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Automated Conductimetric Titrimeter: Use in Studying Ionic Solute-Solute Interactions

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Abstract □ An automatic conductimetric titration apparatus is described in which the delivery of titrant is effected using a motorized automatic syringe having a wide range of injection rates. Two applications of the apparatus are described: (a) determination of the CMC of cationic and anionic surfactants, and (b) study of the interaction of an organic anion (sodium lauryl sulfate) and organic cations (phosphonium salts). The accuracy and precision of results using this apparatus are superior to results obtained by the tedious manual method.

Keyphrases □ Titrimeter, automated conductimetric—design, application to studying solute-solute interactions □ Syringe, motorized automatic—component of automatic conductimetric titration apparatus, application to solute-solute interactions □ Conductimetric titrations—automatic apparatus described, applied to solute-solute interactions

The physical property of solution conductance is well established, and conductimetric titration measurements can be used for various purposes. In pharmacy such measurements find application in studies on association and micellization, interaction (*i.e.*, complexation) between species of opposite charge, and analytical quality control. However, the usual method of addition of titrant or complexing agent to the titration vessel is tedious, and the results are often subject to experimental inaccuracies.

A conductimetric titration of one ion against another of opposite charge will provide information on ion-pair formation, complexation (as described by the solubility product), and, if one ion is surface active, the effect of the added species (counterion) on micelle formation. In addition, a study of the interaction of a large organic ion with congeneric members of a series of ions of opposite charge can lead to the calculation of thermodynamic quantities and, subsequently, the derivation of extrathermodynamic parameters (1) for use in linear free energy relationships to examine structure-activity correlations by regression analysis.

Studies on the variation of the free energy term with temperature should lead to an insight into enthalpy and entropy contributions to the interaction and, in consequence, the processes responsible for such complex formation. Because small errors in

measurement of the solubility product (and any association constant) will lead to greater errors when the free energy-temperature relation is differentiated (2), an essential requirement of measurement is that the experimental data are of high accuracy. Such accuracy cannot be obtained with manual or semiautomatic methods.

Thus, an accurate automatic conductimetric titration apparatus was developed, using commercially available components, which is suitable for pharmaceutical systems. Semiautomatic conductimetric titrimeters for use in analytical measurements were described previously (3, 4).

EXPERIMENTAL

Apparatus (Fig. 1)—A conductivity bridge¹, which is continuously and automatically balanced, is connected to a dip-type conductivity cell contained in a thermostated beaker. The temperature is maintained constant by water pumped from a water bath and cooler unit. The titration mixture is agitated constantly by a magnetic stirrer. The measured conductivity, which can be read directly from the bridge, is normally recorded in the form of a continuous trace on a chart recorder.

In titrations where an external standard is used, a similar thermostated beaker is connected to the water bath; a dip cell, which has a comparable cell constant (± 0.01) to the other cell, is connected to the external standard terminal of the bridge. The stirring conditions in the external standard are maintained the same as in the unknown during the titration.

The delivery of the titrant is maintained constant using a motorized automatic syringe², which has a wide range of delivery rates according to the capacity of the special syringes used. Where an external standard is used, two syringes of the same capacity are employed and driven simultaneously at the same rate.

Calibration—The conductivity bridge was trimmed and calibrated as described in the instrument manual.

The automatic motorized syringe equipment is supplied with special syringes, consisting of a calibrated glass barrel and a steel plunger fitted with a rubber gasket. The accuracy and reproducibility of the volume delivered from the syringes were tested by two techniques: (a) the syringe was allowed to drain into a dry, previously calibrated volumetric flask of a suitable volume; and (b) the syringe was filled with a potassium chloride solution of known conductivity and this was titrated into a blank of double-distilled water of known volume. The conductivity was recorded as a func-

¹ Wayne-Kerr B642 universal bridge, Wayne-Kerr, Surrey, England.

² R. Braun, Melsungen, West Germany.

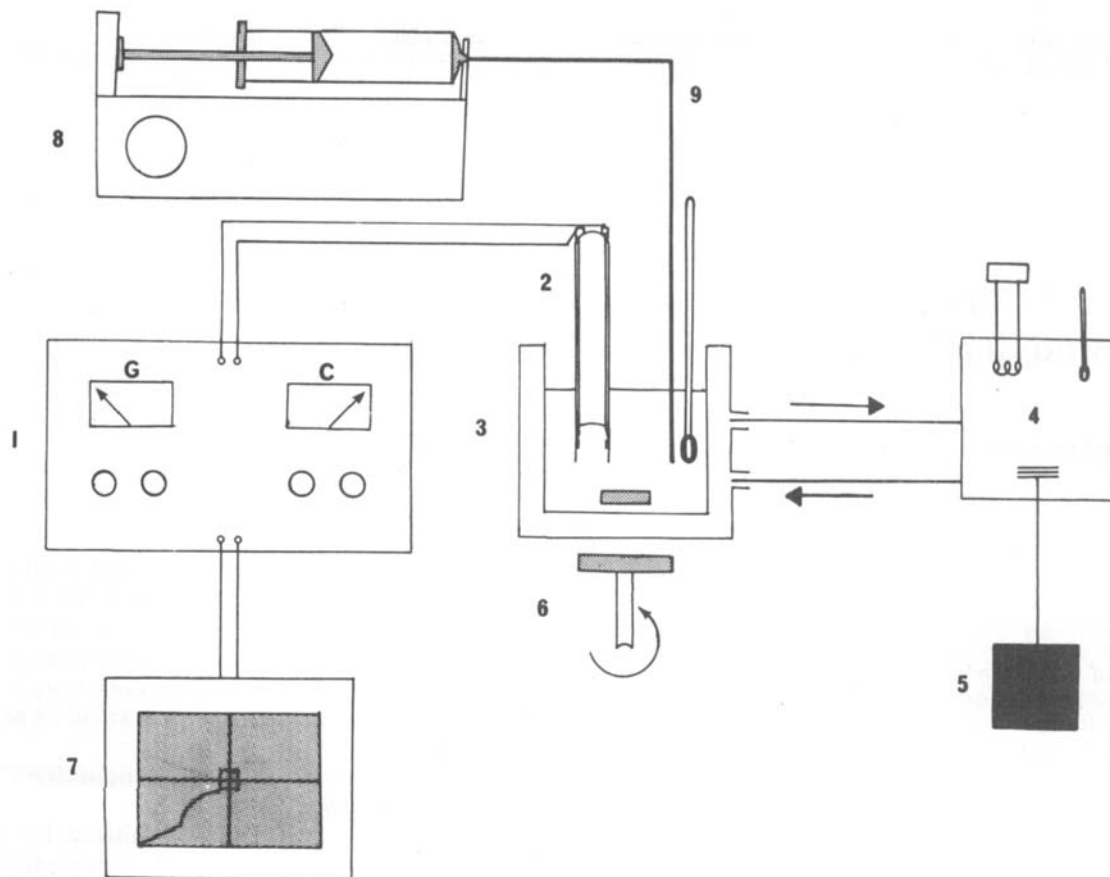


Figure 1—Schematic diagram of automatic conductimetric titrator. Key: 1, conductivity bridge; 2, dip-type conductivity cell; 3, thermostated beaker; 4, water bath; 5, cooler unit; 6, magnetic stirrer; 7, chart recorder; 8, motorized automatic syringe; and 9, stainless steel cannula.

tion of the added volume. The variation as compared to the figures supplied by the manufacturer was $\pm 0.03\%$.

The specific conductance at any instant of the titration can be calculated from the following equation:

$$K_{spt} = (K_i + K_t)F_t C_{cell} \quad (\text{Eq. 1})$$

where K_{spt} = specific conductance at time t of the titration; K_i = initial conductance in the titration vessel at zero concentration of titrant; K_t = recorded conductance at time t ; C_{cell} = cell constant; and F_t = dilution factor at time t where $F_t = [(V + V_t)/V]$, where V = initial volume, and V_t = volume delivered by the syringe.

Average variations of the specific conductivity obtained from the automatic procedure as compared with a calibration curve made for standard solutions of the electrolyte were $\pm 0.1\%$.

In titrations using the external standard technique, the syringes and the dip cells were matched by the electrolyte method alone. The two beakers utilized were filled with equal volumes of double-distilled, deionized water, and the two syringes were filled with equal volumes of the same electrolyte solution. The magnetic stirrers were adjusted to give the same rate of stirring; the conductivity bridge was trimmed, set, and calibrated as before. When properly balanced, there was no change in the recorded conductivity when the same electrolyte solution was titrated into two different beakers.

Applications—Determination of Critical Micelle Concentration (CMC)—A plot of specific conductivity against concentration for a detergent solution leads to a change in the slope obtained in the region of the CMC. Experimental points may be considered to lie along two straight lines, the extrapolated intersection of which can be taken as the CMC (5). For these studies, the conductivity was recorded as a function of volume when surfactant solutions

(benzalkonium chloride³ and sodium lauryl sulfate⁴) were titrated against 50.0 ml of double-distilled, deionized water ($K_i < 1.0 \times 10^{-6}$ mho/cm at 25°).

Interaction between Large Organic Ions of Opposite Charge—The interaction between sodium lauryl sulfate and various phosphonium salts⁵ in an aqueous medium was studied in a range of concentrations. The phosphonium compounds were recrystallized from ethanol before use.

A phosphonium salt solution (50.0 ml) was contained in the titration beaker, and a 1×10^{-1} M solution of sodium lauryl sulfate was added slowly from the syringe.

External Standard Technique for Following Complexation—The interaction between two ions and the subsequent solubilization of the complex can be studied to an even higher degree of precision using an external standard technique. An extra thermostated beaker containing 50.0 ml of conductivity water was fitted with a dip-type conductivity cell that had a similar cell constant to the other cell (1.40 versus 1.39). This was connected to the external standard side of the conductivity bridge. The other thermostated beaker contained the solution of phosphonium compound. The conductivity bridge was then balanced to give a null point reading. The sodium lauryl sulfate solution was then titrated into the two beakers simultaneously.

RESULTS AND DISCUSSION

CMC—It has long been established that the antibacterial action of the quaternary ammonium salts is related to their physical

³ Sterling-Winthrop Research Laboratories, Rensselaer, N.Y.

⁴ Specially purified grade, British Drug Houses, Poole, England.

⁵ Maybridge Chemical Co., Cornwall, England.

properties and, in particular, their relative surface activity to their relative lethal capacity (6). Commercially available benzalkonium chloride products are a mixture of alkyl benzyldimethylammonium salts comprised of the C₈-C₁₆ homologs. Work reported here is part of a study undertaken to examine relationships between the surface activity of pure alkyl benzyldimethylammonium chlorides and their antibacterial activity.

Published literature values for the CMC's of the examined series are at variance (7, 8), and the conductimetric titrimeter provides a rapid and extremely accurate method of establishing the CMC's of benzalkonium chloride.

Figure 2 shows the plot of log CMC *versus* alkyl chain length for data obtained in the present study and previously reported values. The results (7) obtained using a lowering of the surface tension method, although smaller than those in this study at all chain lengths, are in reasonably close agreement. The difference is possibly due to the fact that the surface tension method requires a high degree of purity of the surfactant solution.

The results (8) determined with a dye titration method are far lower and show an anomalous break in the curve at $n = 12$. This is probably due to the dye molecules promoting micelle formation. There is no evidence of "odd-even" effects where values for even-numbered homologs fall on a different line than odd-numbered homologs (9).

The relationship between CMC and chain length (n) in Fig. 2 is given by:

$$\log \text{CMC} = a - bn \quad (\text{Eq. 2})$$

where a and b are constants. The gradient b is 0.36, indicating that the addition of each methylene group reduces the CMC by a factor of 2.3.

If micelle formation is considered as a phase separation process, a free energy value of -507 cal/mole can be calculated for the

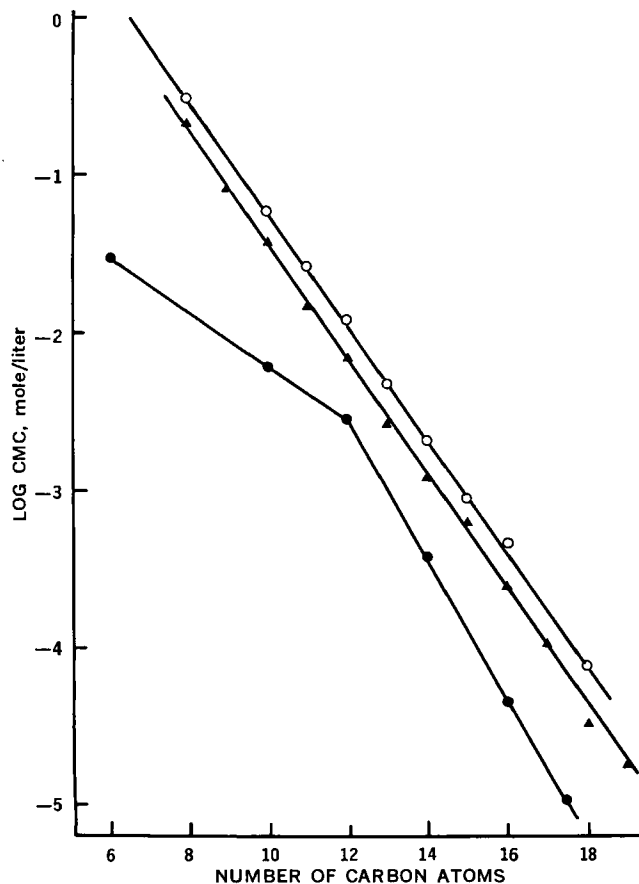


Figure 2—Log CMC *versus* alkyl chain length for alkyl benzyldimethylammonium chlorides. Key: ○, this work; ▲, Ref. 7; and ●, Ref. 8.

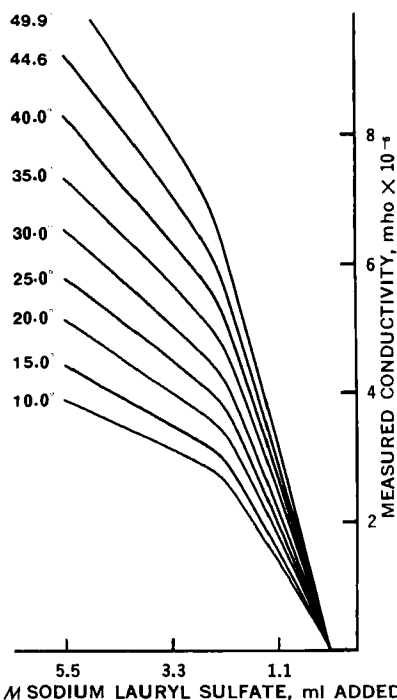


Figure 3—Experimental curves from chart recorder showing change in conductivity with added sodium lauryl sulfate.

transfer of a methylene group from an aqueous environment to the micelle. [The nonideality of monomeric species in solution and the small correction for the entropy of mixing of the micellar phase with the solvent were ignored. These factors will have a small influence on the calculated result (10).]

Figure 3 shows the experimental curves of conductivity *versus* volume of added sodium lauryl sulfate solution (0.2 M) for the 10–50° range. The calculated CMC values at different temperatures were compared to values reported by Goddard and Benson (11) in Fig. 4. At each temperature, slightly higher values for the CMC were recorded.

The conductivity of solutions of sodium lauryl sulfate below the CMC was also monitored using this titrator, and the equivalent conductivities were calculated and compared to the Onsager limiting slope. Deviations from the slope could be attributed to pre-micellar aggregation of surfactant molecules (12).

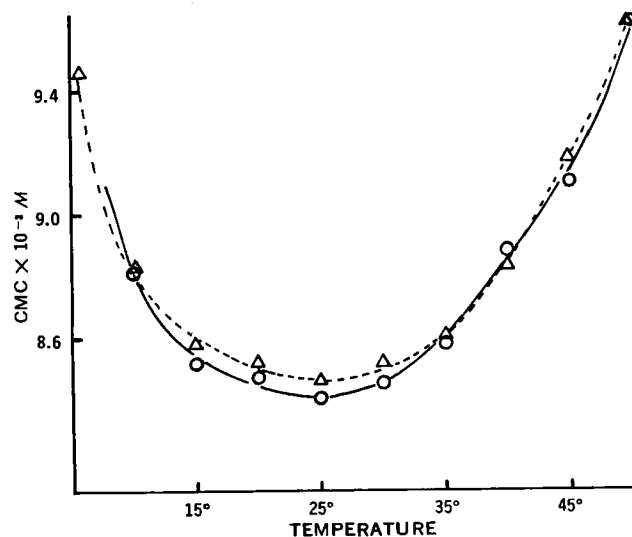


Figure 4—Change of CMC with temperature for sodium lauryl sulfate. Key: △, this work; and ○, Ref. 11.

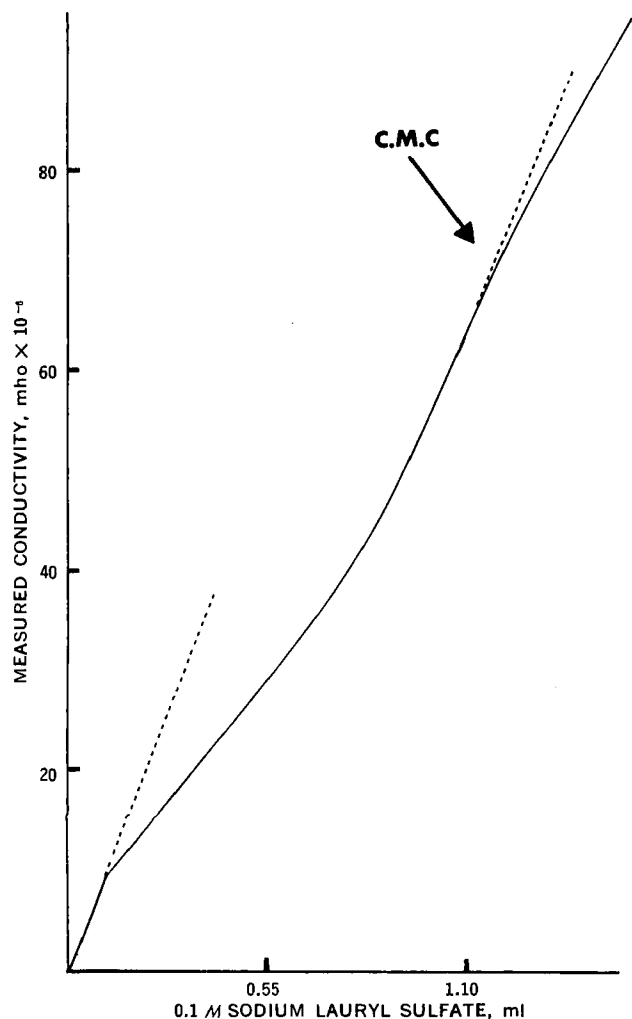


Figure 5—Conductimetric titration of sodium lauryl sulfate (0.1 M solution) against butyltriphenylphosphonium bromide (1.4×10^{-3} M solution).

Interaction between Large Ions—A typical conductivity curve for the titration of sodium lauryl sulfate against a solution of phosphonium compound is shown in Fig. 5. It consists of three separate regions. At a low concentration of added sodium lauryl sul-

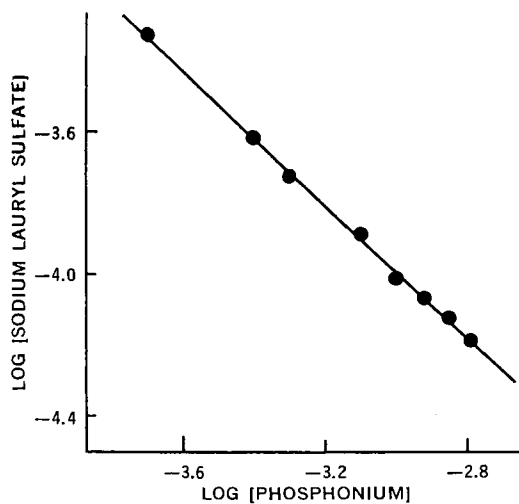


Figure 6—Titration of sodium lauryl sulfate against different concentrations of phosphonium salt (benzyltriphenylphosphonium chloride) (double log plot).

fate, there is a linear relationship between specific conductivity and sodium lauryl sulfate concentration. In this region the components of the solution are in an almost fully ionized state. However, there is the possibility of aggregation and limited ion-pair formation.

A second region is heralded by a break in the curve (the solution normally goes turbid at this point), followed by a curvilinear region. The sudden change in the gradient of the conductivity-volume of titrant plot is due to the separation of a complex between sodium lauryl sulfate and the phosphonium salt.

The change in this end-point with different phosphonium-ion concentrations is shown in Fig. 6 as a double logarithmic plot. The gradient of the straight line is 1.0, indicating that a 1:1 complex has been formed. The solubility product is:

$$K_s = [\text{sodium lauryl sulfate}] \times [\text{phosphonium}] \quad (\text{Eq. 3})$$

Finally, a third region occurs when the CMC of sodium lauryl sulfate is reached. This produces another change in the slope of the conductivity relationship, but it is less distinct than the complexation point. At the CMC, the complex is solubilized and the turbid solution begins to clear.

The coefficient of variation of these titrations in reproducing the same titration curve and the same end-point was $\pm 0.1\%$.

The change in solubility product with alkyl sulfate chain length is shown in Fig. 7. It is apparent that each methylene group added to the alkyl chain changes the solubility product by a constant factor of 3.6. The corresponding change in free energy is -766 cal/mole. This value is much larger than the free energy increment for the methylene group for micelle formation (Fig. 2). However, it is somewhat smaller than the increment for transfer of the methylene group from an aqueous environment to a nonpolar solvent (13). Such values suggest that the turbid phase separating at the first end-point is a liquid-like coacervate system rather than a solid precipitate (1).

A detailed treatment of the thermodynamics of complexation between alkyl sulfates and phosphonium compounds and the effects of different experimental conditions and additives will be published later.

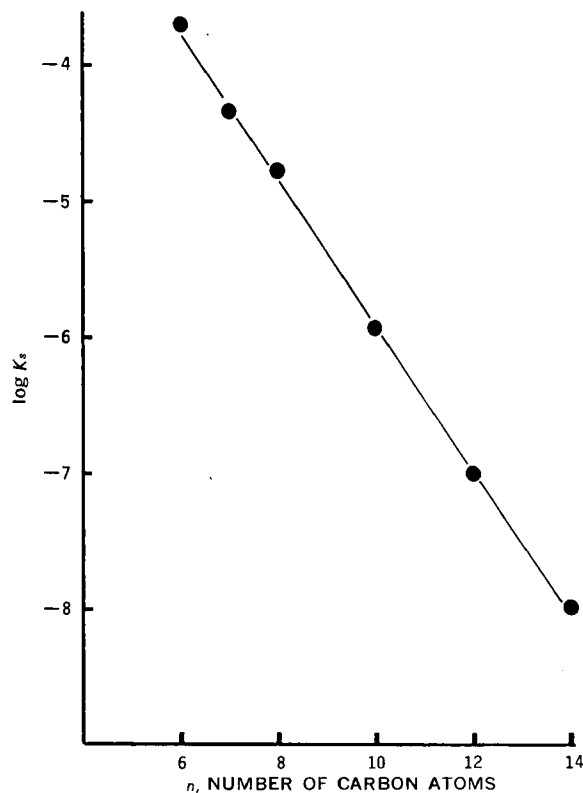


Figure 7—Log K_s versus chain length for the interaction of sodium lauryl sulfate with benzyltriphenylphosphonium chloride.

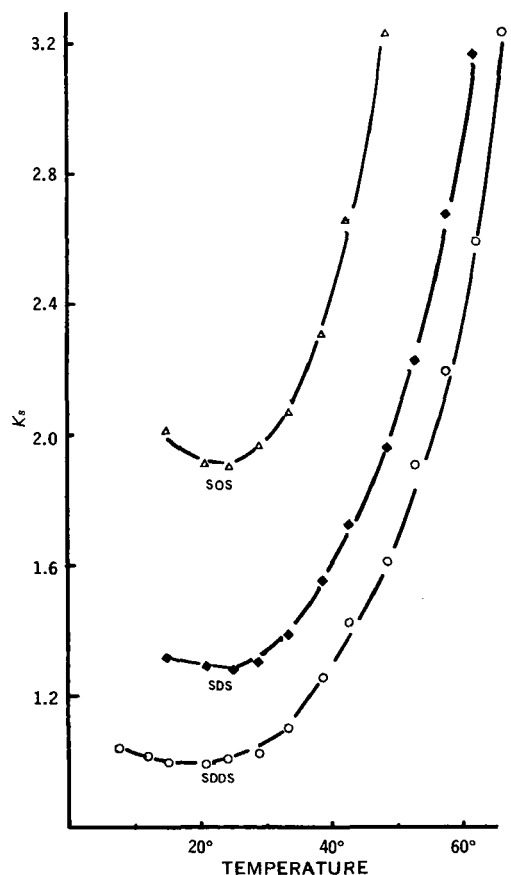


Figure 8—Change of K_s with temperature for the interaction of alkyl sulfates with benzyltriphenylphosphonium chloride. [SOS = sodium octyl sulfate, $K_s \times 10^{-5}$; SDS = sodium decyl sulfate, $K_s \times 10^{-6}$; and SDDS = sodium lauryl sulfate, $K_s \times 10^{-7}$.]

The effect of temperature on the solubility product was studied using a given phosphonium compound and three different alkyl sulfate homologs (Fig. 8). The solubility product passes through a minimum in the region of 25° in a similar manner to the CMC of the alkyl sulfates alone (Fig. 4 and Ref. 11).

Where the external standard technique is used, the conductivity versus volume titrant added plot should be a horizontal line in the absence of complexation. However, for the anion-cation system studied, there is a difference in conductivity reading between the two beakers due to interaction and complexation (Fig. 9). Three distinct regions are evident:

1. An initial region where there is only a small conductivity difference. This is considered to be due to the formation of ion-pairs in water (14) and a possible premicellar aggregation (dimer formation) of the anion (sodium lauryl sulfate) (12).
2. The complexation region.
3. The micellization region.

Therefore, the external standard method provides a rapid and accurate method for the detection of the solubility product and the CMC. An association constant for ion-pair formation can be calculated from the initial region.

The theoretical change in conductivity due to complex formation can be calculated from experimentally determined values of equivalent conductance of the alkyl sulfate, phosphonium compound, and sodium and chloride ions. Above the complexation point, Eq. 3 becomes:

$$K_s = [\text{sodium lauryl sulfate} - x] \times [\text{phosphonium} - x] \quad (\text{Eq. 4})$$

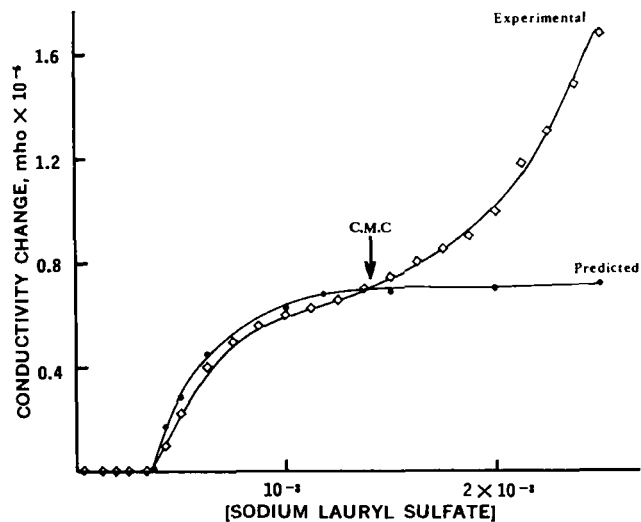


Figure 9—Interaction between sodium lauryl sulfate and benzyltriphenylphosphonium chloride (3×10^{-4} M) using the external standard technique. Key: \square , experimental; and \bullet , predicted.

where x is the concentration of complex formed. The value of x can be found by solving the quadratic equation resulting from Eq. 4, and from this the theoretical fall in conductivity can be calculated. The agreement between theoretical and experimental data is good up until micelle formation. Furthermore, the comparison of theoretical and experimental data allows the CMC for the mixed system to be determined accurately.

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