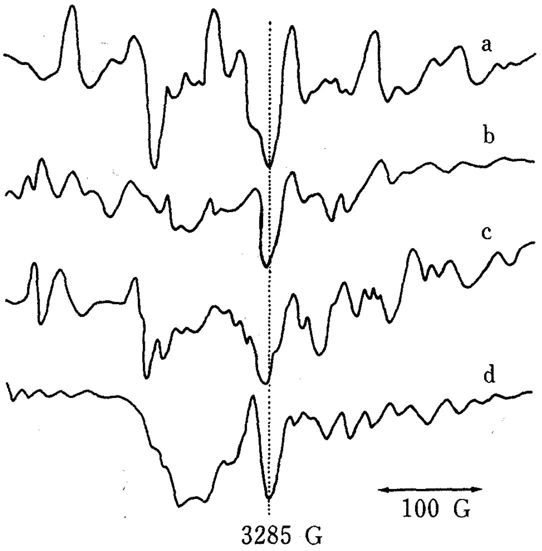

Fig. 1. Typical ESR Spectra of the Free Radicals Generated in the Binary Powders of Silica Alumina and Organic Compounds (10 wt %)

Organic compounds: a; glycolic acid, b; ascorbic acid, c; salicylic acid, d; quinoline. All mixed powders were left in the air at 23° for 24 hours after mixing. Then ESR spectra were recorded with the following instrumental settings: power; 20mW, modulation amplitude; 6.3 G, scan rate; 31.25 G/min, time constant; 3 sec, gain; 2×1000. In our experiments, a signal having $g=2$ is observed at 3285 gauss.

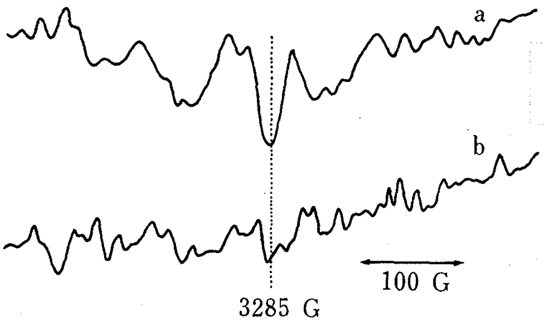

Fig. 2. ESR Spectra of the Free Radicals Generated in the Binary Powder of Silica Alumina and Ascorbic Acid (10 wt %) at a Week after Mixing in an Atmosphere of Nitrogen or of Oxygen

Atmosphere: a; nitrogen, b; oxygen. Mixed powder was left for a week after mixing at 23° in an atmophere of nitrogen or of oxygen. Then ESR spectra were recorded with the following instrumental settings: power; 20mW, modulation amplitude; 6.3 G, scan rate; 31.25 G/min, time constant; 3 sec, gain; 2×1000.

aerosil 200, and 1×10^{14}—7×10^{16} spins/g for the binary powders containing silica alumina, aluminum silicate or Y type zeolite. As far as organic molecules were concerned, OH or COOH group containing molecules, such as glycolic acid, glutaric acid, lactic acid, ethylene glycole, and glycerol were usually found to generate large amounts of free radicals.

Free radicals were found to disappear immediately upon contact with proton donating liquid molecules such as water, alcohols, ether, and acetone. But they were considerably stable in the suspension of benzene. Spectral intensities increased with the elapse of time for almost all binary systems. Spectral shapes were also found to be time dependent at initial stage after mixing in the binary powders of acidic (basic) organic compounds and silicates containing solid base (solid acid), although spectral intensities were rather weak. On the other hand, large amounts of free radical formation and small time dependences in spectral shapes were observed in the binary powders of acidic organic molecules and aluminosilicates containing solid acid sites.

Most of spectral shapes and intensities were found not to be influenced by oxygen. However, free radicals generated in the binary powders containing oxidizing or reducing agents were often found to behave anomalously in an atmosphere of oxygen. For instance, ESR spectrum of the binary powder of silica alumina and ascorbic acid (10 wt %) was almost identical to that depicted in Fig. 1(b) at the beginning in an atmosphere of either nitrogen or oxygen. Fig. 2 illustrates the ESR spectra of the free radicals generated in the binary powders of silica alumina and ascorbic acid (10 wt %) left for a week after mixing in an atmosphere of nitrogen or in that of oxygen. As can be seen from Fig. 2, the magnitude of the spectral change is small in an atmosphere of nitrogen even at a week after mixing. However, in an atmosphere of oxygen, spectral shape changed unusually for a period of a week after mixing, and spectral intensity was found to decrease enormously with the elapse of time.

The amount of free radicals was found to be affected by a mechanical process. For example, the number of free radicals in the binary powder of silica alumina and glycolic acid (10 wt %) was 2.2×10^{16}, 4.2×10^{16}, 5.8×10^{16}, or 7.0×10^{16} spins/g when the powder was stirred for 5, 15, 30, or 60 minutes after mixing, respectively. Furthermore, the number of free radicals was also found to increase with a decrease in particle size, with an increase in grinding time or in compressive stress, or with the raise of heating temperature.

Generally, free radicals begin to disappear even in the solid solutions at 77°K. However, very stable methyl radical formation was observed before now by the photolysis of methyl iodide adsorbed on Vycor glass[3] or on silica.[4] Judging from these facts, our discovery of stable free radical formation in the binary powders seems to be reasonable. Namely we succeeded in observing the remarkable stabilization of free radicals simply by mixing organic molecules with silicates and stirring.

Following studies are known as examples of radical formation upon contact of different kinds of powders: charge transfer complex formation,[5] ion radical formation of organic molecules such as perylene or TCNE adsorbed on the Lewis acid or base sites of metaloxides,[6] and so forth. In these fields of studies, it is easy to observe ESR signals experimentally, because amounts of free radicals were considerably large. But it is difficult to study chemical changes of adsorbates after mixing, because weak signals produced by reactions may be superposed and hidden by the strong original signals. As far as our experiment is concerned, however, the situation is entirely converse. Although it is difficult to find out ESR signals, it is suitable to pursue time dependences of spectral shapes and intensities after mixing. For example, shapes of ESR spectra were liable to change gradually under the conditions of high temperature and humidity. This corresponds to the fact that temperature and moisture are considered to be the main driving forces of chemical incompatibilities of drugs. Therefore, we hope that our discovery of stable free radicals adsorbed on silicates will be used for the developments of studies on incompatibilities of drugs in the future. Furthermore, the number of free radicals was found to be affected by mechanical processes. Therefore, chemical changes or interactions caused by mechanical energies in the manufacture of drugs must also be considered in detail in the future.

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