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# 50. Hisashi Nogami and Noriyasu Nakajima: Studies on Decomposition and Stabilization of Drugs in Solution. III.[1] Chemical Kinetic Studies on Aqueous Solution of 2-Diethylaminoethyl Diphenylglycolate Methobromide

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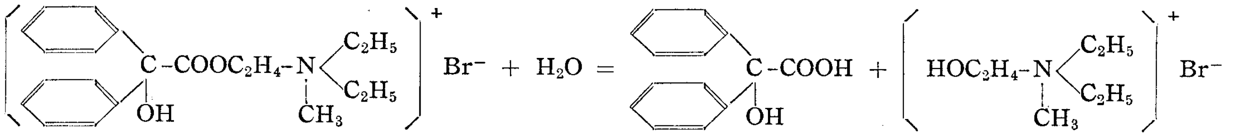
The decomposition of Methantheline Bromide was estimated from its commercial dosage form and its chemical kinetic studies were carried out, as described in the preceding report.[1]

2-Diethylaminoethyl diphenylglycolate methobromide (DDM) is one of parasympathetic blocking agents which has nearly the same ester linkage in its molecule as Methantheline Bromide. Same unstability may be considered from its chemical structure, but no report has been published on the degradation of DDM from the standpoint of chemical kinetics.

It is natural to assume that the degradation will be caused by hydrolysis of the drug.



The evidence of the assumption was obtained from the ultraviolet absorption spectra of DDM and its decomposed solution, as will be described later. This method, however, cannot be used for the chemical kinetic investigation, because the absorption of DDM is from the benzilic acid portion of the molecule.

To determine DDM separately from the decomposed products, colorimetry was adopted as in the preceding report, after examination of the kind of dyes to be used.

## Experimental

**Reagents**—All reagents used in this study were of extra pure grade. DDM and benzilic acid were supplied by Yamanouchi Seiyaku Co. Ltd.

**Ultraviolet Absorption**—Ultraviolet absorption of the following solutions are shown in Fig. 1. Curve (a) is one of DDM solution immediately after the preparation and (b) that of DDM after storage for 6 hrs. at 62.5° in a buffer solution of pH 9.55, in which the decomposition might be complete. Curve (c) is that of an equimolar solution of synthesized diethylaminoethanol methobromide and benzilic acid.

**Colorimetric Procedure**—i) Buffer Solution: Clark-Lubs' buffer solution was used. Optimum pH values for extraction of the complex were 8.0, 5.2, 5.7, and 6.4 for bromothymol blue (BTB), bromophenol blue (BPB), bromocresol green (BCG), and bromocresol purple (BCP), respectively.

ii) Solution of the dye: 200 mg. each of BPB, BCG, BCP, BTB was weighed accurately and ground with 14.9, 14.3, 18.5, and 16.0 cc. of 0.02*N* NaOH in a glass mortar and diluted to 200 cc.

iii) Ethylene dichloride (EDC): It was washed with alkaline and acidic solutions, and with water, and distilled.

iv) Whole procedure was the same as described in Part II of this series.[1] Water layer is determined colorimetrically using Beckman DU spectrophotometer at the wave length of maximum absorption. The maxima were 592, 617, 591, and 591 mμ respectively for BPB, BCG, BCP, and BTB.

v) Selection of dye: The absorbancy of DDM and diethylaminoethanol methobromide was compared for the selection of a dye. 31.7 mg. of DDM, 34.2 mg. of benzilic acid, and 31.8 mg. of 2-diethylaminoethanol methobromide were each dissolved in water and made to 500 cc. An equivolume mixture of the latter two solutions might be the product of completely decomposed DDM solution.

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[1] Prat II.: This Bulletin, **6**, 277(1958).

**Decomposition of DDM**—15.8 mg. of DDM was dissolved in 250 cc. of Clark-Lubs' buffer solution, with pH values of 1.10, 1.52, 2.02, 2.66, 3.12, 3.60, 4.30, 5.01, 5.40, 6.50, 7.21, 8.02, 8.22, 8.90, 8.95, 9.43, 9.60, 9.84, and 10.02, and Sörensen's buffer solution of pH 10.79.

The solution was sealed in ampules and kept in a thermostatically controlled water bath at 37.5°±0.2°, 52.0±0.4°, and 62.5±0.2°, and in ice-water bath. The ampules were taken out after the specified intervals throughout the experiment, cooled in ice water, and determined colorimetrically as described before.

**Salt Effect**—7.31 g. of NaCl (0.5 mole/L.) was added to 250 cc. of the buffer solution (pH 6.50) and decomposition was examined at 62.5°.

**Buffer Effect**—Sörensen's buffer solution (pH 6.50) was used and the effect on velocity constant examined.

## Results and Discussion

It may be considered that the resemblance of the curves (b) and (c) in Fig. 1 supports the assumption that the decomposition of DDM is a hydrolysis of an ester. There is some difference between (a) and (b), but it is impossible to determine DDM from the decomposed solution with sufficient accuracy.

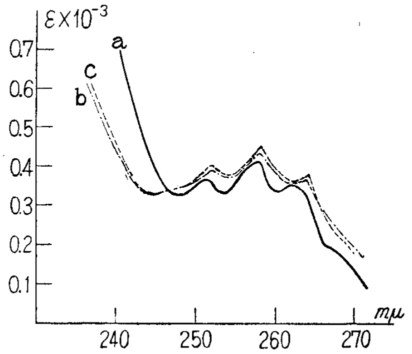

Fig. 1.

Ultraviolet Absorption Spectra

(Unicam SP-500 spectrophotometer)

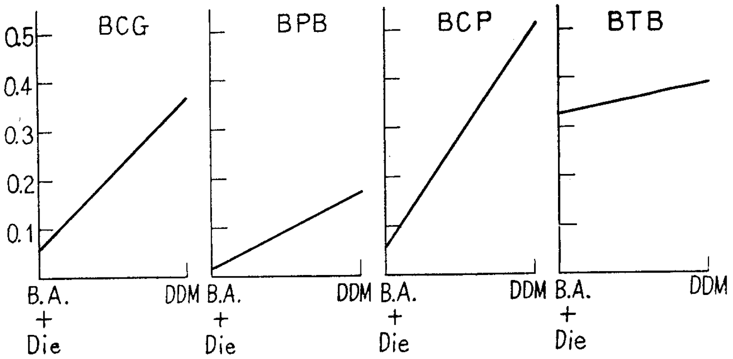

Fig. 2. Effect of Dyes on Absorbance

B. A. : Benzilic acid Die : 2-Diethylaminoethanol methobromide

Only absorbancies of DDM and B. A.+Die were estimated. The intermediate points between them were not estimated, but the solid lines were drawn to show the difference of absorbancies more easily appreciated.

The effect of kind of dye at the optimum pH value is seen in Fig. 2, from which BCP seems most suitable, because it gives the largest slope and lower blank value. The calculation formula using BCP was as follows :

$$Y=0.0299X+0.060$$

where $Y$ is the absorbancy and $X$ the concentration of DDM in 10 mole$^{-5}$/L.

A typical result of the decomposition of DDM at 3 given conditions is shown in Fig. 3, in which first order disappearance is recognized.

log $k$ was plotted against pH value and the result is shown in Fig. 4. Decomposition was not carried out between pH 2.0 and 5.0 at 37.5° because decomposition is very slow.

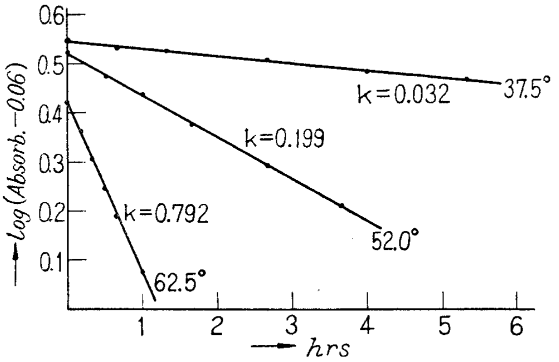

Fig. 3. First-order Disappearance of DDM in Buffer Solution (pH 7.21)

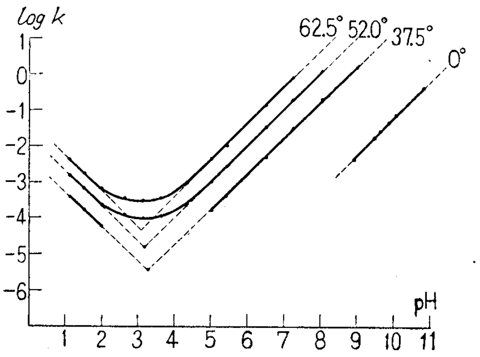

Fig. 4. Relation between pH and $\log k$

The apparent velocity constant of DDM in the whole range of pH value tested is considered to be as follows :

$$\begin{aligned} k &= k_H[H^+] + k_{OH}[OH^-] + k_{H_2O}[H_2O] \\ &= k_H[H^+] + k_{OH}\frac{K_W}{[H^+]} + k_{H_2O}[H_2O] \end{aligned} \qquad (1)$$

where $[H^+]$, $[OH^-]$, and $[H_2O]$ are the concentration of $H^+$, $OH^-$, and water, $k_H$, $k_{OH}$, and $k_{H_2O}$ the velocity constants of $H^+$, $OH^-$, and water molecule, and $K_W$ the ionization constant of water. Eq. (1) may be simplified at the higher and lower pH regions as follows :

$$[H^+] \gg [OH^-] \qquad \log k = \log k_H - \text{pH} \qquad (2)$$

$$[H^+] \ll [OH^-] \qquad \log k = \log k_{OH} + \log K_W + \text{pH} \qquad (3)$$

The pH value of minimum velocity constant $(\text{pH})_m$ is as follows :

$$(\text{pH})_m = \frac{1}{2}\{\log k_H - \log K_W - \log k_{OH}\} \qquad (4)$$

The relationship between $\log k$ and pH was a straight line with a slope of ±1 at higher and lower pH regions, and there was a minimum between them, as expected. Theoretical considerations were given in more detail in Part II of this series.[1]

The temperature dependence of the reaction catalyzed by $H^+$ and $OH^-$ was examined. The result is given in Fig. 5, in which the reactions at pH 6.50 and 1.52 are considered as the representatives of them. From the result of Fig. 5 and the Arrhenius equation, the activation energy and the frequency factor are calculated as shown in Table I.

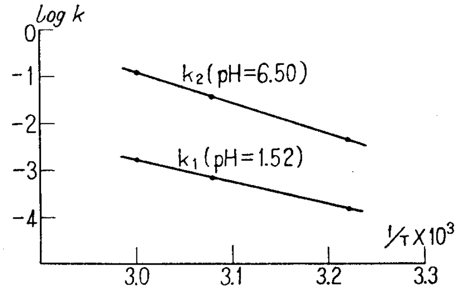

Fig. 5.

Relation between $1/T$ and $\log k$

TABLE I. Activation Energy ($E$) and Frequency Factor ($A$)

| | $k_1$ (pH 1.52) | $k_2$ (pH 6.50) |
|---|---|---|
| $E$ | $20.6 \times 10^3$ cal. | $16.7 \times 10^3$ cal. |
| $A$ | $1.72 \times 10^{12}$ | $3.50 \times 10^{16}$ |

TABLE II. Effect of Neutral Salt (Temp.=62.5°)

| | DDM soln. (pH=6.50) | DDM soln. contg. NaCl (pH=6.15) |
|---|---|---|
| $k$(hrs.$^{-1}$) | $1.25 \times 10^{-1}$ | $5.67 \times 10^{-2}$ |
| $\log k$ | $-0.903$ | $-1.246$ |

The differences of pH and velocity constants of two solutions with and without NaCl were 0.35 and 0.343, so the salt effect might be negligible. The effect of buffer solution was studied with Sörensen's and Clark-Lubs' buffers. The result obtained are shown in Table III, in which the difference between them is within the error of experiment.

The velocity constant of water molecule may be obtained from the procedure described in the preceding report.[1] The result is given in Table IV.

Table III. Velocity Constant at 62.5°, pH 6.50

| | DDM soln. (Clark-Lubs' buff.) | DDM soln. (Sörensen's buff.) |
|---|---|---|
| $k$ (hrs.$^{-1}$) | $1.25\times10^{-1}$ | $1.18\times10^{-1}$ |
| $\log k$ | $-0.903$ | $-0.928$ |

Table IV. $k_{H_2O}[H_2O]$ at each Temperature

| Temp. | $k_{H_2O}[H_2O]$ (hrs.$^{-1}$) |
|---|---|
| 62.5° | $1.96\times10^{-4}$ |
| 52.0° | $6.30\times10^{-5}$ |

Comparison of pH values showing the minimum velocity is shown in Table V, in which the difference between observed and calculated values is negligible.

The half lives of the drug at $(pH)_m$ and pH 7.0 are tabulated in Table VI.

Table V. Minimum pH at each Temperature

| Temp. | (pH)min. obsd. | (pH)min. calcd. |
|---|---|---|
| 62.5° | 3.10 | 3.07 |
| 52.0° | 3.20 | 3.16 |
| 37.5° | 3.30 | 3.31 |

Table VI. Half Lives at each Temperature

| Temp. | (pH)min. | pH 7.0 |
|---|---|---|
| 62.5° | 97.6 days | 1.7 hrs. |
| 52.0° | 316.6 days | 6.3 hrs. |
| 37.5° | — | 40.8 hrs. |

The authors wish to express their gratitude to Yamanouchi Seiyaku Co., Ltd. for the supply of DDM and benzilic acid.

## Summary

1. It was evidenced by the ultraviolet absorption spectral analyses that the decomposition of 2-diethylaminoethyl diphenylglycolate methobromide in aqueous solution is the hydrolysis of ester linkage.

2. The determination of 2-diethylaminoethyl diphenylglycolate methobromide was carried out, separating it from its decomposed substances, by a colorimetric procedure using ethylene dichloride and bromocresol purple in a buffer solution of pH 6.5.

3. The decomposition was recognized as a first-order reaction and catalyzed by hydrogen ion, hydroxyl ion, and water. The constants were determined as follows:

$$k_H = 1.72\times10^{12}e^{-\frac{20,600}{RT}}$$

$$k_{OH} = 3.50\times10^{16}e^{-\frac{16,700}{RT}}$$

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