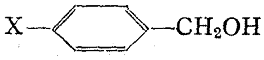
3) The reaction mechanism whereby diphenylmethane is formed by the aromatic electrophilic substitution of  has been clarified.

(Received January 23, 1955)

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25. **Hisakichi Matsumura, Sadao Iguchi, Shigeru Miyamoto, and Magobei Yamamoto** : Colloid Chemical Researches on Suspensions in Pharmacy. I. On Thixotropy in Vegetable Oil-Aluminum Stearate System.

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In the field of pharmacy, the problem of drug form is of great importance. Studies on this problem have made tremendous advances in the past few years with the successive discovery of antibiotics and enlargement of their applications. As one of the problems of drug form, thixotropy, which has often been observed in the now widely used penicillin injection in oil, especially when a mixture of vegetable oil and aluminum stearate system is used as the base, was taken up and fundamental colloid chemical studies were carried out in order to examine its nature.

Studies on thixotropy have been carried out in many laboratories and the characteristics of aluminum and other metallic soaps in various solvents have also been studied extensively,[1~10] in which the phenomenon of thixotropy has often been observed.[4,5,11~13] On the other hand, rheological measurements of the systems showing thixotropy have also been made[14~21] and, with other means of studying gels, such as the dielectric constant,[22,23] scattering[24] and absorption of light,[25] and propagation of sound waves,[26] much knowledge has been gained. However, no such studies have been made on the

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afore-mentioned vegetable oil-aluminum stearate system that constitutes a base for penicillin in oil.

The writers, therefore, first took up the rheological studies on the thixotropy of peanut oil, the most commonly used vegetable oil for penicillin base. At the same time, examinations were also made on castor oil which shows the most specific characteristics among vegetable oils and experimental results were compared.

Experimental

The oils used as sample were all Japanese Pharmacopoeial products. Aluminum stearate was the market product of aluminum monostearate,* which was washed repeatedly with water, acetone, and ether, then dried, and prepared into a fine powder by sifting through a No. 7 sieve J.P. VI of ca. 200 mesh. Considering the analytical results reported by Ikeda, *et al.*,[27] this product is not a pure aluminum monostearate but a mixture of mono- and di-stearates, its mixture ratio probably being about 2:8, or 3:7. For the preparation of a thixotropic system to be used for the measurement, the aluminum stearate powder was added to the vegetable oil with stirring, completely dissolved by heating for 1 hr. at 130° under stirring, and the mixture was rapidly cooled in ice water. In this case, addition of more than 2%** of aluminum stearate to the peanut oil resulted in the maintenance of a gel when allowed to stand and the content did not flow out even when the container was inverted. On the contrary, such thixotropy was not observed with castor oil even on the addition of aluminum stearete up to 5%, which is in good agreement with the facts reported by Nogami, *et al.*[28]

The apparatus used for the rheological measurements of these systems was the same as that used

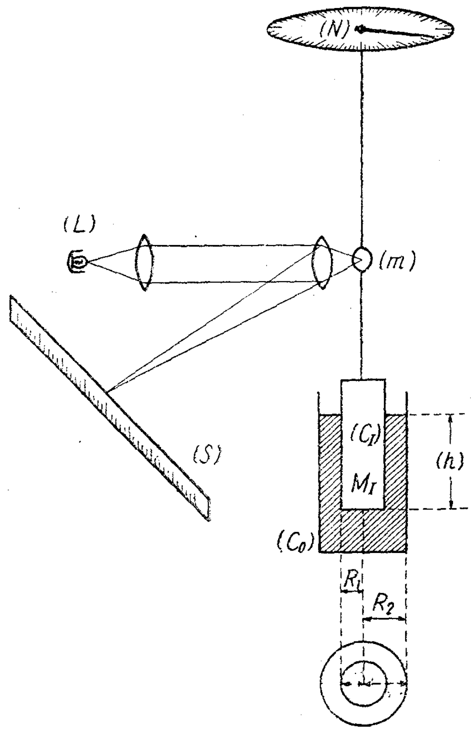

Fig. 1.
Apparatus of the Concentric Cylinder Method used for the Rheological Measurements

N: indicator needle of the protractor
L: light source
m: mirror
S: scale
C_O: outer cylinder
C_I: inner cylinder
R_1: radius of C_I
R_2: radius of C_O
M_1: mass of inner cylinder
h: depth of the inner cylinder immersed in the sample

* Kwanto Chemical Product.

27) H. Ikeda, *et al.*: Sci. Papers Inst. Phys. Chem. Research., **10**, 359 (1949). Analysis for aluminum stearate used: Al, 4.87 (½ Al_2O_3, 9.21); stearic acid, 92.57; C, 68.54; H, 11.51. Ikeda and others calculated the analytical values of aluminum, stearic acid, carbon, and hydrogen when aluminum monostearate and distearate, taking their molecular formulae as $C_{17}H_{35}COOAl(OH)_2$ and $(C_{17}H_{35}COO)_2Al(OH)$, respectively, are mixed in a certain ratio. These analytical values may not give the componental ratio in a strict sense but they were considered to give approximate values, and approximate mixture ratio of aluminum mono- and di-stearates was calculated from the foregoing analytical values.

** Percentage of aluminum stearate to oil always means weight per cent of aluminum in oil.

28) H. Nogami, H. Matsuura: Annual Report of the Hospital Pharmacist Committee (Japan), No. 13, 71 (1954).

by Hatschek[29] and Pool[30] (Fig. 1). The sample was filled between two concentric cylinders made of glass. The inner cylinder was suspended by a copper wire, the top of which was fixed to the indicator needle (N) of the protractor. After stirring the sample filling the space between the two cylinders, the top end of the wire (N) was rotated to a certain degree, and the velocity of the turn by the lower end of the wire was measured. A light coming from the light source (L) was reflected by a mirror (m) fixed to the lower end of the wire and the position of the reflected light spot on the scale (S) was read to measure the rotational angle of the wire. In order to calculate the force applied to the sample by rotating the wire, the torsion constant (K) of the wire must be known. For this purpose, a cylindrical weight (radius, r; mass, M)* was suspended from the wire, and the period (T) of rotational vibration in the air was measured, then the constant (K) was calculated from the following equation:

$$K = 2M(\pi r/T)^2, \qquad \cdots\cdots\cdots\cdots\cdots\cdots (1)$$

It has been confirmed by present experiments that the elastic hysteresis could be disregarded by the repeated rotational vibration of the wire. The apparatus containing the sample was placed in a thermostat and the measurements were carried out at 25°.

Experimental Results and Discussions

The Vegetable Oil—Aluminum stearate system used in the present series of experiments, as can be seen from its thixotropic behavior, possesses a fairly complicated internal structure and rheological properties. For the sake of comparison, pure viscous flow (Newtonian flow) will first be considered. In the case of pure viscous flow, the rate of deformation is given by,

$$d\theta/dt = K{\cdot}C(\theta_0-\theta)/\eta, \qquad \cdots\cdots\cdots\cdots\cdots\cdots (2)$$

where, θ_0 is the rotated angle initially given to the top of the torsion wire, θ, the rotated angle of the lower end of the wire at the time, t, after the top of the wire has been rotated, K the torsion constant of the wire, η the coefficient of viscosity, and C the constant given by,

$$C = (1/R_1^2-1/R_2^2)/4\,\pi h, \qquad \cdots\cdots\cdots\cdots\cdots\cdots (3)$$

where h is the depth to which the inner cylinder is immersed in the sample, R_1 and R_2, the radius of the inner and outer cylinders, respectively (see Fig. 1).

It follows, therefore, that the rate of deformation ($d\theta/dt$) is proportional to the stress applied to the sample $K(\theta_0-\theta)$, and the coefficient of viscosity (η) is calculated as shown by Fig. 2.

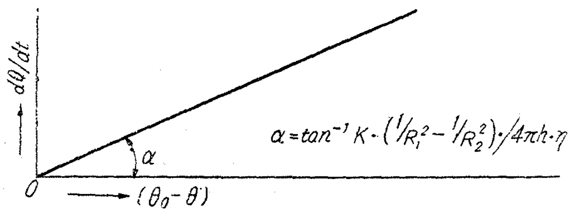

Fig. 2.

On the contrary, such a proportionality cannot be established between the rate of deformation ($d\theta/dt$) and the stress $K(\theta_0-\theta)$ in quasi-viscous flow and in quasi-plastic flow when the stress is small, and these constitute the so-called non-Newtonian flow. It goes without saying that the thixotropic system is not a Newtonian flow and the relationship between the rate of deformation and the stress is assumed to change with passage of time. Therefore, in the present experiments, the measurements were made immediately after stirring of the sample and also at various time of standing after stirring.

29) E. Hatschek: Kolloid-Z., **39**, 300 (1926).
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* The cylindrical weight used throughout our experiments except for the case of Fig. 9 was made of brass (r=1.0 cm, M=109.0 g.). In the case of Fig. 9, a glass cylindrical weight was used (r=0.544 cm., M=26.74 g.).

The first experiment was carried out using castor oil alone, without the addition of aluminum stearate, and the relationship between θ and t is indicated in Fig. 3, from which the relationship between $(d\theta/dt)$ and $(\theta_0-\theta)$ was calculated, as shown in Fig. 4. It can be seen from Fig. 3 that the castor oil behaves as a pure viscous flow and that the same holds when the sample is allowed to stand for a long time, there being no change in the value of the coefficient of viscosity (η). Peanut oil also behaved as a pure viscous flow, as in the case of castor oil, when aluminum stearate was not added (Fig. 5.). These were experiments carried out on oils without any treatment and no change occurred when the oil was heated for 1.5 hrs. at 130~250°. The oil behaved as a pure viscous flow and there is no great change in the viscosity of the oil by heat treatment to this extent.

It has been found by preliminary experiments that the thixotropy was not established until the addition of up to about 2% of aluminum stearate of the product used in the present experiments. As samples, therefore, the system (I) containing 0.5% of aluminum stearate, which did not show thixotropy, and the thixotropic system (II)

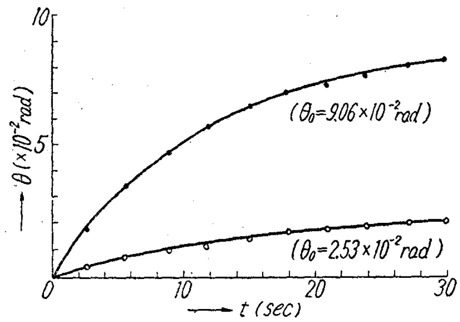

Fig. 3.
Castor Oil
$K=7.85$ dyne/cm²

$R_1=0.55$ cm.
$R_2=1.013$ cm.
$h=5.95$ cm.
M_1 (Mass of inner cylinder) $=26.74$ g.

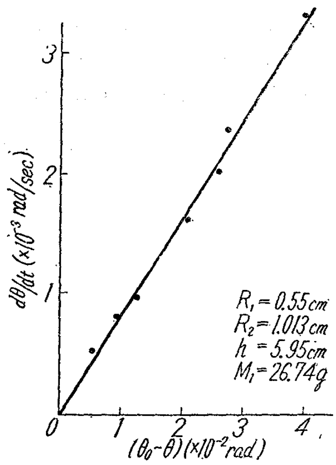

Fig. 4.
Castor Oil
$K=7.85$ dyne/cm²
$\eta=2.9$ poise

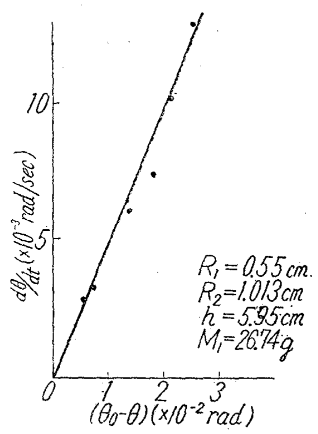

Fig. 5.
Peanut Oil
$K=7.85$ dyne/cm²
$\eta=0.56$ poise

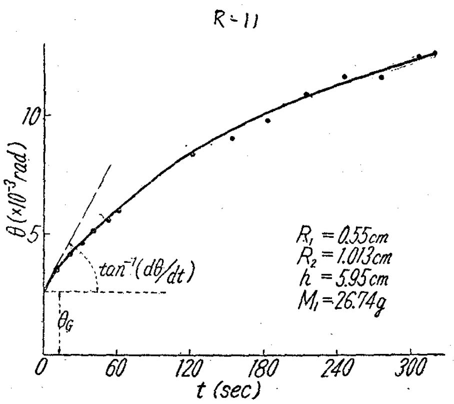

Fig. 6.
Peanut Oil Containing Aluminum Stearate
(0.5%) [Sample I]
$K=7.85$ dyne/cm²
(10 mins. after stirring)

containing 2% of aluminum stearate were selected. The results are shown in Figs. 6~8. Fig. 6 indicates the results obtained with sample (I) allowed to stand for the indicated period of time and the relationship between θ and t measured. In this case, the rotation of the upper end of the wire immediately caused the rotation of the lower end by θ_G, and the rotational angle gradually increased in the course of time. On the other hand, measurement immediately after stirring indicated $\theta_G=0$, the relationship being the same as that indicated in Fig. 3. In these cases, θ_G may be taken as a portion of elastic deformation, and the rigidity (G) may be calculated by,

$$G = K(1/R_1^2-1/R_2^2)\cdot(\theta_0-\theta_G)/4\pi h\cdot\theta_G, \quad\cdots\cdots\cdots\cdots\cdots\cdots(4)$$

In observing the flow following elastic deformation, we can confirm that the system studied was a thixotropic one since the relationship between the rate of flow and the stress is seen to change with time. Therefore, to avoid the change of the rheological property of the system with time (gel formation), and that caused by the stress given to measure the system (gel destruction), the $(d\theta/dt)$ shown in Fig. 6 and $(\theta_0-\theta_G)$ were taken respectively as the rate of flow and the stress given at a certain time of standing after stirring the sample. Fig. 7 shows such relationship between $(d\theta/dt)$ and $(\theta_0-\theta_G)$. As can be seen from this figure, the sample (I) also behaves as a pure viscous flow immediately after stirring, the same as in the case of peanut oil not containing aluminum stearate, although the coefficient of viscosity has become extremely large due to the presence of aluminum stearate. On the contrary, when the mixture is allowed to stand after stirring, elastic deformation appears and its rigidity tends to increase with passage of time, with the increase of viscosity of the flow following it, the values gradually departing from pure viscous flow. This non-Newtonian flow shows greater rate of flow as the force added becomes greater. Although a visible gelation was not observed, it is noteworthy that the characteristics of thixotropy such as these had actually appeared with this sample. In such a case, elasticity and viscosity can be shown by a mechanical model of series connection and the values of viscosity coefficient and rigidity also shown on each figure. Even in the sample (I) with a small amount of aluminum stearate,

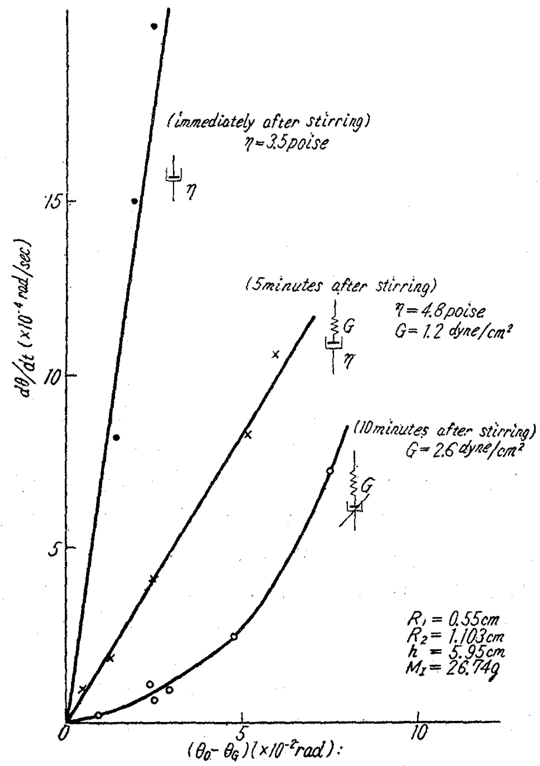

Fig. 7.
Peanut Oil Containing Aluminum Stearate (0.5%) [Sample I]
$K=7.85$ dyne/cm²

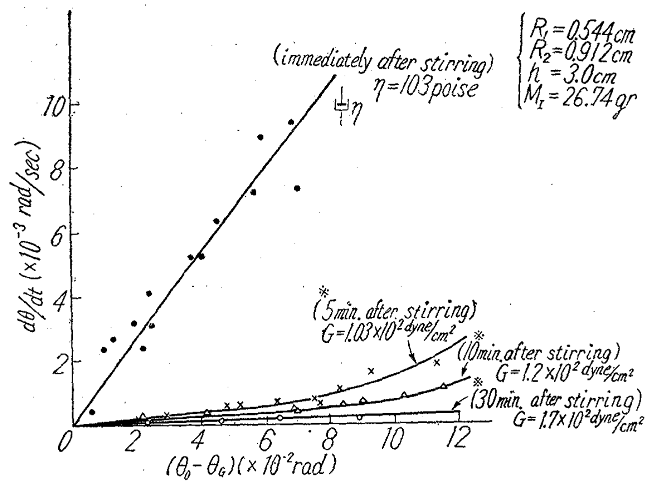

Fig. 8.
Peanut Oil Containing Aluminum Stearate (2%) [Sample II]
$K=2.37$ dyne/cm^2

* Model for these cases may be represeted as —wwʌ—, but the effect of time must be examined with larger measurement data.

the progress of gelation is seen to proceed on standing, as shown before.

Fig. 8 shows the results obtained with the sample (II) in which thixotropic gelation is more apparent. The viscosity of this sample suddenly increases with the increase in the concentration of aluminum stearate, and the foregoing characteristics were seen to appear very markedly.

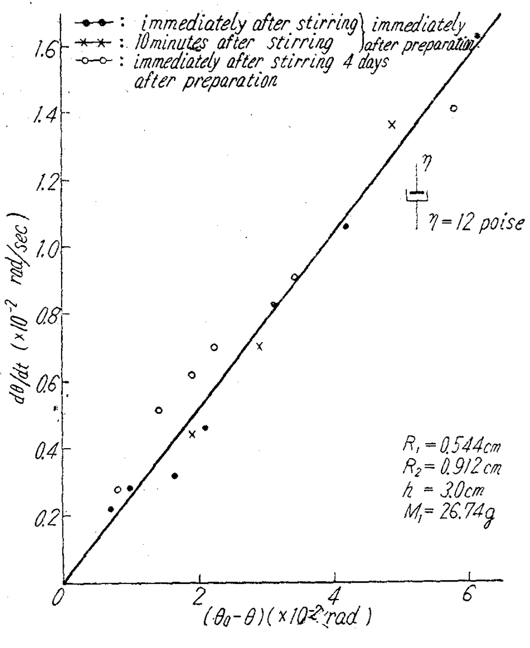

Fig. 9.
Castor Oil Containing Aluminum Stearate (2%) [Sample III]
$K=51.1$ dyne/cm^2

The same experiments were then carried out on the sample (III) of castor oil containing 2% of aluminum stearate, as a control. The results obtained are shown in Fig. 9, in which the values are those obtained from measurements carried out immediately and four days after preparation. These values clearly indicate that the sample (III) shows a pure viscous flow without an elastic deformation.

It was observed that (III), after stirring and standing, showed no change in the mode of flow. This makes a clear contrast to the fact that the sample (I) of peanut oil containing 0.5% of aluminum stearate behaves like a non-Newtonian flow after standing. Further, this is in good agreement with the fact that castor oil does not show thixotropy even on increasing the concentration of aluminum stearate.

The coefficient of viscosity (η) of various samples are listed in the following table:

Sample	η	Sample	η
Peanut oil	0.56 Poise	I. Peanut oil + Al-stearate(0.5%)	3.5 Poise*
〃	〃	II. Peanut oil + Al-stearate(2%)	103.0 Poise*
Castor oil	3.0 Poise	III. Castor oil + Al-stearate(2%)	12.0 Poise*

* Value immediately after stirring.

As shown above, the viscosity of peanut oil markedly increases on the addition of aluminum stearate and such a fact suggests the possibility that aluminum stearate takes a complicated secondary structure by mutual contact immediately after the stirring of a sample. Further development of the structure might result into gelation. On the contrary, such phenomenon does not occur in castor oil and it is presumed that aluminum stearate molecules are dispersed in the oil or even if they form a secondary structure, such bonding may be so weak that the structure does not develop enough to cause gelation.

The question now arises in the above experiments as to whether there is any effect of the torsion wire used for measurements. In a complicated system such as the thixotropic system, difference in the radius of torsion wire causes change in the velocity of automatically decreasing force effected to the system, and there will be a change in the coefficient of viscosity measured. For example, it may naturally be supposed that a fine wire will cause the measurement to be made very slowly, during which time gelation will proceed somewhat and attendant increase in the viscosity will occur. Such points must be examined further by a larger number of measurements. Further, there are the ploblems of the aging of samples, the effects brought about by the repeated mechanical work (stirring and measuring procedures), structure of aluminum stearate in oil, flow of the three component system of the base (oil + aluminum stearate) with penicillin granules, etc. These are important problems which must be attacked further and will be reported in future.

The authors are much indebted to Dr. T. Sasaki, Professor of Tokyo Metropolitan University, for his guidance, and wish to thank Mr. T. Hattori and Mr. T. Maeda for carring out microanalyses. A part of the expenses for this work was defrayed by the Grant in Aid for Scientific Research from the Ministry of Education, to which the authors are also indebted.

Summary

1. By employing the concentric cylinder method, rheological studies were made both on the thixotropy of the peanut oil-aluminum stearate system, the most commonly used base for penicillin injection, and also on the castor oil-aluminum stearate system for the sake of comparison.

2. Peanut oil and castor oil containing no aluminum stearate showed the Newtonian flow. The mechanical behaviours of the oil-aluminum stearate system were expressed by mechanical models.

3. The mechanical models of the system containing aluminum stearate (up to 2%) in peanut oil were as follows. Immediately after stirring, the sample behaves as a pure viscous flow (Newtonian flow), whose viscosity coefficient was very high compared to the oil containing no aluminum stearate. This model became the Maxwell model with Newtonian flow and then it turned into the Maxwell model with non-Newtonian flow in the course of time. On the other hand, the model for the castor oil system containing aluminum stearate (up to 2%) was always Newtonian flow, and neither elasticity nor non-Newtonian flow was observed in the course of time after standing of the sample.

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