Apparatus for Solution Kinetics

By J. THURO CARSTENSEN

An apparatus is described which allows for rapid convenient kinetic studies and overcomes several disadvantages associated with other kinetic study arrangements. The thermal degradation of bromothymol blue in alkaline aqueous solution has been used as a trial system to demonstrate advantages and precautions associated with the apparatus.

IT IS A GENERAL PRACTICE in the pharmaceutical industry to conduct accelerated kinetic studies by placing finished containers (ampuls, bottles) in constant temperature ovens and removing samples at appropriate times and assaying them (discarding the unused sample portions). The problem of an initial lag period in which the temperature increases from room temperature to the desired temperature is always problematic as is temperature variation within the oven itself. The fact that solutions in different containers are used at the various sampling times introduces further uncertainty into the kinetic study. When temperatures above 60° are used, short sampling intervals (2–6 hr.) are frequently necessary and under such circumstances the lag-time error becomes large and although compensation methods (equilibrium-time-temperature-equivalent) for this have been described by Eriksen (1), a straightforward method of studying a reaction which is initially at the desired temperature would be desirable. It would furthermore be advantageous to be able to sample from the same bulk at all sampling intervals.

The use of a good thermostatically controlled water (or oil) bath for this purpose can overcome the lag-time problem but is cumbersome and expensive. Agitation is difficult to achieve and sampling usually requires opening the system to the atmosphere, so that oxygen-sensitive reactions may require further precautions.

A simple and more direct means of achieving constant temperature, avoiding lag time, and minimizing air exposure and interactions with oxygen results from the apparatus setup described in the following.

APPARATUS

A schematic layout of the apparatus is shown in Figs. 1 and 2. A 500-ml. round-bottom flask with thermometer joint and equipped with a 24/40 condenser joint (G) is modified by the side arm sampling arrangement ABCD and a sample introduction well (E) with a solid stopcock (F). The stopcocks A, B, C, and D are all solid. The round-bottom flask is attached to a condenser,

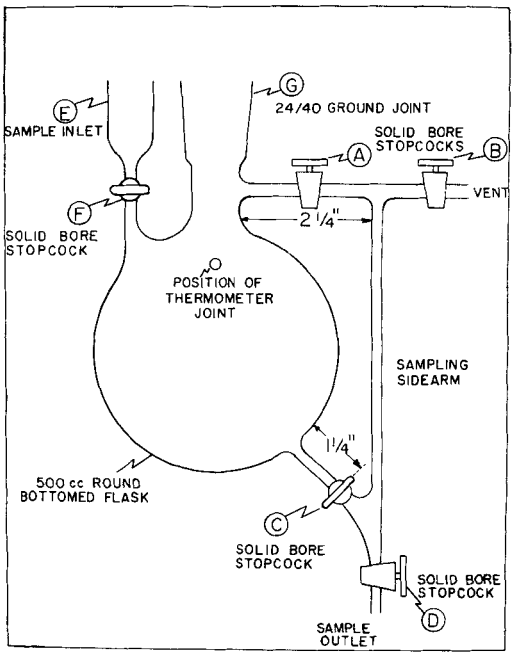

Fig. 1—Reaction flask used in apparatus arrangement showing stopcocks, joints, and sample introduction well.

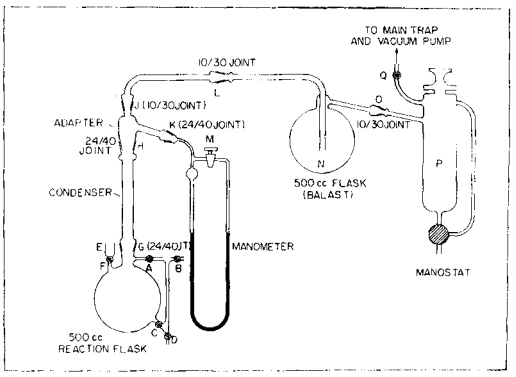

Fig. 2—Apparatus arrangement showing reaction flask, manometer, ballast, and manostat. Cross-hatched circles represent stopcocks.

which in turn is attached at (H) to an adapter with two 24/40 joints and one (top) 10/30 joint. The 24/40 side arm is attached to a direct reading manometer. The top joint (J) is connected *via* a 5-mm. tube equipped with a 10/30 ground joint inlet (L) and outlet (O). This latter is connected to a cartesian manostat[1] which in turn is connected

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[1] Manostat Corporation, New York, Manostat No. 7, dimensions: 15 in. high, 2½ in. wide at widest joint.

to a vacuum pump. If desired, a trap may be inserted between manostat and vacuum pump.

The principle and operation of the manostat is described elsewhere (2). By means of the diver the pressure of the system may be adjusted to a desired pressure.

OPERATION

The system is first run empty with the vacuum stopcock (M) open and stopcocks A, B, C, D, and E closed at full vacuum.[2] After the right side arm of the manometer has been evacuated in this fashion, stopcock M is closed and air let into the system by opening E.

The system is now operated by introducing 300 ml. of water (or other liquid)[3] *without boiling stones* or other boiling aids into the reaction flask with stopcocks A, B, C, D, and E closed. If a study at $t°$ is planned, the vacuum pump is started and the manostat operation fixed when a pressure, equivalent to the vapor pressure of water (or other liquid) at $t°$, is reached. A heating mantle[4] with the side opening is then attached to the reaction flask, so that both the bottom and the lower side arm down to stopcock C is covered. The rheostat connected to the heating mantle is adjusted to allow the water (or other liquid) to boil gently and the temperature and pressure checked periodically to ensure that the temperatures and pressure are constant. Since most studies, to which the apparatus applies, are conducted at temperatures between 60 and 100°, the temperature gradient dT/dp is very small (or conversely, dp/dT is large) so small fluctuations in pressure result only in very small fluctuations in temperature.

It usually takes less than 0.5 hr. for the temperature to stabilize. Once the temperature is stable, a concentrated solution of the substance(s) whose degradations are to be followed, are placed in the sample introduction well (E) and sucked into the system by opening and closing stopcock F, and (if desired) washing with a small amount of water. An initial sample is then taken by opening stopcock A, effecting equilibration of the pressure in the sampling side arm with the pressure in the system. Opening stopcock C will then allow the liquid to flow into the side arm. Closing stopcocks A and C and opening B restores atmospheric pressure to the sampling side arm. Opening D allows the sample to be collected. Samples are than collected at predetermined intervals in the same fashion, and assayed by suitable means.

EXAMPLES AND DISCUSSION

A kinetic study of the degradation of bromothymol blue at a concentration of 0.00134% in 0.1 NaOH was conducted by introducing 300 ml. of 0.1 NaOH into the reaction flask, and obtaining constant temperature. The 466 mg. of dibromothymolsulfonphthalein[5] was then dissolved in ethanol and the volume adjusted to 100 ml. with ethanol. The absorptivity (a) at 619 mμ in 0.1 N NaOH is 60.5. One milliliter of the ethanolic solution was then diluted to 10 ml. with 0.1 N NaOH and introduced *via* the sample introduction well, and the first sample taken 2 min. afterwards; the absorbance (A) was then determined at 619 mμ. In this manner, a true initial assay is not achieved. However, to demonstrate that this is not a particular drawback, a study at 90° was performed so that the first sample was not taken until 1 hr. after the start of the degradation study. The ensuing plot of $\ln_e (A)$ *versus* time yields good linearity and extrapolates to an absorbance at zero time, which equals the theoretical figure, calculated from the amounts added and the absorptivity cited above.

The Naperian logarithms of the first-order rate constants obtained in this fashion were plotted against reciprocal absolute temperature, and linearity is quite obvious, as seen from Fig. 3.

The study at 70° was conducted for a total of 45 hr. with the temperature fluctuating between 70 and 70.5°. Twelve samples were removed during this period. The fluctuation in the first 8-hr. period was about 0.3°.

The apparatus, hence, works well, but the following phenomena were observed and serve as good operating practices. The tighter the system is, the better the pressure control. Every time a sample is taken, a small amount of air is introduced. This causes a slight, transient temperature rise. Stopcock C would occasionally freeze up on prolonged runs, preventing the sample from flowing into the sampling side arm. The run need not be discontinued in such a case. By opening stopcock D (stopcocks A and B being closed) and then carefully opening stopcock C, a small amount of air is allowed to enter the reaction flask and the grease will dislodge. The usefulness of the apparatus is probably limited to studies of less than 48-hr. operation, and temperatures should be selected accordingly. It is, however, in these short interval studies, that initial lag time errors are cumbersome to account for, when conventional methods are used, and the method should be viewed as an adjunct to, not a replacement for, common practices.

Figure 4 shows kinetic data obtained in this latter fashion at lower temperatures and longer storage periods. In this case, sample solutions were deaerated by bubbling through nitrogen, and storing the solutions in sealed ampuls (with nitrogen in the head space) in constant temperature ovens (±0.5°). The correlation appears to be good. Finally the results from a study in closed containers in a 37° constant temperature bath is also shown in Fig. 4 and falls in line with the remaining points.

It will be noted that the apparatus described here results in solution kinetics in the absence of dissolved oxygen. This was demonstrated by checking the oxygen content after 0.5 hr. of operation (*i.e.*, when the temperature had stabilized, but prior to sample addition). Oxygen content was determined by an oxygen analyzer[6] and found to be 7.3 p.p.m. before operation and 1.7 p.p.m. after 0.5 hr. of operation.

A loss of solvent may be expected during operation, based on the temperature of the cooling water in the condenser. Using 5-mm. tubing beyond the condenser keeps this loss low. A 48-hr. run at 90° of 350 ml. water gave a total loss (by weight) of

[2] It is advantageous to cool the trap during this operation, but the trap is not needed for subsequent operations.

[3] The type of liquid (water, buffer solution, alkali, organic solvent, *etc.*) is dictated by the kinetic study in question.

[4] Glass-Col Ser. No. 553607, Scientific Glass Co. 1-1-1860-3.

[5] Eastman Kodak Co., Rochester, New York.

[6] Beckman Oxygen Sensor, Bulletin 70139, Beckman Instruments, Inc., Fullerton, California.

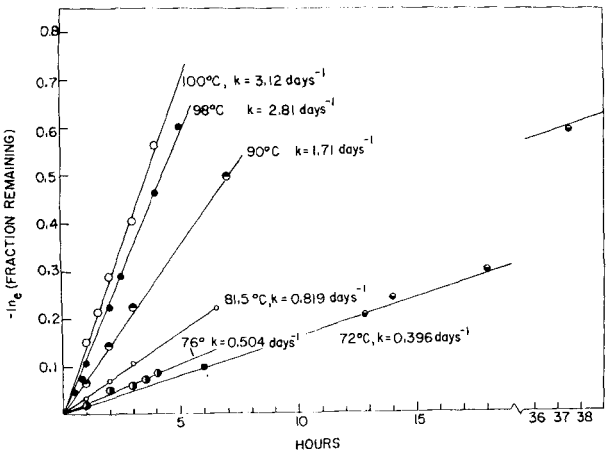


Fig. 3—Results from degradation of bromothymol blue in 0.1 NaOH at various temperatures. The run at 100° was performed at atmospheric pressure, i.e., system disconnected at joint H.

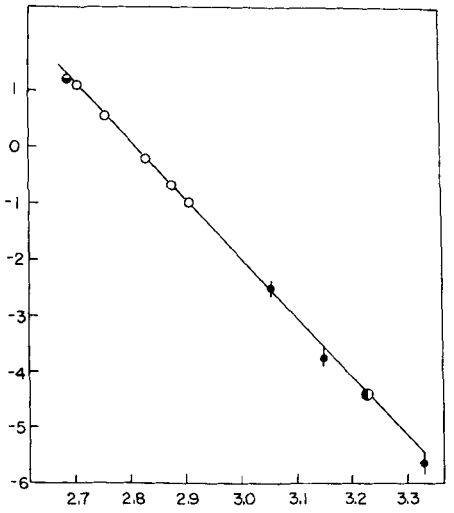


Fig. 4—Arrhenius plot of bromothymol blue degradation in 0.1 NaOH. Ordinate is the natural logarithm of the Naparian rate constant; abscissa is 1,000 × reciprocal temperature (°K⁻¹). Key: ●, runs in stationary ampuls; ◓ ◐, run in constant temperature bath; ○, runs in apparatus described here.

about 1–2 Gm. This aspect hence contributes less than a 1% error on long runs and can be considered negligible on short runs.

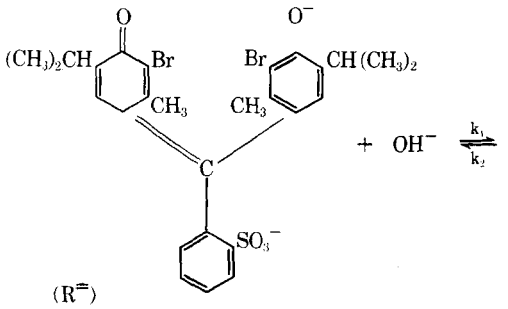
Although the operation of the manostat may be performed with the bleed valve slightly open, it appears best for stable operation, to keep it closed at all times after the required pressure has been reached.

A final point, which is also no shortcoming, is that in starting the manostat in operation at the desired pressure, the pressure attained usually differs slightly from the pressure aimed for. Letting the pressure drop slowly prior to setting the manostat can be accomplished by suitable operation of stopcock Q, and will allow fixing the temperature at the desired point fairly accurately. The point is not critical since one might, at worst, be conducting a study at, say 72°, rather then 70°, and so on, and it is not difficult to obtain six suitably separated temperatures in six separate runs, and this, after all, is the only intent of the kinetic study.

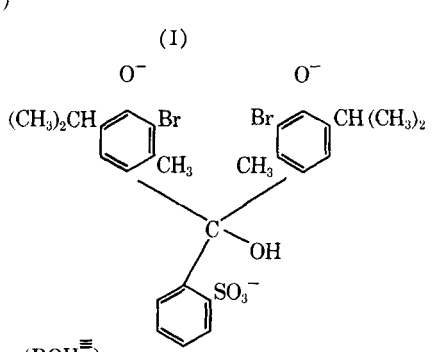
Although the mechanism of breakdown of bromothymol blue in alkaline solutions is not the primary question here, a few notes on the subject are in order. Sager *et al.*(3)[3] have reported on the alkaline degradation of bromothymol blue and find the following rate expression:

$$\frac{d(R^-)}{dt} = 0.028 \cdot 10^{-3}(R^-)(OH^-) - 0.0016 \cdot 10^{-3}(ROH^{\equiv})$$

in units of M^{-1} min.$^{-1}$, at 25.° R^- and $ROH^{\equiv}$ have the structures I and II.



(I)



(II)

At a hydroxyl ion concentration of 0.1 M, therefore, the rate constant should be 2.8×10^{-6} min.$^{-1}$ or 3.98×10^{-3} days^{-1}. The data in Fig. 4 imply a room temperature rate constant of anti-ln$_e$ (−5.45) $= 4.3 \times 10^{-3}$ days^{-1}, *i.e.*, in good agreement with the data of Sager *et al.*

SUMMARY

An apparatus is described which permits kinetic studies in solution. Bromothymol blue degradation

in alkaline solution was checked with this system and gave results in accordance with literature values.

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Keyphrases

Solution kinetics apparatus
Schematic diagram—solution kinetics apparatus
Bromothymol blue—alkaline, aqueous degradation

Effect of Size on Other Physical Properties of Granules and Their Corresponding Tablets

By ALAN M. MARKS* and JOHN J. SCIARRA

Investigations were conducted to determine the relationship and effect of granule size upon the physical properties of the granule and the tablets produced from these granules. These properties were evaluated in the areas of spacial capacity, mobility, and physical stability. Additional studies were conducted which involved the manufacture of tablets and the subsequent correlation of the results of the physical testing of these tablets to the corresponding granule size. The physical properties of the granule were found to be interrelated and for the most part, related to the granule size. In the range of the granule sizes studied in this experiment, no direct relationship was found between granule size and granule volume. Both the degree of granule friability and flowability were found to increase as the size of the granule decreased. As the granule size became smaller, the weight variation of the tablets was found to decrease. No defined or observable relationship was found to exist between the granule size and the hardness of the corresponding tablet. The effect of granule size upon tablet disintegration was not distinguishable under the conditions of this study and probably was due to the variability and limitations of the disintegration apparatus used for this determination.

VARIOUS METHODS useful for the measurement of several physical properties of granules have been indicated in the literature. Arambulo and Deardorff (1) conducted a study which showed the relationship between granule size and the resulting tablet weight. They noted that as the granule size was reduced, the average tablet weight increased, presumably due to the decrease in void space. Large granules were found to contain a greater percentage of intergranular void space as compared to smaller granules and the resulting die fill, containing a smaller volume of material, produced tablets of a lighter weight. Arambulo, Fu, and Deardorff (2) noted the effect of granule size upon the weight variation of compressed tablets. As the granule size decreased, the weight variation decreased, passing through a minimum at 400–800 μ and then increased. They also noted that larger granules were found to yield greater weight variation. This effect was presumed to be caused by variation in the proportion of voids, which they attributed in part to the varying amount of breakage of granules and the resultant removal of the powder by the movement of the feed shoe of the single-press tablet machine.

Forlano and Chavkin (3) reported a definite relationship among granule size, disintegration time, and degree of capping. Using a sodium bicarbonate granulation, tablets compressed with granules in the 8–40-mesh range exhibited a rise in disintegration time and a decrease in capping. Tablets compressed using granules of 60 mesh or smaller exhibited a decreased disintegration time and an increase in capping. It was found that the optimum granule size of the granulation they used was found in the range of 16–60 mesh. Augsburger and Shangraw (4) described a method of measuring the fluidity of semifluid powders. They felt that the measurement of tablet weight would not only give comparable fluidity values but would also have practical importance from a production standpoint.

Fonner, Banker, and Swarbrick (5) tested

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