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THE THERMOMETRIC AND ENTHALPIMETRIC DETERMINATION OF ORGANIC COMPOUNDS*

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Two main parameters determine the methods for the assay of organic compounds in industrial systems; these are the rates of reaction of the molecular organic and often non-aqueous systems which differ from those in ionic and aqueous systems, and secondly, the fact that in most organic systems an organic functional group is required to be determined by a general method applicable to the functional group in a variety of chemical environments. In pharmaceutical products it is desired to determine the functional groups without prior separation from excipients of various kinds and to obtain rapid assays, often with precision much lower than those normally required in inorganic systems. These methods are discussed with examples taken from the foodstuff industry, the pharmaceutical industry, etc.

When the problems involved in the applications of solution thermochemistry are considered it is seen that there are two main areas of practical limitations, and these are:

(1) The speed of the chemical reaction involving the analyte.

(2) The transfer of the heat change to an appropriate sensor.

It does not matter whether the system is considered to be inorganic, organic or biochemical, these technical limitations govern the whole of the applications of solution thermochemistry, whether or not the system is in one of the subdivisions of thermometric or enthalpimetric analysis. There are, however, for each class of the chemical systems, some problems which are particular to that class and hence it is necessary to consider those parameters which affect organic systems more than they affect inorganic systems. For this purpose it is necessary to consider each of the limitations in some detail, but with the restriction for this particular paper, that the more practical and pragmatic aspects are being considered, and whilst the rigidity of thermodynamic calculations may not always be maintained, the effects of all approximations will be considered in interpretation of the results obtained.

When the various types of simple chemical reactions are considered, it is postulated that there are two extremes of reactions, *viz.* an ionic reaction which results

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from a reaction between two ionic species to produce products, and on the other end of the "reaction spectrum" there are reactions which may be considered to be between molecules. Between these there are a series of reaction classes which are possible and depend upon the chemical environment of the chemical species.

For example, a reacting species may contain a dipole by virtue of its structure and environment, or a dipole which has been induced by the approach of an ion or another strong dipolar species. It may well be that a molecule will react with an ion, but it is more probable that an intermediate of this system is a dipole reaction. Since all reactions involve the outer electron shells and result from a disturbance and redistribution of the electron density, there will not be equivalent energies or velocity of reaction in all systems. The environment of the reacting species will play a significant role in determining the ease and speed of the reaction; for example, although an ionic equation is generally considered to be a reaction between two point sources of electron density, each ion is surrounded by a solvent sheath, the "thickness" of which will depend upon the size of the electronic charge and the polar/dipole induced character of the solvent species. At some point when A^{+n} approaches B^{-n} we must have a transient species in which A and B are partially solvated and then perhaps, following release of solvent, become AB which is solvated. The process may extend to nucleation and then precipitation with simultaneous release of solvent. The change in the entropy resulting from the change in the number of individual species is therefore extremely important and it may well be that although the change in free energy ΔG is important for all systems, the $T\Delta S$ term in the fundamental equation $\Delta H^\circ = \Delta G^\circ + T\Delta S^\circ$ is of especial significance in organic systems, since as well as changes in environment and solvation caused by precipitation, many organic reaction systems can give polymerisation reactions in which the entropy change is relatively vast. It is therefore possible to devise systems in which this entropy factor plays a very important part. There is no indication from the equation whether the reaction is fast enough to be observed by the rapid techniques of thermometric and enthalpimetric methods, neither does it give any indication whether or not an equilibrium state exists which is an acceptable condition for analytical measurement purposes. In the use of solution thermochemistry in analysis, it must always be remembered that the analysis must be completed in a time which is industrially acceptable and financially viable, i.e. rapid analysis is required, and moreover the result must be from the measurement of a completed or practically completed reaction.

When the speeds of reactions are considered, it is generally accepted that for aqueous systems the mobility of the ions is fairly fast and the removal of and the creation of a solvent sheath are rapid phenomena. The mobility of solvated molecular dipolar species may approach or equal that of ions in aqueous systems, but if we consider reactions of organic materials in aqueous systems a problem often arises as a result of the relatively low solubility of the organic species; since we can have only relatively small concentrations, the actual heat changes are correspondingly small, even if we have equivalent reactions. Thus, in general, for pragmatic purposes and practical systems it is necessary to consider the use of non-aqueous

solutions. These solvents are generally solvents which have a low molar thermal capacity and often have a zero or relatively low dipole content and are incapable of dissolving any appreciable amount of polar solute. For example, if one considers a solute, in different systems, which is analysed by the same reaction, the effects

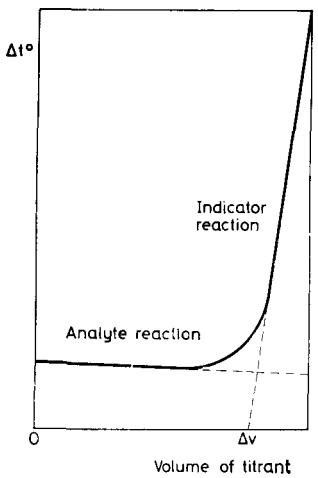

Fig. 1

of the different systems are exemplified. Thus if 2 : 4 dichlorophenol is dissolved to equal concentrations in water, and a solvent, which is a mixture of 1 : 4 dioxane, methanol, acetone and ether (3 : 5 : 1 : 1) and titrated thermometrically, respectively, with aqueous sodium hydroxide solution, and sodium methoxide dissolved in the non-aqueous mixture, in both cases there is an ion-ion reaction; in the aqueous system the end point is sharp, and in the non-aqueous system the curvature at the end point is more pronounced and the end point must be obtained by extrapolation.

However, the "temperature step", the change in temperature, of the non-aqueous system is much more pronounced, and using the technology available for altering the abscissae as well as the ordinate of a graphical reproduction of the thermal curve it is possible for organic systems of low thermal capacity to obtain, both with thermometric and with enthalpimetric systems, a relatively large increase in the sensitivity of the system.

The use of organic solvent-matrix systems with a low specific heat is an essential feature in solution thermochemistry involving organic, non-aqueous solutions, since it introduces into the considerations a factor which controls the sensitivity of the whole reaction monitoring.

For example, glacial acetic acid has a specific heat of approximately 0.45, and toluene has a specific heat of approximately 0.25. It must be appreciated that this means that for a reaction involving toluene as the solvent, then for a particular

enthalpy change there may be a fourfold enhancement of the sensitivity for the equivalent aqueous reaction system. Thus the use of selected organic solvents may confer significant advantages, with respect to thermal sensitivity, when they are used in particular reaction systems.

Although most organic solvents have a lower thermal conductivity than has water, this does not in practice noticeably alter the rate of the transfer of energy (or temperature change) throughout the system and to the temperature sensor, and therefore the analyst need not take special precautions regarding the rate of addition of the reagent or the speed of stirring when dealing with organic systems.

The role of the solvent is not confined solely to acting as a "carrier" or "vessel" for the solute; not only does it have a function in the entropy changes as a result of solvation changes, but in organic systems some solvents may also play a significant role in overall analytical procedure in a manner that is not possible for water. (This aspect is discussed later.)

When the speeds of reactions are considered, it is obviously useful to have some attempt at classification of reactions; whilst in inorganic systems there are acid-base, redox, complexation, precipitation reactions, and the reactions used for the determination of a particular analyte species may fall into one or more of these classes; traditionally and pragmatically in organic analysis, practising analysts use a classification based on functional groups.

Thus, for example, one may consider many organic compounds as having one or more of the following functional groups:

$$-COOH;\ -OH;\ >C=O;\ >C=C<;\ -N-;\ -S-.$$

Many of these are subdivided; for example, $-OH$ is divided into at least for alcohols 1°, 2°, 3° and phenols, and the juxtapositioning of 2 hydroxyl groups gives rise to other specialised functionalities.

In the case of nitrogen compounds, for example, the nitrogen may be in alkaloids, amines, amides, hydrazides, proteins, etc.

It is the situation that for any division, whether it be main or subdivision, there will be variations in the speed and the ease with which a particular functional group-selective reagent reaction will occur, and this will have a direct bearing on the type of reaction system and the thermometric-enthalpimetric technique which is used for the determination of the particular analyte in its particular matrix.

It must always be borne in mind that in "wet thermal analysis" ultimately one measures a fast reaction. In some cases it may only be necessary to mix the reagents in stoichiometric proportions, and at room temperature, in order to obtain a reaction to be complete in the time allowed for the measurement. In other systems it may be necessary to have a large excess of the reagent and to use heat to drive the reaction system to an analytically acceptable state of equilibrium. Thus the divisions are considered to be:

(a) Fast reactions obtained by mixing stoichiometric amounts at room temperature; for such a direct reaction either the thermometric method or the enthalpimetric method may be used.

(b) Slow reactions obtained by mixing stoichiometric amounts at room temperature; for such reactions there are two alternative techniques depending upon the nature of the sample:

(i) Use a known and excess of the reagent at room temperature and force the reaction to go to completion. In such a reaction system the technique used is either the enthalpimetric method or, if the thermometric method is used, a second reaction of type (a) is used to determine the previously unused reagents.

(ii) React the sample with an excess of the reagent, at a relatively higher temperature, followed by the determination of the excess by a fast reaction at room temperature using either the enthalpimetric or the thermometric technique.

It must be emphasised that the environment in which the functional group is found in the analyte will generally determine which reaction system is used. An illustrative example is the determination of aromatic aldehydes of the type RC_6H_4-CHO, which are found in some essential oils and in some materials used in permitted food flavourings. There are several reactions theoretically suitable for an analytical system; it is, for example, possible to react the aldehyde groups with sodium bisulphite to give a bisulphite addition compound, or with hydroxylammonium chloride to give an oxime, or with hydrazine or a substituted hydrazine to give a hydrazone. Although a direct differential method using 4 methyl-phenylhydrazine had been reported [1], it was not considered [2] to be suitable for routine use for all such aldehydes by workers of various levels of skill. Experience had indicated that there is such a wide variation in the ease and rate with which various aldehydes react at room temperature or at any fixed temperature, that no direct method would be generally applicable. Thus the sample, dissolved in isopropanol, was reacted with a known and excess amount of 2 : 4 dinitrophenyl hydrazine in sulphuric acid at approximately 80 $\pm$ 2° C for 10 minutes. The mixture was then cooled to room temperature and the excess amount of the hydrazine was determined by titration with a solution of 4-methoxy benzaldehyde in isobutanol containing 8% of 1 : 1v/v H_2O : H_2SO_4; the composition of the solvent mixture was the same as that of the titrand so that any heats of mixing were eliminated. 4-Methoxy benzaldehyde was chosen partly on a theoretical basis, since the structure lends itself readily to dipole inducement and hence the compound should readily condense with the hydrazine, but also because it is easily purified and is relatively stable to oxidation for an analytically acceptable time. Moreover, it had one of the fastest reaction rates of all the aldehydes tested and hence gave a sharp end point.

The shape of the enthalpogram obtained is of interest; an apparent irregularity is caused by delayed precipitation of the product and may be regarded as a nucleation period. If 4-methoxy benzaldehyde is present in the original sample then obviously there is a precipitate of the required crystalline dimensions present and no such abnormality exists. It has been noted that with some aldehydes other than 4-methoxy benzaldehyde there was little or no abnormality, and microscopic comparison of the crystals of these products and of the hydrazone of 4-methoxy benzaldehyde showed crystal similarities.

Such reaction systems, where the product and the excess of the reagent have many similar chemical properties, confront the organic analytical chemist with the problem of choosing a suitable reaction for the determination of the excess of the reagent. In the above reaction system it is not feasible to use for the determination of the excess of the hydrazine, any redox reactions, since it is quite probable that under the conditions used, some of the hydrazone may decompose to release the hydrazine. It is therefore essential to use a reaction in which the original product cannot take part; an obvious method is thus to determine the excess of the hydrazine by a reaction similar to that which has already been completed.

Although organic compounds may be classified according to functionality, this is alone insufficient to predetermine the mode of analysis. To some extent the philosophy adopted by the particular analyst plays a part in assigning the technique. For example, the present author is of the opinion that for routine analysis of samples there should be the minimum number of operations before making the thermometric-enthalpimetric reading. This means the obviation, where possible, of accurate and precise weighting, or dispensing of solutions, or the separation of the analyte from the matrix prior to the analyte determinant reaction. The precision required for the result should be carefully considered in the light of the industrial use of the result. Many industrial-commercial samples are simple solutions or suspensions, but others are complex mixtures of analyte and matrix, the latter often being determined by ethical commercial interests as well as expediency. Industrially there are 4 main groups of organic compounds; those used in the pharmaceutical and biochemical industries; those found in the fuel industries, including coal, coal tar products, oils, and petrochemicals; those used in the manufacturing industries for the synthesis of polymers, and industrial chemicals such as surfactants; and finally those used in the food industries. Each of these groups presents its own problems, which are mainly associated with the matrix in which we find the analyte and with the sensitivity demanded by the particular industry. If a simple example is considered and we choose a compound which is used in the food industry in relatively large amounts and in high concentrations, that is the compound sorbitol (a hexahydric alcohol which is used as a non-fattening sweetening agent in food manufacture, especially for diabetic subjects and others whose carbohydrate intake must be limited and controlled). The analytical requirements are for a rapid method which can be automated and which is accurate to about $\pm 1\%$ at the range of 100 – 500 mg of sorbitol per 1 g of sample. The method must be cheap, since hundreds per week will be done on similar samples in order to monitor the manufacturing process. Theoretically, the basic chemistry of the reaction is simple and is a reaction of vicinal dihydric groups with potassium periodate. The reaction is not specific for sorbitol but is analytically selective, since for sorbitol the reaction is fast and can be used directly, but for the other diols, which are likely to be present in the material an excess of the oxidant is required, and the excess must then be titrated with a suitable reagent. The main problem lies in the nature of the matrix, since the samples include such products as mayonnaise or salad cream, orange marmalade, or chocolate. Each has its own

problems; for example, food seeds and skin, the colouring material, the fats and other suspended matter make it essential for an extractive procedure to be used for any other method other than the thermometric-enthalpimetric. The alternative British Pharmacopoeia (B.P.) method includes an extraction, a filtration, and a final assay using a polarimeter. In the hands of a skilled analyst this method takes approximately 30 minutes for each determination. The proposed method [3] takes approximately 5 minutes, including an approximate weighing (to the nearest mg), suspension of the foodstuff, and then titration. The results are comparable with those obtained by a B. P. method (see Table 1).

Table 1

Sorbitol assay

Sample	Thermo	Polar^{m}	Nominal.
Orange conserve	59.21	58.35	60
Chocolate	34.2	N/P	33
Strawberry jam	60.25	60.1	60
Salad cream	17.45	17.6	>20

g/100 g of sample

N/P = Not possible in 30 minutes

By suitable adjustment of the concentration of the titrant and the speed of delivery of the titrant and the chart speed, the distance in mm between the start and finish of the titration can be made to indicate the direct reading in mg/g of the sorbitol. With suitable electronic differentiation and a digital print-out it is now possible to obtain a direct reading of percentage of sorbitol. For the salad cream, which contains only sorbitol and no other sugars, the assay may be done by an enthalpimetric injection. It should be noted that potentiometric methods cannot be used for these materials since each of them contains surface active materials as part of the matrix.

In industry, samples often have coloured impurities which makes spectrophotometry and other visual methods unsuitable. Some are complex mixtures and full analysis is not required, but for industrial use a "functional group value" is often preferred. For example, polyethers formed from propylene oxide, either alone or with ethylene oxide and involving the use of glycerol as an initiator, are widely used in the manufacture of polyurethanes by reaction with aryl hydrocyanates. Polyesters prepared from butane 1 : 4 diol and adipic acid find numerous applications, including the production of adhesives and thermoplastics. A single polyether or polyester contains condensates with a range of relative molecular masses and the determination of any physical property will yield a value that is a weight average. The most useful way of describing such a product for commercial purposes is to specify the number of hydroxyl groups (i.e. the number of reactive sites) per unit mass.

This so-called "hydroxyl value" is usually expressed as the number of mg of potassium hydroxide required to neutralise the amount of acetic acid that combines with 1 g of the sample. The conventional method for determining hydroxyl values is time-consuming, since the condensate is refluxed with an excess of phthalic anhydride in pyridine for 1 hour and the residual anhydride is then titrated against the sodium hydroxide solution after hydrolysis. The process takes from 2–2.5 hours to complete, and hence it results in high costs as a result of the storage of intermediates awaiting final assay, before they can be used.

A D.I.E. method, in which the sample, dissolved in a chlorohydrocarbon, was injected into the reactant (acetic acid–sulphuric acid and acetic anhydride) has been evolved [4]. The method is rapid, the temperature rises for 2 samples and a standard being recorded in duplicate in about 10 minutes. Although the accuracy is about 1%, it is acceptable for this particular use, and a storage time of 2 hours per batch of intermediate is saved, along with the concomitant storage costs.

In pharmaceutical analysis, problems are often associated with the matrix and with the amount of active ingredient present. Dosage forms of pharmaceutical products, including pills, capsules, etc., usually contain diluents in the form of excipients; these are starch; lactose; calcium lactate; magnesium stearate for solids, and colouring agents for both solids and solutions and often flavourings to give acceptability to the product. Rapid monitoring processes, which are relatively easily automated, are required. Whilst it is necessary to have high selectivity of chemical reaction, it is not usually necessary to have high accuracy; generally ±2% is acceptable. The presence of these materials, some coloured, some surface active, many insoluble in the aqueous or non-aqueous solutions used, render direct methods of analysis involving absorptiometry an impossibility; many electrode systems used in electroanalysis are affected by the presence of the surface active agents; hence the classical or standard methods of analysis generally require dissolution, filtration, and sometimes a solvent extraction step before the active ingredient is amenable to analysis.

Provided that the components of the matrix do not react with the reagent used for the assay of the functional group, then thermometric and enthalpimetric methods can be used without separation of the matrix. It is perhaps fortunate that many of the excipients are relatively chemically inactive. Indeed, the pharmaceutical manufacturers desire this to be so, so that there are no side-effects on ingestion of the material. This, in turn, means that they are not reactive in many of the simple reagent systems used in analysis. It therefore means that prior separation is not necessary. Thus, many classes of compounds have been assayed in dosage forms: for example, sulphonamides in cream using silver nitrate [5]; the physiologically active alkaloids using 12-silicotungstic acid [6], or tetraphenylboron [7, 8] as precipitants; hydrazides in isonicotinichydrazide, used in the treatment of tuberculosis, has been determined with potassium ferricyanide [9]. In general, the heats of reaction are so such that single tablets may assayed either by thermometric or by enthalpimetric methods. Enthalpimetry is favoured for routine monitoring

systems simply because of the ease of the readings being converted directly to mg of active ingredient per tablet, or to arbitrary units which can be compared directly to those of the concentrations of standards. It must be emphasised that for mixtures it is necessary to have special precautions and to use a series of reactions to give simultaneous equations, solvable by microcomputer, in order to give direct readings.

There are several disadvantages with enthalpimetric titrimetry, but the main is that serial reactions are not possible since an excess of the reactant is added and the whole of the analyte is titrated. For certain materials, however, the method has great advantages and especially where single analytes are to be investigated.

The role of the solvent

It has already been indicated that the role of the solvent is extremely important in organic analysis; the fact that it generally has a low specific heat is advantageous with respect to the overall sensitivity of the reaction system. One disadvantage, however, is that the solvents are often highly volatile and evaporation, caused by stirring or excessive high heats of reaction, often results in loss of solvent and consequently loss of thermal energy in the system. This is especially disadvantageous with automated enthalpimetric titrations, and is one disadvantage which must be noted and taken into account when automatic systems are envisaged.

However, in general this is a minor effect, and a much more important effect is that based on using the solvent matrix in a catalysed reaction sequence. Essentially the sequence is:

$$\text{Analyte} + \text{Reagent} \overset{(\text{Matrix})}{=} \text{Products (fast reaction} - \text{proceeds first)}$$

$$\text{n Matrix} + \text{Reagent (in XS)} \overset{(\text{Polymerization})}{=} (\text{Matrix})_n + \text{XS Reagent}.$$

The first reaction need not produce any noticeable heat change since the onset of the second and the major thermal reaction is assumed to occur at the end of the first reaction. Hence, if by a graphical or other method, one is able to determine the onset of the second reaction then it is possible to determine how much titrant has been used in the primary reaction.

The first reaction reported which claimed to use this phenomenon was that reported in 1965 by Vaughan and Swithenbank [10]. They showed that when acetone was used as a sample solvent in the titration of weak tar acids (phenols) with an isopropanolic solution of potassium hydroxide as the titrant, a large temperature rise occurred in the vicinity of the expected end point. The temperature rise resulted from the exothermic, alkali-catalysed dimerisation of the acetone solvent to form diacetyl alcohol. Later, in 1967, Vajgand and Gaal [11] reported on the use of the heat of reaction of the perchloric acid catalysed hydrolysis, via hydrolysis of acetic anhydride to indicate the end point in the titration of amines. This had been previously noted by Hume and Keilly [12] but had not been interpreted by them as a catalysed thermometric analysis.

Only a few reactions have proved to be analytically feasible for use as indicator reactions, and these fall broadly into three groups:

(1) Polymerisations catalysed by strong alkalis or strong acids and by iodine. These include ketone and aldehyde condensations, anionic polymerisations of compounds such as α-methylstyrene, and cationic polymerizations of compounds such as acetonitrile.

(2) Esterification and hydrolysis reactions catalysed by strong acids.

(3) Oxidation-reduction processes catalysed by iodine ion in the presence of some transitional metal ions.

Greenhow, 1977 [13], has produced a chemical review on catalimetric titrimetry which lists most of the functional groups which have been determined by these methods and also explains the mechanism of the various indicator reactions. It is a review which gives an understanding of the criteria for the selection of some of the reaction conditions.

The type of curve produced often has the "end point" area rounded because of a series of reactions taking place at or near the equivalence point. The catalysed reaction may commence slightly before the equivalence point because of the non-homogeneity of the solution during the addition of the titrant. Choice of a suitable solvent can, to a large extent, eliminate doubt about the exact end point. For example, in the determination of some barbituric acid derivatives which are used clinically and pharmaceutically, the end points have been sharpened using 1–2% v/v of chloroform in the acetone or acrylonitrile solvent [14]. In this particular method the hitherto standard method requires the analyst to take 20 tablets (1 being the usual dosage amount) and from these obtain an amount of analyte sufficient to give a result on approximately 10–15 tablet weights. The standard method requires the separation of the active ingredients from the tablet. However, since the excipients do not interfere with the titration of the barbiturate using a thermometric method, they are not required to be removed and, moreover, the method is sufficiently sensitive to allow 1 tablet (the dosage form) to be used.

Biochemical applications

Some biochemicals in milligramme quantities have been assayed by both thermometric and enthalpimetric methods, and whilst the results are of interest since they indicate the scope of the technique at relatively low concentrations, in most circumstances the concentrations of the analyte are below that which can be determined with sufficient precision and accuracy by normal thermometric and enthalpimetric methods. There are, however, exceptions to this; for example, the use of the solvent in an acid base catalysed titration has been employed for the determination of catecholamines. The technique involves the acid polymerization of α-methylstyrene, which is used as a solvent for adrenaline, noradrenaline, dopamine, L-dopa, and similar compounds. These have been titrated using a dilute acid which has, in excess, catalysed the polymerisation of the methylstyrene. The

amounts of the bases determined ranges from 0.01 m equiv. to 0.0001 m equiv., i.e. 10^{-7} equiv. [15].

Marini [16] has determined the prototropic groups of haemoglobin but little work has been done in these areas with simple titrimetry.

A fairly large field of micro-calorimetry is now being established for the determination of compounds such as sera, antibiotics, and enzyme preparations by methods involving a bio-assay. Jordan and co-workers [17] have developed thermometric enthalpy titrimetry (TET) and have used it for the determination of proteins as well as for the determination of enzymic substrates [18, 19]. Other workers, including Carr [10], Beezer [21], and Grime [22], have contributed in this area.

Whilst this may be one of the developments of the technique in the future, it is outside the scope of any work dealing with thermometric and enthalpimetric analysis since it is really and essentially micro-calorimetry.

Future developments

Future developments in organic analysis will certainly be in one of two areas:

(1) The use of more sensitive detectors for the determination of small amounts of material. Already the diode has been reported as a replacement of the thermistor [23]. This instrument has a response of at least 2 orders of magnitude greater than has the thermistor, has no Joule effect, and has a truly linear response with respect to temperature change. The linear response means that for enthalpimetric work at elevated temperatures it is not necessary to have an exact control of the temperature, except that the ambient temperature should remain constant over the period of the experiment. Furthermore, since there is linearity of response with respect to temperature it is not necessary to have strict control over the system used for the calibration determinations.

(2) The second area is in the production of specific reaction systems based upon the heat sensor. For biochemical systems it has already been suggested that the sensor is coated with a specific enzyme system so that only selected antibody reactions take place upon the enzyme coating and hence only those give a heat change in the system. It is intended that these systems will be able to work on 1 – 2 drops of, say, a body fluid instead of 10 – 20 mls of the system.

The future prospects for thermometric and enthalpimetric analysis in organic fields are really based upon two papers which incidentally deal with the first reported work in thermometric and in enthalpimetric analysis and both of which deal with some aspects of organic analysis. The first paper [24] involves the preparation of a neutral solution of ammonium citrate from solutions of ammonium hydroxide and citric acid. This could not be done by any other titrimetric method and indicates that thermal methods can often lead the way. The second deals with the first application of enthalpimetry and is by Richmond and Merrywether [25], who assayed acetic anhydride in acetic acid. They used a mixture of 186 ml of toluene and 12 ml of aniline in a Dewar flask and injected into it 2 ml of the sample.

They used as a temperature sensor a mercury in glass thermometer graduated in 0.5°F.

They quote "They had a $\Delta T°$ of 6°F for each 1% of free anhydride, with readings within 0.5°F". Moreover, they concluded with a statement which can still be taken as the aim for all workers in these techniques: "They (the determinations) are, moreover, carried out easily by an ordinary, intelligent workman; the time required for the determination should not exceed 3–4 minutes from thestart".

With all the modern methods of dispensing the titrant, sensing the heat changes, and computing the answer, this is still a worthy aim.

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Резюме — Два главных параметра определяют методы анализа органических соединений в производстве: скорости реакций молекулярных органических соединений, протекающих часто в неводных средах и которые отличаются от таковых в ионных и водных средах. Вторым фактором является то, что для большинства органических систем требуется определить какую-либо органическую функциональную группу общим методом, применяемомк функциональной группе в различном химическом окружении. В фармацевтических препаратах желательно определять функциональные группы без предварительного разделения органических соединений от инертных наполнителей различных типов. Наряду с этим желательным является получение быстрых анализов и часто с намного меньшей точностью, чем это требуется для неорганических систем. Методы обсуждены на примерах, имеющих место в пищевой промышленности, фармацевтической промышленности и др.