Some Possible Applications of Aqueous Thermometric Titration to Pharmaceutical Analysis

Sir:

Recent work in thermometric titration has indicated that there is a wide range of systems to which this powerful analytical method should be applicable (1). The enthalpy change of a reaction, in addition to having a free energy component, has a contribution from the entropy change, *viz.*, $\Delta H = \Delta F + T\Delta S$. Thus, thermometric titration (being an enthalpy method) will often work where free energy methods, such as potentiometric titration, fail. Since almost every reaction has associated with it a measurable enthalpy change, thermometric titration may prove extremely useful for pharmaceutical analysis.

Briefly, a thermometric titration involves adding a concentrated titrant to a dilute titrate in an "adiabatic" titration cell and measuring the temperature change as a function of the volume of titrant added. A quantitative measure of the amount of titrate is obtained either from the volume of titrant necessary to reach the end point (a change in slope in the temperature–volume plot) or from the amount of heat absorbed or evolved during the reaction (1). (See Curve A in Fig. 1.)

Well-defined thermograms for titrations in aqueous solution can be obtained with several substances whose official or other assay procedures require nonaqueous titration with perchloric acid in glacial acetic acid. While such nonaqueous titrations are quite useful, the authors feel that, in general, aqueous thermometric titration is more convenient. The main disadvantage of thermometric titration is that while it can be performed without electronic instrumentation, such a procedure is tedious and time-consuming. On the other hand, the rapid instrumental procedure requires only simple equipment.

The thermograms shown in Figs. 1 and 2 were obtained by adding titrant at a rate of 0.6 ml./minute from a Menisco-matic buret (American Instrument Co., Silver Spring, Md.) into 100 ml. of titrate contained in a Dewar flask equipped with a stirrer. The temperature was measured with a 2000-ohm bead-in-glass-probe thermistor in a bridge circuit similar to that described by Jordan (2). The output of the bridge was recorded with a 1.25 or 5-mv. recorder. For these exploratory titrations, no particular precautions were taken to assure that the titrant and titrate were initially at the same temperature.

Figure 1 shows three thermograms for systems which exhibit at best poorly defined aqueous potentiometric titration curves. Curves A and C in Fig. 1 have reasonably well-defined end points. The official assay procedures (3) for both chlorpheniramine maleate and nicotinamide require acetous titration with perchloric acid and visual end point detection. In aqueous solution, neither titration gives a discernible potentiometric end point. An advantage of the thermometric method over the U.S.P. method for chlorpheniramine maleate assay is that while in the latter both the pyridine nitrogen of the chlorpheniramine and the bimaleate ion are titrated *together*, in the thermometric method the one end point observed reflects only the chlorpheniramine concentration. While the curvature in the thermogram for the titration of the theophylline in aminophylline with NaOH (Curve B) makes the detection of the end

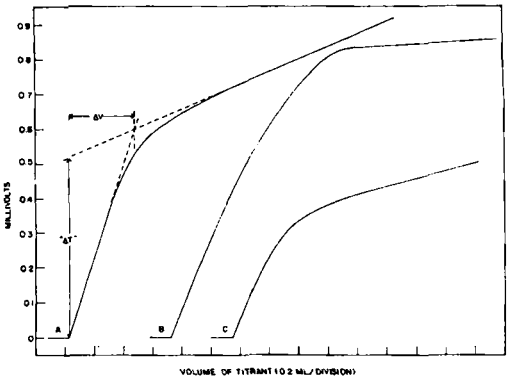

Fig. 1.—Thermograms for titrations in aqueous solution. Key: A, 100 ml. 0.01 *M* chlorpheniramine maleate *vs.* 2 *M* HCl; B, 100 ml. 0.01 *M* aminophylline *vs.* 2 *M* NaOH; C, 100 ml. 0.01 *M* nicotinamide *vs.* 2 *M* HCl. All concentrations are approximate.

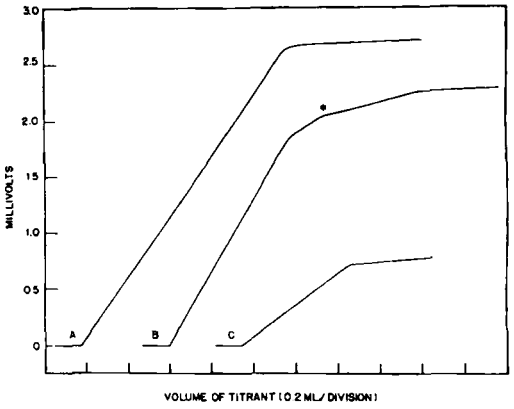

Fig. 2.—Thermograms for titrations in aqueous solution. Key: A, 100 ml. 0.005 *M* aminophylline *vs.* 1 *M* $AgNO_3$; B, 100 ml. 0.01 *M* chlorpheniramine maleate *vs.* 2 *M* NaOH; C, 100 ml. 0.01 *M* chlorpromazine hydrochloride *vs.* 2 *M* NaOH. All concentrations are approximate.

point difficult, the measurement of the temperature rise is quite easy. The corresponding aqueous potentiometric titration curve exhibits a poorly defined end point (4).[1] Medwick and Schiesswohl (5) have described a nonaqueous potentiometric assay of ethylenediamine and theophylline in aminophylline using acetous perchloric acid and an acetic acid–acetic anhydride solvent. No theophylline end point was observed in aqueous thermometric titration with acid.

Figure 2 shows thermograms for three titrations which give fair-to-good potentiometric end points in aqueous solution. In each case, however, the thermometric end point is at least as easy to identify as the potentiometric end point. Curve A represents the titration of theophylline in aminophylline with silver ions. In comparison with the titration of chlorpheniramine maleate with acid (Fig. 1, Curve A), the titration with alkali (Curve B) exhibits two true end points, the first corresponding to the neutralization of the bimaleate ion and the second to the neutralization of the chlorpheniramine ion. The false "end point" indicated by the asterisk is due to the delay of the precipitation of the chlorpheniramine base after the start of the second neutralization. The U.S.P. procedure (6) for chlorpromazine hydrochloride assay calls for acetous potentiometric titration with perchloric acid in the presence of mercuric acetate. No end point is apparent in the direct aqueous thermometric titration of chlorpromazine hydrochloride with acid since neither the phenothiazine nitrogen nor the chloride ion is sufficiently basic. The aqueous titration with base shown in Fig. 2 (Curve C) represents the neutralization of the protonated quaternary nitrogen of the chlorpromazine ion.

The precision obtainable even from titrations without rigid titrant–titrate temperature control is indicated by the following data. End point determinations of five replicate titrations of a solution of chlorpheniramine maleate with 2 M HCl gave an average value of 0.01073 M with an average deviation of ± 0.00005 M. The temperature rise was constant to $\pm 1.1\%$. For nine replicate titrations of ~ 0.005 M aminophylline with 1 M $AgNO_3$, the end-point-determination result was a theophylline concentration of 0.00951 $\pm$ 0.00006 M with the temperature rise constant to $\pm 0.7\%$.

In cases where the end points are fairly sharp, we have been able to run titrations with an automatic end-point-determination device (7). The details of thermometric assay procedures of the type reported here for pure materials and for substances in various dosage forms are now being investigated.

[1] The curve obtained by Bartilucci and Discher (4) using a smooth platinum indicating electrode is slightly more definitive than a potentiometric titration curve that the authors have obtained using a glass electrode.

(1) See Zenchelsky, S., *Anal. Chem.*, **32**, 289R(1960); see also Jordan, J., and Ewing, G. J., "Handbook of Analytical Chemistry," Meites, L., ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1963, Sect. 8, p. 3 ff.
(2) Jordan, J., *Rec. Chem. Progr., Kresge-Hookee Sci. Lib.*, **19**, 193(1958).
(3) "United States Pharmacopeia," 16th rev., Mack Publishing Co., Easton, Pa., 1960, pp. 155, 453.
(4) Bartilucci, A., and Discher, C. A., THIS JOURNAL, **39**, 641(1950).
(5) Medwick, T., and Schiesswohl, F., *ibid.*, **52**, 843(1963).
(6) "United States Pharmacopeia," 16th rev., Mack Publishing Co., Easton, Pa., 1960, p. 158.
(7) De Leo, A. B., and Stern, M. J., to be published.

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Received March 24, 1964.
Accepted for publication May 25, 1964.