HIGH FREQUENCY TITRATIONS IN PHARMACEUTICAL ANALYSIS

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During the last ten years, considerable attention has been directed, particularly in the United States of America, to the detection of the end-point of a titration by the use of high-frequency methods. In ordinary conductometric analysis, two platinum electrodes are immersed in the solution and the change in electrical conductivity during the titration measured by means of a bridge circuit energised by an alternating current with a frequency of about 2000 cycles per second. This method has several disadvantages; the electrodes are costly and require careful washing and storing if their sensitivity is to be maintained, while in some instances the presence of the electrodes may have undesirable effects on the titration. In high frequency methods the electrodes are placed outside the titration vessel and by virtue of the high frequency of the energy applied to the electrodes, coupling between them and the solution takes place through the walls of the cell.

Measurements on systems of this kind are a composite function of both the dielectric constant and the conductance of the sample solution, as well as the cells walls and of any air space between these and the electrodes, and any system which displays significant changes in either or both of these properties with varying concentrations or composition will give a satisfactory high frequency end-point.

Instruments

The types of instrument used in high frequency titrations can be classified into several groups according to the electrical property actually measured. If the sample container is introduced into the tank coil of an oscillator, energy is absorbed from the circuit to an extent largely dependent upon the conductivity of the sample. This loss of energy can be followed by measuring the change in various circuit factors of the oscillator such as anode, grid or cathode voltages or currents as the conductivity of the sample changes during the titration. Instruments of this type have been described by a number of authors including Dowdall, Sinkinson and Stretch[1] with whose instrument we have had considerable experience.

The second group of instruments comprises those which indicate a change in capacitance of the cell by a change in frequency of the oscillator, which is measured either by mixing the output with that of a standard oscillator and measuring the change in frequency of the beat note produced or by some form of frequency discriminator. In addition to these two broad groups, a number of instruments have been devised which respond to both the conductance changes and the capacitance changes[2,3], while Hall and Gibson[4] have described the use of a high frequency

impedance bridge by which one can measure both the capacitance and conductance changes of a suitable cell independently.

Cell Design

The design of a cell suitable for high frequency titrations depends to some extent upon the type of instrument used for detecting the change in electrical properties of the sample during the titration. Blake[5] suggested the use of a glass tube with two metal bands round it to form the electrodes (Fig. 1) and he used this type of cell in his "Rectified Radio-frequency Impedance" method whereby energy from a signal generator was applied between one electrode and earth and the change in high frequency current

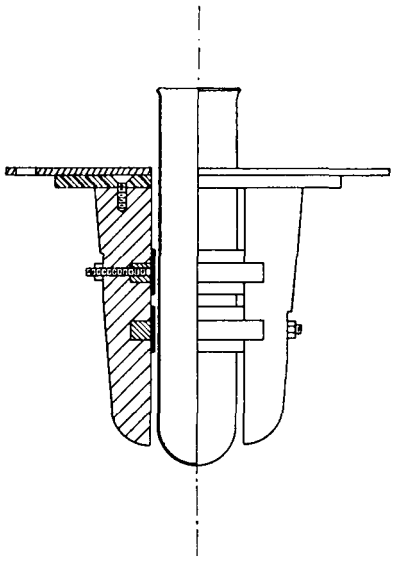

FIG. 1. Band type cell (after Blake).

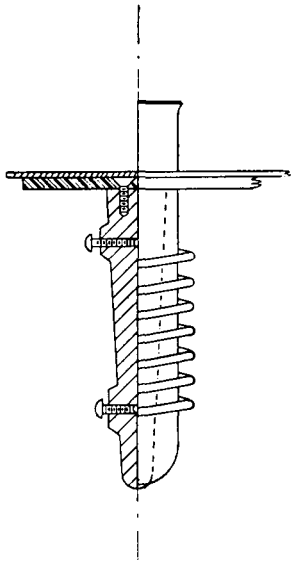

FIG. 2. Coil type cell.

measured, after rectification, between the other electrode and earth. We have used this method and we find that it is relatively insensitive to small conductance changes in solution; we also experienced some difficulty caused by the formation of resonant peaks in the response curve due to the band electrodes and the self-capacitance of the crystal rectifier.

This type of cell can be used with instruments measuring capacitative changes and Reilley and McCurdy[6], and Clayton, Hazel, McNabb and Schnable[7] have investigated the effect of cell geometry on the type of response obtained, the former using an impedance bridge and the latter a frequency discriminator type of instrument.

The coil type of cell (Fig. 2) is used in many published designs and, although it is somewhat more difficult to analyse the behaviour of such cells theoretically than is the case with the capacitor type cell, experience suggests that the choice between the two types must mainly depend upon the design of the instrument employed. In certain titrations, however,

we have found that while a satisfactory response is to be obtained with a coil type cell, no change of slope is obtained with the capacitor-type cell (Figs. 1 and 3) when using an instrument adapted for use with either type.

EXPERIMENTAL

In this work, we have used three methods of measuring the electrical changes at the end-point of a titration.

1. The tuned-anode-tuned-grid oscillator of Dowdall, Sinkinson and Stretch[1], was built with the modification suggested by Lane[8]. The layout of the circuit was varied from that suggested by the originators of the design so that it could be incorporated into a small steel instrument case. This entailed external connections to the batteries, but this has not in practice been found to have any disadvantages. As in the original, the titration cell was accommodated through a hole in the top of the case and the anode coil was rigidly mounted on a polystyrene frame secured to the inside of the case so that the cell could easily be removed for cleaning without disturbing the coil. The change in anode current during the titration was indicated by a Scalamp taut-suspension mirror galvanometer. The nominal frequency of oscillation of this instrument is approximately 16 megacycles per second.

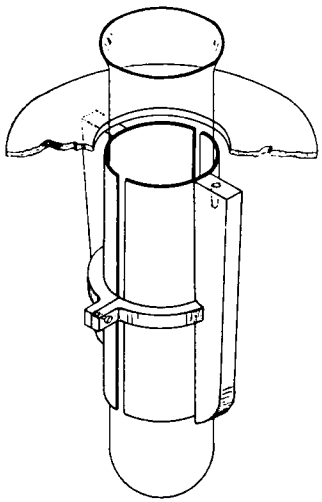

FIG. 3. One form of capacitative type cell.

2. Blake's "Rectified Radio-frequency Impedance" method[9,10], the circuit of which is shown in Figure 4 has been applied to a number of titrations. Blake described an oscillator giving energy at a frequency of 1175 kilocycles per second, but in an attempt to extend the range of concentrations to which this apparatus could be applied, we used an

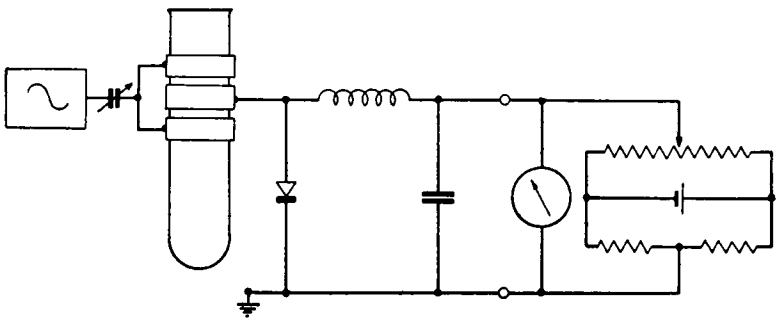

FIG. 4. Circuit of Blake's rectified radio-frequency impedence apparatus.

Advance Type E2 signal generator, taking the unmodulated ouput from the "full R.F." socket (1 volt into 1000 ohms). The frequency range of this instrument extends to 100 megacycles per second but reasonable responses could only be obtained at the resonance peaks, which with the particular cell and detector circuit used, occurred at 45 megacycles per second with the first harmonic slightly less pronounced at 90 megacycles per second. At other frequencies, the changes of current indicated by the galvanometer during the titration were too small to be of use. The occurrence of these resonant peaks is undoubtedly a function both of cell design and of rectifier design and modification of these portions of the apparatus may well enable satisfactory response curves to be obtained over a range of frequencies.

3. Using a coil type cell, any change in the electrical properties of the contents will affect the "Q-factor" of the coil. This can be defined as the ratio of the energy stored in the coil to the energy dissipated and it can be measured by means of a circuit magnification meter. In this instrument the coil is made part of a resonant circuit which is fed with a small voltage of known frequency from a generator of negligible impedance and the voltage drop across the coil measured at resonance by a valve voltmeter of negligible admittance.

Blake[5], uses the term "Q-metric" to describe the method whereby he measures the damping effect of a solution in a band-type cell on the Q-factor of a capacitor in the tank circuit of an oscillator when the cell is connected in parallel with the capacitor. The actual measurements made are of the anode current of the oscillator; thus the principle of the method is similar to that described by Dowdall, Sinkinson and Stretch[1]. Several types of circuit magnification meters are available commercially and we have used this method with both the Marconi circuit magnification meter type TF329G and the Advance "Q" meter.

In our experience, the most generally applicable instrument is the circuit magnification meter. The tuned-anode-tuned grid oscillator has been applied to a great many titrations satisfactorily, but it is somewhat more sensitive to the concentration of the solution in the cell and, although the formation of a precipitate during the titration adversely affects both instruments, this is not so marked with the Q-meter. We have not found Blake's rectified radio-frequency impedance method so sensitive as either of the above instruments; with non-aqueous titrations in fact, very little change in impedance appears to take place at the end-point. The results presented below, have been obtained using either the Advance Q-meter or the tune-anode-tuned-grid oscillator; all the titrations have been carried out with both instruments and, unless otherwise stated, either is equally suitable.

Results

The precise method of making a titration depends upon the particular instrument used. The cells were designed to take 1 in. diameter Pyrex glass boiling tubes and the following details are generally applicable.

Transfer a suitable quantity of the sample solution to the cell, dilute to

such a volume that the electrodes (bands or coil, etc.) are below the level of the liquid and titrate by adding the titrant in increments, stirring and reading the instrument after each addition. In our experience the best method of stirring is by means of a stream of nitrogen gas bubbles, the gas flow being stopped while a reading is taken; a satisfactory degree of

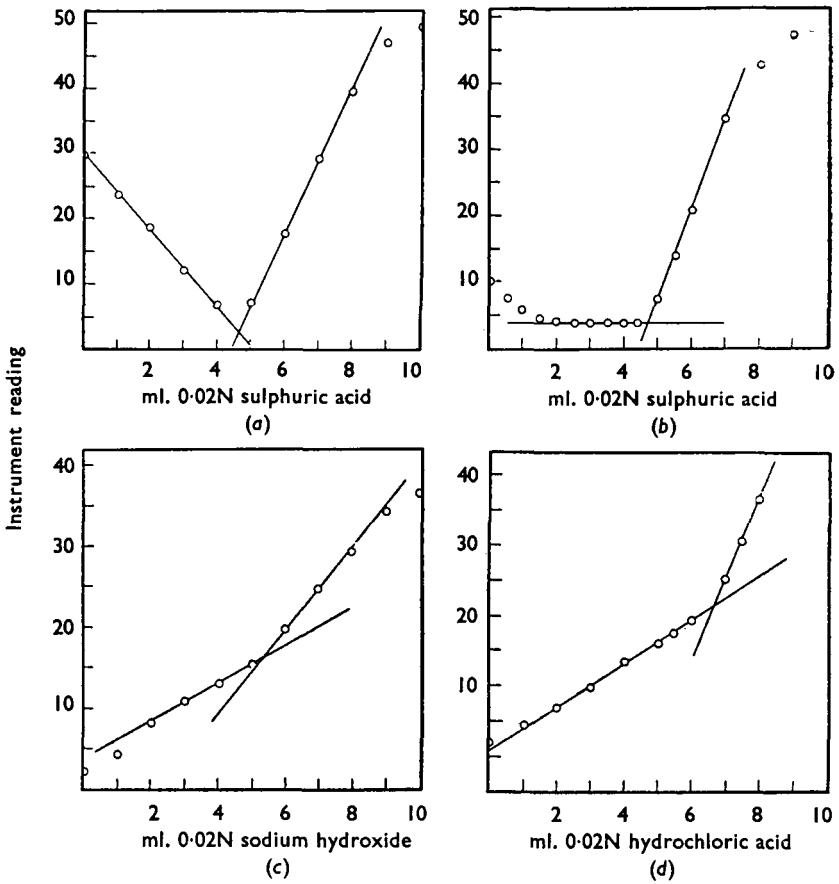

FIG. 5. Acid-base titration curves. (*a*) Sulphuric acid–sodium hydroxide. (*b*) Sulphuric acid sodium carbonate. (*c*) Sodium hydroxide–acetic acid. (*d*) Hydrochloric acid–pyridine.

mixing is obtained by turning on the gas-cylinder supply for about two seconds after each addition of titrant. In the case of the Q-meter, it is advisable to adjust the circuit capacitance after each addition to give the maximum reading; this is easily done by means of the trimmer provided.

Acid-base Titrations

No difficulty has been experienced with simple acid-base titrations using any of the three methods described. Using the tuned-anode-tuned-grid oscillator, and plotting change in anode current against volume of

titrant added, the findings of Dowdall Sinkinson and Stretch[1], have been confirmed and a representative selection of curves is shown in Figure 5. The optimum concentration for this apparatus is about 0·02N and we obtained the best results by diluting the sample under examination to about this concentration in base in the titration vessel and titrating it with 0·1N or 0·05N acid from a micro-burette. By this means undue dilution of the sample during the titration, with consequent production of curved plots, is minimised. Using Blake's method and applying energy at a frequency of 45 megacycles per second, good results were obtained at a concentration of 0·1N.

A sample of sodium phosphate B.P. has been assayed by titration with 0·02N hydrochloric acid using the simple tuned-anode-tuned-grid oscillator. The curve produced is shown in Figure 6. From this the purity of the sample is 99·78 per cent. By the official method 99·74 per cent. was indicated. A similar result was obtained using the Q-meter.

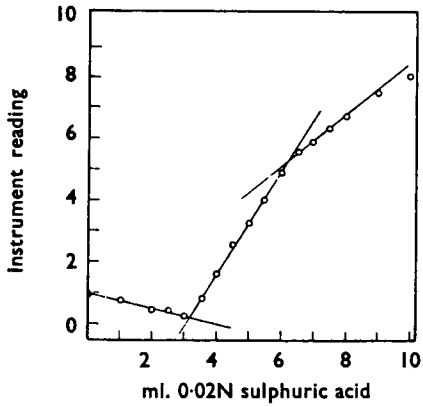

FIG. 6. Curve for the titration of sodium phosphate B.P. with sulphuric acid.

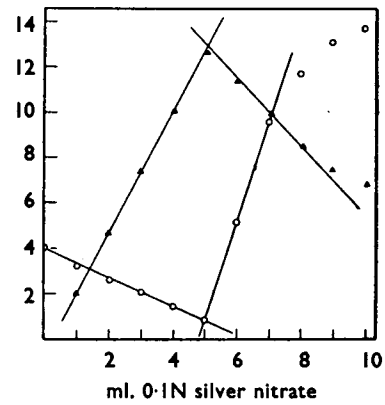

FIG. 7. Titration curves with silver nitrate. ○——○ Sodium chloride. ▲——▲ Hydrochloric acid.

Precipitation Reactions

(*a*) *Silver titrations.* No difficulties have been experienced in the titration of halides with silver nitrate at a concentration of about 0·02N so long as the presence of an excess of acid is avoided. Thus, sodium chloride and hydrochloric acid give normal response curves with a well-defined break at the end-point but the addition of hydrogen ion beyond that equivalent to the halide present increases the overall conductance of solution to an extent that masks any change at the end-point. Standardised solutions were used to obtain the curves reproduced in Figure 7.

Ammonium chloride, which is assayed in the B.P. by a modified Volhardt procedure, can be titrated directly. The curve is given in Figure 8 and the indicated purity of the sample used is 99·76 per cent. The corresponding figure by the official method is 99·81 per cent.

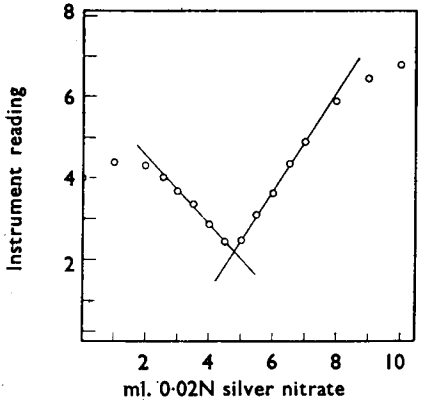

FIG. 8. Titration curve of ammonium chloride with silver nitrate.

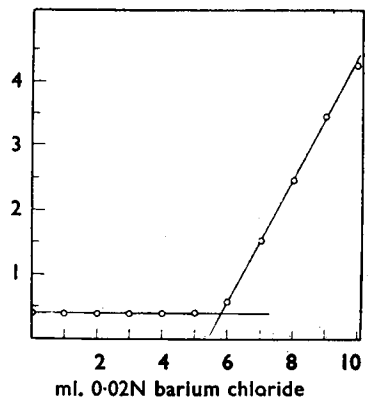

FIG. 9. Titration curve of sodium sulphate with barium chloride.

(*b*) *Titration of sulphate.* Milner[11], has reported that if the titration of sulphate with barium chloride solution is conducted in the presence of ethanol and is seeded with a trace of barium sulphate, a satisfactory end-point is given using an oscillator virtually identical with that of Dowdall, Sinkinson and Stretch, so long as the excess electrolyte calculated as sodium chloride is kept below a concentration of about 0·03M. Reasonable results have been obtainable only in the absence of excess of electrolyte and at a concentration of 0·02 to 0·05N. Within these limitations, a direct determination of sulphate is possible and the curve obtained by assaying sodium sulphate B.P. by titration with barium chloride under conditions recommended by Milner is given in Figure 9. The indicated end-point gives an assay figure of 99·6 per cent., while the official procedure carried out on the same sample gives 99·45 per cent., both calculated as the dry material. This swamping effect of excessive quantities of electrolyte, more particularly of hydrogen ion, is a major disadvantage of the apparatus used in this work. However, it is probable that the use of frequencies of the order of 200 megacycles per second and above may eliminate this. Work on devices employing these very high frequencies is in hand.

Non-aqueous Titrations

The most immediately useful application of the high frequency method of end-point detection is in non-aqueous titrations. Visual indicators are rarely entirely satisfactory and are, in fact, empirical, being based upon potentiometric results.

Using the simple oscillator described above, Lane[8] has shown that accurate and precise indications of end-point can be obtained with a variety of titrations and we have confirmed his work. In our hands, the method of Blake has proved insufficiently sensitive where non-aqueous media are concerned, whereas the circuit magnification meter with a coil type cell can give a satisfactory indication of the end-point in many cases. We have found that titrations using acetous perchloric acid give the best

results with this instrument and curves obtained in the standardisation of acetous perchloric acid with potassium hydrogen phthalate are given in Figure 10. The tuned-anode-tuned-grid oscillator cannot be used satisfactorily with this particular titration.

Beckett, Camp and Martin[12], have shown that the alkali metal salts of aliphatic and aromatic acids can be determined by titration with perchloric acid in glacial acetic acid solution, but they point out that the indicator colour changes at the end-point are affected by the type of cation present.

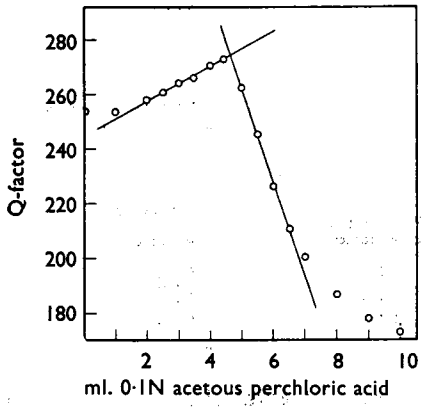

FIG. 10. Curve for the standardisation of 0·1N acetous perchloric acid with potassium hydrogen phthalate.

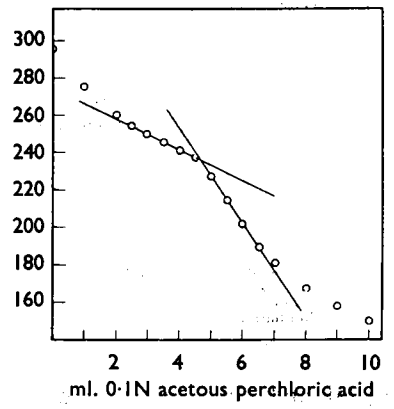

FIG. 11. Titration curve for sulphanilamide with acetous perchloric acid.

Using the Q-meter, good indication of end-point has been observed with a representative selection of this type of compound as shown in Table I.

Sulphonamides can be titrated satisfactorily with perchloric acid in glacial acetic acid[13]. Figure 11 shows the high-frequency titration curve of sulphanilamide; the results of the assay of a number of sulphonamide tablets are given in Table II together with the results by the official method for comparison. These have been obtained by crushing several tablets to a fine powder and warming a weighed portion (such that the solution in the cell was approximately 0·02N) with glacial acetic acid containing a trace of acetic anhydride. The sulphonamide dissolves but much of the excipient remains insoluble; this can be ignored and the mixture titrated with 0·1N acetous perchloric acid as described above. It is preferable to use the Q-meter for this particular titration.

The Q-meter is to be preferred for these titrations, but both this and the tuned-anode-tuned-grid oscillator can be used.

Potassium methoxide in benzene and methanol has not proved very satisfactory when the potassium salt of the acid being titrated is insoluble in the solvent system used. Precipitation appears to cause random deflections as the end-point is approached and it is difficult to select the exact breakpoint of the curve with certainty. This instability in the presence of a precipitate was reported by Lane[8], who found that in the reactions he studied, satisfactory indication of end-point could be obtained

TABLE I

COMPARISON OF OFFICAL ASSAY METHOD WITH THE HIGH FREQUENCY METHOD USING ACETOUS PERCHLORIC ACID

Chemical	Purity per cent.	
	Official method	High frequency method
Sodium citrate	99·70	99·70
Sodium benzoate	99·91	99·87
Sodium salicylate	99·90	99·86
Potassium citrate	99·90	99·90
Potassium benzoate	99·83	99·85
Potassium tartrate	99·98	99·89

TABLE II

COMPARISON OF THE OFFICIAL ASSAY METHOD FOR SOME SULPHONAMIDE TABLETS WITH THE HIGH FREQUENCY METHOD USING ACETOUS PERCHLORIC ACID

Tablet	Assay	
	Official method g. per tablet	High frequency titration g. per tablet
Sulphaguanidine (Sample I) ..	0·503	0·505
Sulphaguanidine (Sample II) ..	0·509	0·508
Sulphadiazine	0·505	0·501
Sulphathiazole	0·517	0·509

by taking the instrument reading at the same interval of time after adding each increment of the titrant. We have not found that this control of the time intervals during the titration effected any marked improvement in the particular reactions we studied. For the titration of very weak acids in non-aqueous media, Harlow, Nobel and Wyld[14], describe the preparation and use of tetrabutylammonium hydroxide and the possibility of detecting the end-point by high frequency means when this substance is used as titrant is being examined.

SUMMARY

1. A description is given of simple instruments which provide a satisfactory indication of the end-point of a titration using high-frequency energy.

2. The application of high-frequency titrations to a number of pharmaceutical analyses has been described.

3. The method is shown to give results comparable with those of the official assays.

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DISCUSSION

The paper was presented by MR. J. ALLEN.

DR. F. HARTLEY (London) said it was clear that the method had considerable potentialities. To be able to place electrodes outside the vessel in which the material was being titrated offered obvious advantages, and one would suppose that provided the excipients themselves were non-electrolytes there was no reason why the method should not be applied to some otherwise quite intractable mixtures.

MR. C. A. JOHNSON (Nottingham) said unfortunately the paper did not show that the method had any advantage over other available methods. In an American abstract of a paper read by Dr. Stuckey in May on the use of complexones in analytical work, he was reported as having said that end-point determinations in E.D.T.A. titrations often presented difficulties, and high frequency titration could be used with advantage. It was a pity that this was not brought out in the paper.

DR. A. H. BECKETT (London) said the authors were critical of Blake's method. They had changed the frequency in an attempt to extend that method's range and scope, whereas he had found that the electrode size and spacing was far more important than the frequency. For instance, at 2·5 megacycles, 1·0 cm. electrodes 1 mm. apart were suitable for about 0·1 to 0·2N, whereas 2 cm. electrodes similarly spaced were useful for about 0·1 to 0·01N. It was the easiest method to manipulate and had the advantage of being free from error due to thermal effect in the solution. There were no end capacity effects and crystal control could be easily used. In the non-aqueous titration field, Blake's method was at a disadvantage, because it was dielectric constant rather than conductance changes that were taking place in the medium. The authors seemed to be using a large volume of solution, and it would be interesting to apply the method to small amounts for measuring rates of hydrolysis.

MR. E. H. B. SELLWOOD (London) asked if the authors had any experience of the use of the simple oscillator of Alexander, consisting of a magic eye tuning indicator which functions as a crystal controlled oscillator and gives an indication of end-point at the same time. It was designed primarily for determination of dielectric constant and was based on the capacitance effect.

MR. J. ALLEN, in reply, emphasised that the paper was in the nature of an introduction. The instruments used were "low definition instruments". There were other high definition instruments with which one could obtain almost unparalleled sensitivity. It had been suggested that higher frequencies than those used might overcome the difficulty caused by electrolytes. That was in fact the case. At 250 megacycles one could

titrate satisfactorily in the presence of 10 per cent. potassium chloride. It was true that in the paper no application had been suggested which was better than standard methods. However, the method outlined was quicker than the normal potentiometric procedure, because it was not essential to plot many points around the end-point. As to the end-point of the complexiметric titrations, there were a number of anomalies which they were unable to explain at present. The Blake method had been tried, but it was insufficiently precise for any reasonable degree of analytical accuracy. The volume of solution depended upon the precision of the measurement of capacitance change. If one started with large capacitance one could measure small changes; but it was very difficult to measure smaller changes if the total capacitance were small. The only instrument which might satisfactorily do that was the very costly Twin "T" impedance bridge. The Alexander type of oscillator was applied to analytical work by Hall in the United States about 1952 and although in theory the use of the crystal controlled oscillator, which could be tuned in and out of oscillation by altering the capacitance in the anode circuit of the valve, and the use of the magic eye to indicate the sudden change in voltage as the valve came into and out of oscillation, was attractive, in fact the apparatus was not satisfactory because it "pulled". This means that different values of capacitance are obtained whether one begins with the instrument oscillating and tunes until it just stops or vice versa. Further, since this "pulling" is non-symmetrical about the critical point, depending on external conditions, it is not practicable to take a mean.