

## Calorimetric study on the solubilization of butanol by alkylphosphate and alkylphosphate-lecithin systems

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**Abstract**—Microcalorimetric studies on alkylphosphate-butanol and alkylphosphate-butanol-lecithin systems were carried out as a first step to study the role of butanol (used as cosurfactant) in the formation of microemulsions. The enthalpy of solubilization,  $\Delta H$ , of the same amount of butanol ( $1.806 \text{ mol kg}^{-1}$ ) in aqueous sodium monoalkyl-phosphates, with a hydrocarbon chain varying from 6 to 10 carbon atoms, was investigated as a function of alkylphosphate concentration. Measurements were performed in the presence and in the absence of lecithin. The enthalpy values measured upon addition of butanol to the mixtures were negative in all cases. Below the critical micelle concentration (CMC) of the alkylphosphates, the heats of butanol dissolution were found to decrease upon increasing the concentration of the alkylphosphate. This behaviour was related to the dissolution of butanol in water and to the formation of mixed butanol-alkylphosphate and butanol-alkylphosphate-lecithin micelles. Above the CMC essentially constant  $\Delta H$  values were found. The  $\Delta H$  measured may be the sum of simultaneous effects—heat of alcohol dissolution and the simple alkylphosphate micelle dissociation or alkylphosphate-lecithin mixed aggregate dissociation and the heat of mixed micelle formation. The  $\Delta H$  at the plateaus were linearly related to the corresponding CMC values of the alkylphosphates.

Microemulsions are clear, stable dispersions usually obtained by mixing oil, water, surfactant and co-surfactant, which is generally a medium chain length alcohol (Bourrel & Schechter 1988). In the last few years, some authors (Chien 1987; Kemken et al 1991) have developed microemulsions as possible therapeutic systems to allow a prolonged drug release and to increase transdermal and topical absorption.

In previous work (Gasco et al 1989), oil/water microemulsions were studied in an attempt to prolong the time of release of timolol and to enhance absorption of the drug by the cornea. The microemulsion proposed employed a physiological substance, egg lecithin, as a surfactant, in order to make a biocompatible therapeutic device.

The evaluation of the enthalpies associated with the process of microemulsification of similar systems, with and without added drugs, was also studied (Fubini et al 1988, 1989). An oil/water microemulsion, containing lecithin, was studied (Trotta et al 1990) as a vehicle for parenteral administration of diazepam to minimize the side-effects induced by the organic cosolvents added to water in the commercial formulations. A dramatic decrease in the amount of lecithin necessary to obtain such clear systems was noted upon addition of monoalkylphosphates. To elucidate the effect of alkylphosphates on the microemulsification process, the enthalpy of solubilization of a constant amount of butanol in aqueous sodium monoalkylphosphate solutions in the presence and in the absence of lecithin was measured as a function of the surfactant concentration.

To investigate the effect of the chain length on the overall effect, four alkylphosphates with the number of carbons varying from 6 to 10 were employed.

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### Materials and methods

**Materials.** Monoalkylphosphoric acids were prepared by the action of phosphoryl chloride on *n*-hexanol, *n*-heptanol, *n*-octanol and *n*-decanol (Wieland & Lambert 1956). The corresponding sodium monoalkylphosphates (C6, C7, C8, C10) were obtained by neutralization of aqueous solutions of monoalkylphosphoric acid by sodium hydroxide and recrystallized twice from ethanol.

Phosphoryl chloride and the alcohols were provided by Merck and used as received. Water was bidistilled.

Lecithin from egg yolk (crude) was from Merck and was purified (Fubini et al 1988) and then stored under acetone in a deep-freeze at  $-20^\circ\text{C}$ .

**Calorimetry.** The heats of solution were determined in a Setaram C80 microcalorimeter operated at  $37 \pm 0.1^\circ\text{C}$ . Two twin cells, connected in opposition, were used to allow a differential signal to be recorded and thermal disturbances to be cancelled. Each cell is composed of two chambers where the reactants may be introduced and kept without any contact until the thermal equilibrium in the calorimeter was attained. In the internal chambers, a defined amount of water and alkylphosphate; or water, alkylphosphate and lecithin, were introduced, whereas the external one always contained a fixed amount of butanol. In the reference cell, the external chamber was maintained empty whereas the internal chamber contained the same mixture as in the experimental internal cell. After introduction of the vessels, the calorimeter was left to reach internal thermal equilibrium which was usually attained in less than an hour. The reactants were brought into contact by inverting the calorimeter; a continuous oscillation of the calorimetric body ensured a regular mixing of the two solutions. In all cases an endothermic peak lasting about 30 min was recorded.

**Composition of mixtures.** A fixed amount of water (2.0 g) and an increasing amount of alkylphosphate (0.0350 g) were introduced in the internal chamber. In the external chamber, a fixed amount of butanol (0.330 mL) was introduced. For experiments with lecithin the internal chamber contained 0.20 g lecithin.

**Critical micelle concentration.** The measurements of the critical micelle concentration (CMC) of the alkylphosphates in water were carried out using electrical conductivity. Electrical conductivity was measured by an Orion 101 conductimeter operating at 3 kHz. Samples were equilibrated at  $37 \pm 0.1^\circ\text{C}$  and the conductivity was recorded after it remained constant for at least 4 min.

**Light scattering.** The QELS instrument was a model PCS 100, from Malvern Instruments. The optical source of the light scattering apparatus was a He-Ne laser operating at 632.8 nm and the scattering angle was fixed at  $90^\circ$ . The sample was injected into a clean rectangular fluorimetric cell directly through a syringe filter with a  $0.2 \mu\text{m}$  membrane from Millipore. The sample was maintained at  $37 \pm 0.1^\circ\text{C}$  during the measurement. The refractive indices of the samples were determined on an Abbe refractometer at  $37 \pm 0.1^\circ\text{C}$ .

## Results and discussion

Figs 1, 2 report the enthalpies measured upon addition of butanol as a function of the alkylphosphate concentration for ternary and quaternary (lecithin) systems, respectively. All the curves exhibit similar trends whose main features may be summarized as follows.

Two main domains in alkylphosphate concentration are identified; one, at low concentrations, where the enthalpy measured varies linearly with alkylphosphate concentration, followed by another, at higher alkylphosphate concentrations, where the enthalpy is totally insensitive to the alkylphosphate concentration. The onset of the plateau depends upon the alkylphosphate chain length; the shorter the chain length, the larger is the first domain. The critical concentrations for the transition from the two domains are reported in Table 1.

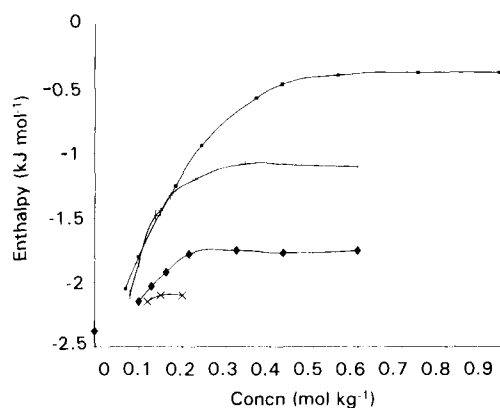


FIG. 1. Standard enthalpy ( $\text{kJ mol}^{-1}$ ) of solutions of butanol in aqueous hexyl- (■), heptyl- (+), octyl- (♦) and decylphosphate (x) solutions as a function of surfactant concentration.

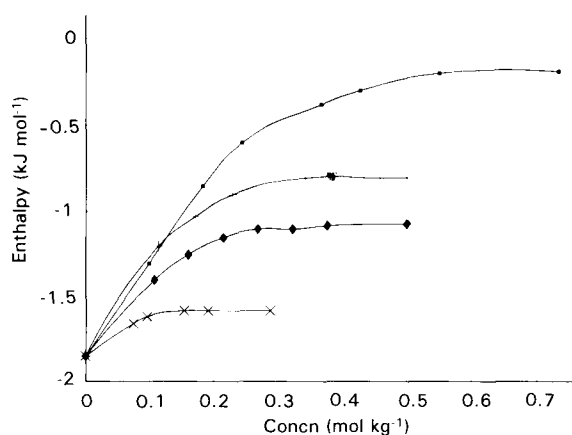


FIG. 2. Standard enthalpy ( $\text{kJ mol}^{-1}$ ) of solutions of butanol in aqueous lecithin dispersions containing hexyl- (■), heptyl- (+), octyl- (♦) and decylphosphate (x) as a function of alkylphosphate concentration.

The plateau values also depend upon the alkylphosphate concentration; the longer the chain, the larger the absolute enthalpy value.

The addition of lecithin does not change the overall trends but the absolute enthalpy values at the plateau are higher than in the absence of lecithin.

Table 1. CMC and concentrations corresponding to the transition from the two domains of sodium monoalkylphosphates for ternary and quaternary systems ( $\text{mol kg}^{-1}$ ).

Number of carbons in the chain	6	7	8	10
CMC	0.51	0.26	0.15	0.032
Ternary	0.52	0.30	0.20	0.12
Quaternary	0.55	0.32	0.20	0.10

*Ternary systems (alkylphosphate, water, butanol).* The CMC values reported in Table 1 are in good agreement with those reported in the literature (Chevalier & Chachaty 1984). Water and butanol are only partially miscible; the solubility of the alcohol is  $1.061 \text{ mol kg}^{-1}$ . In the absence of alkylphosphate and in excess of butanol, the measured enthalpy was found to be  $-2.37 \text{ kJ mol}^{-1}$ . This value was the result of an exothermic effect due to the solubilization of butanol in water and an endothermic effect due to the solubilization of water in excess butanol (Goodwin & Newsham 1971).

Since the amount of butanol used in the calorimetric determinations was higher than the solubility of the alcohol, in the first part of the curve, up to  $0.06 \text{ mol kg}^{-1}$  C6,  $0.08 \text{ mol kg}^{-1}$  C7-C8 and  $0.10 \text{ mol kg}^{-1}$  C10, demixing occurred, with the formation of coarse emulsions, while, above these concentrations, homogeneous ternary systems were obtained.

The systems containing monodecylphosphate could be examined only partially, because of its low solubility in water.

In all our systems a constant  $\Delta H$  value was reached just above the CMC of the alkylphosphates in water (Table 1). It has to be pointed out that, below the plateau values, the alcohol was added to a solution of alkylphosphate present in monomeric form so that, as light scattering spectroscopy shows (Table 2), mixed micelles of alkylphosphate-butanol could be formed. In a previous work (Trotta et al 1993) a decrease of the CMC of hexylphosphate was noted in the presence of alcohol. In particular, the CMC of hexylphosphate in water saturated with butanol, was  $0.05 \text{ mol kg}^{-1}$ , i.e. much below the value obtained in pure water. In this range the variation of  $\Delta H$  (exothermic) could be due to the simultaneous dissolution of butanol in water and the formation of mixed alkylphosphate-butanol micelles (endothermic). The enthalpy of micellization is in fact often an endothermic process (Corkill et al 1964; Maa & Chen 1987). As a result the overall enthalpy measured decreases upon increasing the concentration of the alkylphosphate.

At the plateau, butanol was added to alkylphosphate present in micelles. The measured enthalpy may be the sum of heat of alcohol dissolution, alkylphosphate micelle dissociation and mixed alkylphosphate-butanol micelle formation.

Increasing the alkylphosphate concentration, mixed micelles with decreasing butanol-surfactant ratio could form. In the constant part of the plots no solute-solute (butanol) interactions should be present, as indicated by the constancy of the  $\Delta H$  value. The enthalpy had the same trend for all the examined alkylphosphates, but different values of  $\Delta H$  at the plateaus.

The standard heat of transfer of butanol from water to  $n$ -

Table 2. Collective diffusion coefficients ( $10^6 \text{ cm}^2 \text{ s}^{-1}$ ) of ternary and quaternary systems as a function of hexylphosphate concentration

System	Hexylphosphate concn ( $\text{mol kg}^{-1}$ )			
	0	0.25	0.50	0.60
Ternary	—	1.32	1.45	1.54
Quaternary	0.79	0.78	0.77	0.79

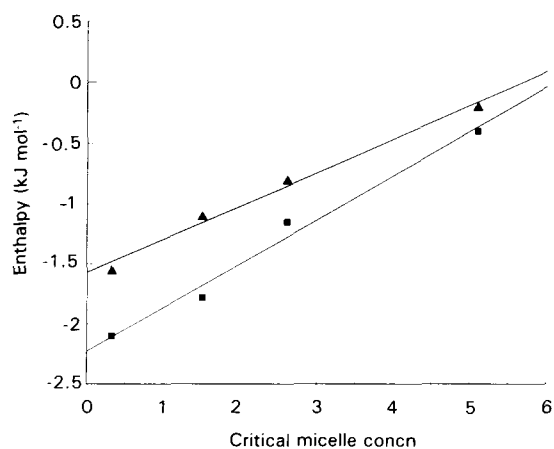


FIG. 3. Correlations between the critical micelle concentration values of the alkylphosphates ( $\text{mol kg}^{-1}$ ) and the absolute  $\Delta H$  values ( $\text{kJ mol}^{-1}$ ) at the plateaus for ternary (■) and quaternary (▲) systems.

alkane is an endothermic process, and was constant upon increasing the chain length of the *n*-alkane from C8 to C16, whereas the distribution ratios of butanol between aqueous phase and *n*-alkane phase was found (Aveyard & Mitchell 1969) to increase upon increasing the chain length of the alkane. According to these findings, as the alkylphosphate chain length of the surfactant increased, the amount of butanol partitioned into the micelles decreased; consequently the  $\Delta H$  value at the plateau decreased. The  $\Delta H$  value at the plateau obtained for the different alkylphosphates could be principally related to a different distribution of the butanol between water and micelles, depending on the length of the alkylphosphate chain.

**Quaternary systems (alkylphosphate, water, butanol, lecithin).** Lecithin, a double-tail surfactant, in an aqueous dispersion, is presumably in the form of bilayers (Zimmerer & Lindenbaum 1979). These milky-white lipid bilayer dispersions are solubilized by butanol to form optically clear micellar solutions (Table 2). Under the experimental conditions adopted, the heat of butanol dissolution was  $-2.05 \text{ kJ mol}^{-1}$ . This heat measured may be regarded as the sum of the heat of butanol dissolution and mixed lecithin-butanol micelle formation.

In the presence of alkylphosphates, below the CMC, the milky bilayers of lecithin were dispersed in an aqueous solution of alkylphosphate surfactant. However, a fraction of the alkylphosphates would be partitioned into the bilayers. The addition of butanol would lead to the formation of a complex micellar solution.

Above the CMC, butanol was added to the alkylphosphates probably in micellar form and to lecithin bilayers or lecithin-alkylphosphate bilayers.

Heat evolution during this process is difficult to understand on the basis of the limited information available. However, comparison of the dissolution heat of butanol in the alkylphos-

phates, in the presence and in the absence of lecithin, shows that the results are similar.

A correlation between CMC and  $\Delta H$  at the plateau value of ternary and quaternary systems was found (Fig. 3), indicating that enthalpies could be related to the surface activity of alkylphosphates.

These results suggest that the extent of interaction of lecithin in the dissolution of butanol plays only a minor role and that the enthalpies observed are mainly due to alkylphosphate-butanol interactions.

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