88.   Ken Ikeda :   Studies on Decomposition and Stabilization of Drugs in Solution.   V.*[2]   Stabilization of Barbiturate in Aqueous Solution of Polyalcohols and Sugars.

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In the previous study,[1] it was proved that the decrease of alkaline degradation of barbiturate in alcohol–water mixture was attributable to the decrease of dielectric constant of the medium.   Many other organic substances are used to dissolve and stabilize barbiturates.   Among those substances polyalcohols or their derivatives are frequently used. Glycerol, its ethers, and esters have been used as a vehicle for barbiturates for some time.   Recently propylene glycol came into prominence and has come to replace glycerol as a vehicle for barbiturates.   Polyethylene glycol is also a newly developed vehicle for barbiturates.   These substances are used in general as aqueous solution of several tens per cent.   Besides these substances, sugars are also compounded with barbiturate particularly in an elixir.   As the concentration of sugars are considerably high, they must affect the stability of barbiturates.   The effect of these substances on stability seems to be not so simple as that of monohydric alcohols, because their molecular structure is more complicated.

The object of the present study is to investigate the effect of these polyhydric alcohols or sugars on degradation rate of barbiturate with respect to dielectric constant.   However, as will be stated later, it was found that the strict test by theoretical equations employed in previous study was not applicable and the effect of these substances may not be attributable only to dielectric constant of the medium.   The results were examined to see whether the magnitude of the decrease of reaction rate was as large as that attributable to the change of dielectric constant or not.   Finally possible mechanism for stabilization activity of these substances is discussed.   Methylhexabital J. P. (hexobarbital I. P.) (MHB) was selected as the object of the present as in the previous work.   Binary solvents investigated were aqueous solutions of ethylene glycol, propylene glycol, glycerol, glucose, mannitol, and sucrose.

Experimental

The procedures of kinetic study, spectrophotometry, and calculations are essentially the same as those described in the previous study.   Dielectric constants were calculated from the tables prepared by Åkerlöf[2] and other investigators.[3,4]   The weight percentage of polyhydric alcohols and sugars in binary system investigated are shown in Table I.

Result and Discussion

The relationship between degradation rate and ionic strength at various dielectric constants in ethylene glycol–water and glycerol–water mixtures at 50° is shown in Fig. 1.

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*2   This work was undertaken in the Faculty of Pharmaceutical Sciences, University of Tokyo, and constitutes a part of a series entitled " Studies on Decomposition and Stabilization of Drugs in Solution " by H. Nogami.
1)   Part IV : This Bulletin, 8, 504(1960).
2)   G. Åkerlöf : J. Am. Chem. Soc., 54, 4125(1932).
3)   C. G. Malmberg, et al. : J. Research Natl. Bur. Standards, 45, 299(1950).
4)   Y. Kato : Yakugaku Zasshi, 78, 565(1958).
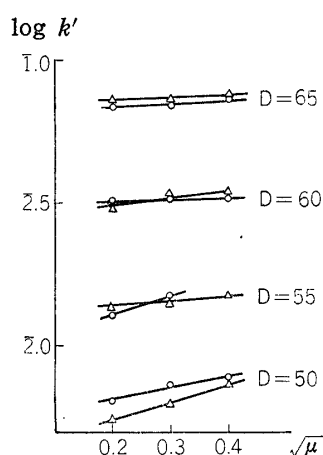
Fig. 1. Effect of Ionic Strength on k'

△ Ethylene glycol

○ Glycerol

As seen in this graph, reaction rate decreases as the dielectric constant decreases as was predicted by Eq. (1) in the previous work.[1] The magnitude of decrease is a little larger than that in monohydric alcohols, but the effect of ionic strength was not so evident and deviation of error in kinetic data were relatively larger. It was therefore difficult to calculate accurately the effect of ionic strength using Eq. (4) in the previous work. Furthermore, contrary to the theory, the observed activation energy decreased with the decrease of dielectric constant of the medium. In ethylene glycol–water mixture, activation energy was found to be 26.8 and 19.7 kcal./mole at dielectric constant of 65 and 55, respectively. In glycerol–water mixture, they were found to be 20.6 and 14.6 kcal./mole, respectively. If the difference of activation energy at two different dielectric constants is accounted by the difference of coulombic energy, activation energy must increase as dielectric constant decreases as predicted by Eq. (3) in the previous work. Moreover, the magnitude of increase was as much as several kilocalories. This may indicate that the effect of these polyhydric alcohols on reaction rate cannot be attributed only to the change of dielectric constant of the medium.

Comparison of relationship between dielectric constant and half–life of MHB, adding $0.09N$ sodium hydroxide at 30°, is shown in Table I and Fig. 2.

TABLE I. Dielectric Constant, Weight Percentage, and Half–life of MHB in Various Mixtures at 30°C

Org. component		Dielectric constant	w%	Half–life (min.)
(pure water)		76.7	—	148
Ethanol	{	70.0	11.90	274
		65.0	20.62	443
		60.0	29.12	740
		55.0	37.61	1080
Methanol	{	65.0	25.20	809
		55.0	46.67	4248
Ethylene glycol	{	65.0	39.62	1160
		55.0	66.15	4170
Glycerol	{	65.0	41.49	1100
		55.0	68.21	2260
Propylene glycol	{	68.5	25.62[a]	431
		59.0	50.45[a]	1770
Glucose	{	74.4	10.00	1610
		71.8	20.00	4400
Mannitol	{	75.2	10.00	309
		73.6	20.00	558
Sucrose	{	74.4	10.00	442
		71.9	20.00	993

a) Calculated from Kato's data.[4]
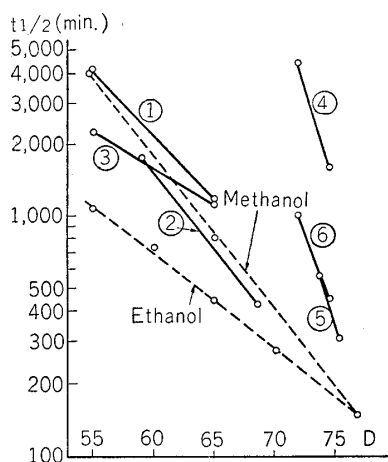
Fig. 2. Relationship between Dielectric
Constants and Half-life of MHB
in Various Mixtures at 30°C

1 Ethylene glycol	4 Glucose
2 Propylene glycol	5 Mannitol
3 Glycerol	6 Sucrose

Dotted lines in Figs. 2 and 3 show the half-life in ethanol–water and methanol–water mixtures. The reaction rate was found to decrease with decrease of dielectric constant in all media. The magnitude of decrease of reaction rate with respect to dielectric constant in ethylene glycol–, propylene glycol–, and glycerol–water mixtures was slightly higher than or almost equal to that in alcohol–water mixtures. However, the presence of sugars retarded the reaction rate much more than was expected by the change of dielectric constant and the effect of glucose was particularly distinct. Fig. 3 shows the relationship between weight percentage of organic substances and half–life. The effect of sugar is also evident in this graph.
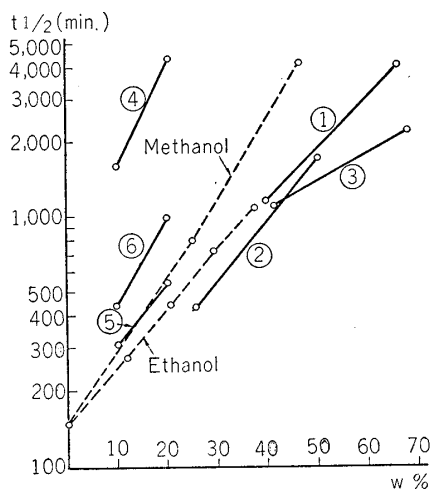

Fig. 3. Relationship between Weight
Percentage of added Organic
Substances in the Mixtures
at 30°C

1 Ethylene glycol	4 Glucose
2 Propylene glycol	5 Mannitol
3 Glycerol	6 Sucrose

Such disagreement with theoretical requirement for ion–ion reaction in polyhydric alcohol–water medium as found in the present study was reported by Amis, *et al.* in alkaline degradation of bromophenol blue.[5] They found that the reaction between negative bivalent dye ion and hydroxyl ion was in accordance with the theory in methanol–water and ethanol–water media, but in glycerol–water mixture the trend of activation energy was opposite to the theory on dielectric constant. They presumed some products between sodium hydroxide and glycerol for the explanation of this discrepancy. This presumption seems to be supported by Kubota's studies[6] on the formation of metal complex ion consisting of alkali metal ion, hydroxyl ion, and polyhydric alcohol or sugar which was proved by ultraviolet absorption. It is reasonable to suppose that

5) E. S. Amis, *et al.* : J. Am. Chem. Soc., **63**, 2621(1940).
6) M. Kubota : Nippon Kagaku Zasshi, **61**, 1176(1940); **62**, 214(1941).

hydroxyl ion which catalyzes the degradation of barbiturate forms a complex ion and reaction rate is retarded. The result by Kubota showed that although ethylene glycol or glycerol formed a complex ion at relatively higher concentration of alkali and polyhydric alcohols, sugars formed complex ion even at a lower concentration. These facts seem to elucidate the result in the present study that sugars retard the degradation even at lower concentration than alcohols or polyhydric alcohols. Furthermore, it is also known that polyhydric alcohols or sugars are very weak acids.[7~11] The order of values of pK of polyhydric alcohols or sugars is in general 10^{-14}, but that of glucose is 10^{-12}. The relatively large value of pK of glucose which is attributable to the formation of dienol form may be related to the fact that glucose distinctly retards degradation of MHB.

In addition to the above, the observation on degradation in acetone–water mixture must be reported. In this mixture, the reaction rate decreased markedly with time even at the initial stage of the degradation. This was quite different from the observations in other media. Hence it may be said that there is some specific reaction between a reactant and acetone.

From the results obtained in this study, it may be concluded that the mechanism of stabilizing effect of polyhydric alcohols and sugars on the degradation of barbiturates is not so simple as that of methanol or ethanol, because they form complex with hydroxyl ion and they themselves are weak acids. However, some parts of the effectiveness of polyhydric alcohols and sugars that are frequently used in the dosage forms such as parenteral solution or elixirs may be understood by the decrease of dielectric constant of the vehicles.

Summary

Subsequent to the previous work, the stabilizing effect of polyhydric alcohols and sugars on the alkaline degradation of methylhexabital J.P. (hexobarbital I.P.) was studied with respect to dielectric constant of the medium and following conclusions were drawn :

1) The magnitude of retardation of the reaction rate by ethylene glycol and glycerol was as large as or slightly larger than that by alcohols, but activation energy markedly decreased as the dielectric constant decreased. This proves that the stabilizing activity of these substances cannot be attributed only to the decrease of dielectric constant of the medium.

2) Sugars retarded degradation much more than was expected from the change of dielectric constant. The effect of glucose was particularly distinct.

3) The retardation of degradation by polyhydric alcohols and sugars would be attributed to the binding of hydroxyl ion to metal complex ion consisting of alkaline metal ion, hydroxyl ion, and polyhydric alcohol or sugar. Distinct retardation by glucose may be attributed to its relatively large value of pK.

7) F. Petuely, et al. : Chem. Ber., 86, 1255(1953).
8) P. Souchay, et al. : Bull. soc. chim. France, 1950, 819.
9) J. M. Los, et al. : Rec. trav. chim., 73, 941(1952).
10) J. Thamsem : Acta Chem. Scand., 6, 270(1952).
11) N. Konopic, et al. : Monatsh., 80, 426(1950).