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87. **Ken Ikeda**: Studies on Decomposition and Stabilization of Drugs in Solution. IV.[*1] Effect of Dielectric Constant on the Stabilization of Barbiturate in Alcohol-Water Mixtures.

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It is usual to use sodium salt for the preparation of solutions of barbital derivatives, because the solubility of free acids is very small. However, aqueous solution of these salts is not stable so that it is impossible to store them for longer period or to sterilize them by heat without noticeable degradation. For these reasons, some sodium barbiturates for parenteral use are sealed in ampules in crystalline form and dissolved immediately before use. Another usual method for avoiding degradation is to dissolve barbiturates in a mixed solvent of water and organic solvents such as alcohol, propylene glycol, glycerol, or polyethylene glycol.[1~3] Usefulness of these solvents for stabilization is reported by many investigators but the reason that barbiturates are stabilized by those media has not been revealed.

There are many instances where medicaments which are easily decomposed are stabilized by the addition of some substances. Addition of a reducing agent to solutions of medicaments which are easily oxidized is an instance. Stabilization of ascorbic acid in a mixed solvent was reported by Bandeline, *et al.*,[4] who concluded that it was stabilized by the decrease of dissolved oxygen in the mixed solvent, but the stability of barbiturates in a mixed solvent cannot be explained by these mechanisms, because the major route of degradation of barbiturates is a hydrolysis and not an oxidation. Recently, inhibition of hydrolysis of some anesthetic esters by the addition of caffeine was proved by chemical kinetic studies to be attributed to the formation of a complex between esters and caffeine.[5] However, because the complex compound is formed only between specific combination of substances, such stabilizing methods are not useful in all cases.

Since the concentration of organic solvents in a mixed vehicle is considerably high, organic solvents cannot be considered as a stabilizer and the stability of medicament in those vehicles must be caused by the change of property of the medium itself. From the stand-point of chemical kinetics, dielctric constant is known as one of the fundamental properties which influence the reaction rate.[6] However, studies on the relationship between stabililty of medicament and dielectric constant of a medium had not been seen unitl Marcus, *et al.* reported recently on the hydrogen ion-catalyzed solvolytic reaction of chloramphenicol in propylene glycol-water medium.[7] They found, contrary to their expectations, that reaction rate of the antibiotic increased as the proportion of propylene glycol increased. From these results, they assumed that the reaction is an ion-dipole molecule type rather than an ion-ion type.

The object of the present study is to investigate the relationship between degradation

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[*2] Kita-4-bancho, Sendai (池田 憲).

1) W. A. Husa, *et al.*: J. Am. Pharm. Assoc., Sci. Ed., **33**, 217(1944).
2) G. Raine, *et al.*: Pharm. J., 1955, 427.
3) J. I. Bodin, *et al.*: J. Am. Pharm. Assoc., Sci. Ed., **44**, 296(1955).
4) F. J. Bandelin, *et al.*: *Ibid.*, **44**, 241(1955).
5) T. Higuchi, *et al.*: *Ibid.*, **44**, 521(1955), **45**, 290(1956), **46**, 32(1957).
6) E. S. Amis: "Kinetics of Chemical Change in Solution," (1949). The Macmillan Company, New York.
7) A. D. Marcus, *et al.*: J. Am. Pharm. Assoc., Sci. Ed., **48**, 77(1959).

rate of barbiturate and dielectric constant in binary systems of water–ethanol and water–methanol to account for stabilization in these media.

In the previous study,[8] it was found that the degradation of phenobarbital in aqueous solution proceeded by two routes, i.e. degradation in molecular and ionic forms. The mechanism seems to be quite the same in other barbiturates, because corresponding malonuric and malonic acids or malonylurea derivatives are found in alkaline degradation.[9,10] For instance same decomposition procedure as phenobarbital was also ascertained in the degradation of N–methylphenobarbital in a recent study.*3 In solutions of sodium barbiturates, degradation seems to proceed mainly by the reaction between barbiturate ion and hydroxyl ion, because the pH of the salt solution is considerably high. In the present study, the reaction between barbiturate ion and hydroxyl ion was particularly investigated with respect to dielectric constant of the medium. A monobasic barbiturate is preferable to a dibasic barbiturate for chemical kinetic study because the former decomposes by alkali in one direction, i.e. reaction between univalent ion and hydroxyl ion, while the dibasic barbiturate decomposes in two directions, i.e. degradation in uni– and bivalent ionic forms. As a matter of fact, the degradation of monobasic barbiturate such as methylhexabital J.P. (Hexobarbital I.P.) (MHB) was proved to proceed in typical first–order reaction by addition of alkali, while dibasic barbiturate such as phenobarbital did not undergo degradation in a constant manner. Therefore, MHB was selected as the object in the present study.

The effect of dielectric constant on the rate of reaction between negative organic ion and hydroxyl ion in water–organic solvent mixtures was studied by Amis, *et al.*[11~14] In the present studies, chemical kinetic data were examined by the following equations. Eq. (1) shows the influence of dielectric constant on the reaction rate between two ions :

$$ln\ k'_0 = ln\ k'_{\substack{\kappa=0 \\ D=\infty}} - \frac{z_A z_B \epsilon^2}{DkTr} \qquad (1)$$

where k'_0 is the reaction rate at zero ionic strength, $k'_{\substack{\kappa=0 \\ D=\infty}}$ is the limiting rate at infinite dielectric constant and zero ionic strength, z_A and z_B are valencies of the two ions, and D, k, T, ϵ, and r are respectively dielectric constant, Boltzmann constant, absolute temperature, charge of ion, and distance to which two ions must approach in order to react. According to Eq. (1), reaction rate between like–sign ions decreases as dielectric constant decreases, and reaction rate between unlike–sign ions increases as dielectric constant decreases. This is interesting to pharmaceutical compounding of drugs, because it may be said that the addition of organic solvents such as alcohol, glycol, or glycerol is not always effective for the stabilization of medicaments in solution, but these solvents may sometimes accelerate degradation. A linear relationship between log k'_0 and $1/D$ is also shown by Eq. (1). The slope of this line, S, can be written as

$$S = \frac{d\ ln\ k_0'}{d(1/D)} = -\frac{z_A z_B}{kT}\ \frac{1}{r} \qquad (2)$$

The value of S is obtained from the results of experiment and the unknown value in Eq.

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*3 Will be published in this series of studies.

[8] J. Hasegawa, *et al.* : This Bulletin, **6**, 36(1958).

[9] H. Aspelund, *et al.* : Acta Acad. Aboensis, Math. et Phys., **10**, No. 10(1937), **14**, No. 14(1944), **18**, No. 4(1952), **20**, Nos. 3, 4(1955).

[10] H. Nuppenau : Dansk Tidsskr. Farm., **28**, 261(1954).

[11] E.S. Amis, *et al.* : J. Am. Chem. Soc., **61**, 905(1939).

[12] *Idem* : *Ibid.*, **63**, 2621(1941).

[13] W.J. Svirbely, *et al.* : *Ibid.*, **72**, 5699(1950).

[14] *Idem* : J. Phys. Chem., **56**, 1006(1950).

(2) is only r. By substituting proper values, r is calculated. The order of magnitude of r should be that of the radius of a molecule, i.e. 10^{-8} cm. If the experimentally obtained r is in this order, it can be said that the change of reaction rate to be tested is attributable to the change of dielectric constant and there is no specific solvent effect on the reaction rate. Another test with respect to the effect of dielectric constant is the difference of activation energy in the solvents of different dielectric constant. According to theory for a reaction between like-sign ions, a larger activation energy is necessary in a medium of lower dielectric constant, because repulsion between ions increases as dielectric constant decreases. The difference in activation energies between those at dielectric constant D_1 and D_2 is represented as follows⁶⁾ :

$$\varDelta E_c = -329.7 \frac{z_A z_B}{D_1 D_2 r} \varDelta D \qquad (3)$$

where $\varDelta D$ is the difference of two dielectric constants and $\varDelta E_c$ is the difference of the energy estimated from the change of coulombic energy. Eq. (3) shows that activation energy of the reaction between like-sign ions must increase as dielectric constant decreases.

Experimental

Estimation of MHB—Ionized MHB has characteristic maximum in its ultraviolet spectrum in aqueous solution[15,16] (above pH 10.0). Sample removed with 2-cc. pipette from the reaction flask was diluted to 50 cc. with a buffer solution of pH 10.0. Residual MHB was estimated by Hitachi spectrophotometer at 243 mμ. The buffer solution of pH 10.0 was composed of 55 volumes of 0.1M glycine-NaCl and 45 volumes of 0.1M NaOH solutions.

Preparation of Isodielectric Solvent—Dielectric constants of EtOH-H_2O and MeOH-H_2O mixtures were calculated from the tables prepared by Åkerlöf.[17] Weight percentage of the alcohol in the mixtures, which have appropriate dielectric constants investigated in this study, are tabulated in Table I. The amount of alcohol necessary to obtain a mixture with appropriate dielectric constants was calculated from the density of a mixture, which was determined with a pycnometer if not found in the references. Alcohols were purified as described by Åkerlöf.

Table I. Weight Percentage of Alcohols and Dielectric Constant of Mixtures

t°C	Dielectric constant	EtOH (w%)	MeOH (w%)
50	65.0	9.06	11.43
	60.0	18.53	22.37
	55.0	27.77	33.60
	50.0	36.98	44.99
40	65.0	15.25	18.18
	60.0	24.24	
	55.0		39.62
30	65.0	20.62	25.20
	60.0	29.19	
	55.0	37.61	46.67

Procedure of Chemical Kinetics—A suitable amount of alcohol was taken into a 100-cc. volumetric flask, 50 mg. of MHB was dissolved in it, and distilled water was added to bring the volume to 70 cc. The flask was stored at above 40° overnight with occasional shaking to dissolve MHB completely.

Distilled water used in this study was previously boiled to expel CO_2 and stored in a bottle stoppered with a soda-lime tube. N NaOH solution was prepared immediately before use with saturated NaOH solution and distilled water, and its factor was determined.

Calculated amount of NaOH solution was added to the flask to make appropriate concentrations

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15) Y. Sato : Nippon Kagaku Zasshi, **78**, 382(1957).
16) A. I. Biggs : J. Chem. Soc., **1956**, 2485.
17) G. Åkerlöf : J. Am. Chem. Soc., **54**, 4125(1932).

(0.16, 0.09, and 0.04*N*). Distilled water was then added to just below the graduation and the flask was mounted in a water bath regulated to an appropriate temperature. After about 15 min. distilled water was added to adjust the volume. Ten min. later, the first sample was removed and initial concentration of MHB was determined as mentioned above. At adequate intervals, samples were removed and residual MHB was estimated. In one kinetic procedure, residual MHB was estimated at least eight times. First-order reaction rate was calculated in the usual manner and second-order reaction rate, k', was calculated by dividing the first-order rate with concentration of NaOH. As the reaction proceeded, there was a tendency for the reaction rate to decrease. This seems to be caused by degradation products. Therefore, rate constant was determined by the average of data obtained before 20% of MHB was decomposed.

Estimation of log k'_0—Eq. (4) was used to estimate log k'_0 from log k' which was obtained at a certain ionic strength.[6]

$$\log k' = \log k'_0 + \frac{2z_A z_B A' \sqrt{\mu}}{1+\beta a_i \sqrt{\mu}} \tag{4}$$

where z_A and z_B are both -1 in this reaction, and A' and β are constants. The ionic strength, μ, is equal to molar concentration of NaOH. Eq. (4) predicts a positive effect of ionic strength on the reaction between like-sign ions. By trial and error, a value of parameter, a_i,[*4] which gave consistent value of k'_0 over the range of ionic strength studied was estimated.

Determination of Activation Energy—Activation energy was calculated from the reaction rate at $\sqrt{\mu}=0.3$, using the integrated Arrhenius equation. As dielectric constant varies with temperature, the proportion of alcohol in the mixture with a constant dielectric constant varies with temperature. Weight percentage of alcohol in the mixture investigated which have appropriate dielectric constant at various temperatures are tabulated in Table I.

Results and Discussion

Effect of Ionic Strength on Degradation—Fig. 1 shows several examples in which alkaline degradation of MHB proceeds in pseudo-first order reaction. The relationship between ionic strength and log k' at 50° is shown in Figs. 2 and 3. As seen in Figs. 2 and 3, there are seen positive effects of ionic strength which are predicted by Eq. (4). It was found that 7.0 Å was suitable as a value of a_i in EtOH–H_2O mixture and in pure water, and 6.0 Å in MeOH–H_2O mixture. Substituting these values, k'_0 was calculated. Black dots at zero ionic strength in Figs. 2 and 3 show average of calculated k'_0 and dotted lines show limiting slopes.

Relationship between log k'_0 and $1/D$—As seen in Fig. 4 the relationship between log k'_0 and $1/D$ is linear with a negative slope down to a dielectric constant of 55. This is in accordance with Eq. (1). The values of r calculated from the slopes were 1.2 Å and 0.90 Å in EtOH–H_2O and MeOH–H_2O mixtures, respectively. Although these values are

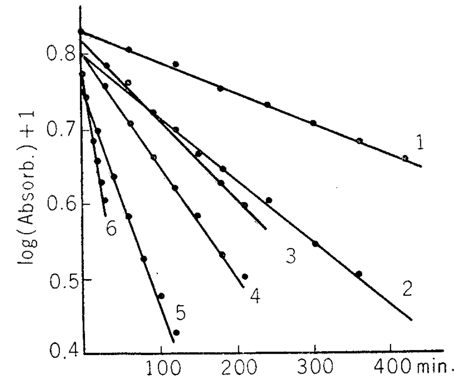

Fig. 1. First-order Degradation of Methylhexabital (50°C)

	Alcohol	D	$\sqrt{\mu}$
1	MeOH	50	0.3
2	〃	50	0.4
3	EtOH	50	0.3
4	〃	55	0.3
5	〃	55	0.4
6	MeOH	65	0.4

[*4] The distance of closest approach of the ions.

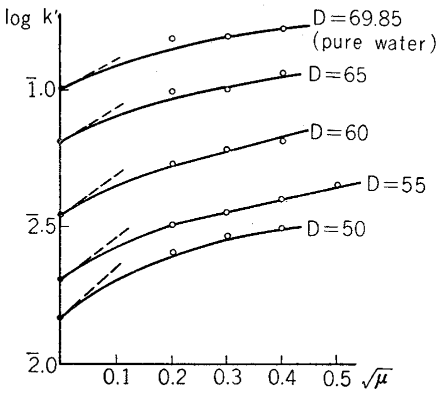

Fig. 2. Effect of Ionic Strength on *k'* in EtOH-H_2O Mixture (50°)

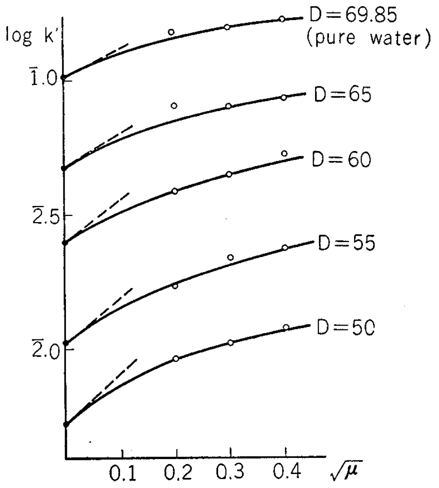

Fig. 3. Effect of Ionic Strength on *k'* in MeOH-H_2O Mixture (50°)

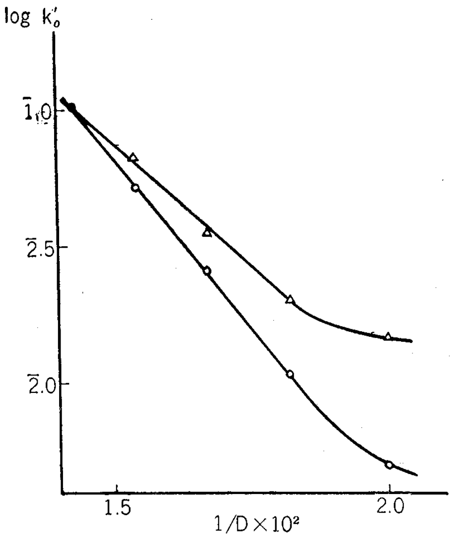

Fig. 4. log k'_0 vs 1/D (50°)

• H_2O
△ EtOH-H_2O
○ MeOH-H_2O

somewhat small, orders of magnitude are not notably out of the theoretical requirements.

Test by Activation Energy—Relationship between log *k'* at $\sqrt{\mu}=0.3$ and $1/T$ in isodielectric media is shown in Fig. 5. Activation energies calculated from these results in EtOH-H_2O mixtures were 16,900 and 17,100 cal./mole at the dielectric constant of 65 and

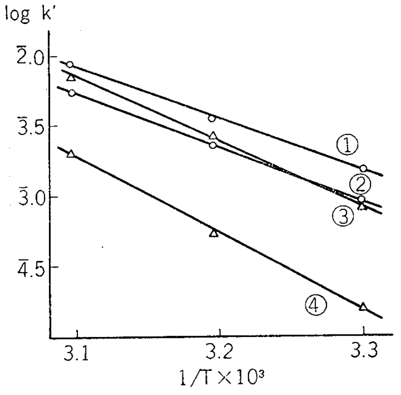

Fig. 5. Relationship between log *k'* and $1/T$ ($\sqrt{\mu}=0.3$)

	Alcohol	*D*
1	EtOH	65
2	〃	60
3	MeOH	65
4	〃	55

60. Observed ΔE is 200 cal., and that calculated by Eq. (3) is 350 cal. In MeOH–H_2O mixtures activation energies were 20,600 and 24,500 cal./mole at the dielectric constants of 65 and 55, respectively. Observed ΔE is 3,900 and that calculated is 1,020 calories. There is some disagreement of ΔE between values observed and that calculated, but it is observed that E increases as dielectric constant of the medium decreases.

From these observations it may be concluded that the decrease in the rate of alkaline degradation of MHB in solution, which is accompanied with addition of MeOH or EtOH, is attributed to the decrease of dielectric constant, and this conclusion may be extended to other barbiturate derivatives.

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Summary

The alkaline degradation of methylhexabital J. P. (hexobarbital I. P.) in ethanol–water and methanol–water mixtures was carried out and the following results and conclusions were obtained.

1) The change of reaction rate was tested by simplified Scatchard's equation (1). In both mixtures, relationship between logarithm of reaction rate at zero ionic strength and reciprocal of dielectric constant was negatively linear down to a dielectric constant of 55 to 50. The values of r, distance of approach sufficient for the reaction, were 1.2 Å and 0.90 Å in ethanol–water and methanol–water mixtures, respectively. The order of the magnitude of these values is not out of theoretical requirements.

2) Activation energies of the reaction in ethanol–water mixtures were found to be 16,900 and 17,100 cal./mole at the dielectric constant of 65 and 60, respectively. In methanol–water mixtures, they were 20,600 and 24,500 cal./mole at the dielectric constant of 65 and 55, respectively. It was found that activation energy increases as the dielectric constant decreases, in both mixtures.

3) From these observations, it may be concluded that the stabilization of a barbiturate in solution by addition of ethanol or methanol is attributable to the decrease of dielectric constant of the medium.

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