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Microcalorimetric study of microemulsions as potential drug delivery systems. I. Evaluation of enthalpy in the absence of any drug

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Summary

Two microemulsions with the same oil/water/surfactant mixtures, but differing in the surfactant (lecithin or Aerosol AOT) have been studied. The enthalpy variations ($\Delta H > 0$) upon addition of separate doses of the co-surfactant (butanol) to a fixed mixture of the other 3 components were measured calorimetrically in a closed system. A linear relationship between ΔH and molar fraction of added co-surfactant was found at the molar fractions below the one required for microemulsion formation. A marked variation in the linearity (minimum in endothermicity) was found at the microemulsion formation. An exothermic contribution due to the microemulsion formation was hypothesized also on the basis of data obtained when the microemulsion was prepared upon addition of water to oil, surfactant and co-surfactant. Addition of co-surfactant in the absence of surfactants yielded different ΔH values.

Introduction

The use of colloidal therapeutic systems for the controlled release of drugs has been reported by many authors (Illum and Davis, 1984, 1985). Microemulsions are clear, stable dispersions usually obtained by mixing oil, water, surfactant and co-surfactant, the diameter of the disperse phase droplets always being below 100 nm (Shah, 1985).

The use of microemulsions as possible therapeutic systems is interesting for two main reasons: on the one hand, they could allow a prolonged drug release, on the other, they might increase transdermal and topical absorption (Jürgen, in press). Besides, they offer the advantage to vehicle drugs of different lipophilicity in the same system (according to the different solubilities in the disperse and continuous phase). A question to be answered is whether the high stability of a microemulsion could be influenced by the presence of a drug. The evaluation of the enthalpies associated with the process of microemulsification can give information about the stability of the system. A comparison with similar data obtained in the presence of drugs should allow the evaluation of the influence of a fifth component on the stability of the system. Several calorimetric studies were performed to investigate the thermodynamics (Denoyers et al., 1980) of micellar systems (Mazer and Olofsson, 1982), examining the heat and heat capacity changes associated with the transfer of detergent molecules

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from the monomeric to micellar state (Bury and Treiner, 1985), and determining the standard enthalpy of transfer of a number of solutes between water and micellar solutions (Benjamin, 1964).

Very few data, on the other hand, are available on microemulsions: to our knowledge, the only data available so far are those relating to a microemulsion employed in the mineral oil recovery industry (Roux-Desgranges et al., 1981; Roux et al., 1982), where direct measurements of the heat capacity of toluene in the process of formation of the microemulsion are reported.

The aim of the present work was the calorimetric evaluation of the enthalpy changes involved when different amounts of co-surfactant were added to a fixed mixture of the other components up to the microemulsion formation and above. In the present paper two microemulsions of oil-in-water, having the same qualitative composition as far as aqueous/oleous phase/co-surfactant (water, isopropylmyristate and 1-butanol, respectively) are concerned, but differing in the surfactant (dioctylsulphosuccinate (AOT) and purified egg lecithin) (Gallarate et al., 1987) were examined in the absence of any drug.

The influence of a drug as a fifth component will be reported in a future paper.

Experimental

Materials

Isopropylmyristate (ISM) (98% pure) and 1-butanol (reagent grade) were from Merck; water was freshly distilled; bis-2(ethyl-hexyl)sulphosuccinate sodium salt (AOT), wax-like (98% pure) was from Merck, and was further purified (Eicke, 1979) and stored over phosphorous pentoxide in a desiccator; lecithin from egg yolk (crude) was also from Merck, and was purified as previously described (Gallarate et al., 1987) and then stored in a refrigerator at −20 ° C.

Apparatus

A microcalorimeter Calvet type (C_{80} Setaram) was used: it is a heat flow calorimeter operating at fixed temperature, in the range 0–300 ° C. The heat evolved in the reaction vessel is quantitatively transferred to a heat sink, and the heat flow, being proportional to the thermal power evolved is recorded by a thermopile wall positioned between the calorimetric vessel and the heat sink; the temperature gradient over the thermopile gives rise to a voltage signal, proportional to the heat flow. Two twin cell–heat flowmeter assemblies, connected in opposition, allow a differential signal to be recorded and thermal disturbances to be cancelled: any heat exchange in a complex system within the 'measure' cell would be eliminated by introducing the same system in the 'reference' cell.

Methods

Microemulsions. Two microemulsions, o/w type, were studied. The compositions were respectively:

Microemulsion no. 1: ISM = 19.3% w/w ($x_1 = 0.02011$); water = 58.4% w/w ($x_2 = 0.92518$); AOT = 10.1% w/w ($x_3 = 0.00644$); 1-butanol = 12.2% w/w ($x_4 = 0.04827$).

Microemulsion no. 2: ISM = 7.5% w/w ($x_1 = 0.00853$); water = 53.3% w/w ($x_2 = 0.92715$); egg lecithin = 26.6% w/w ($x_3 = 0.01137$); 1-butanol = 12.6% w/w ($x_4 = 0.05295$).

Both microemulsions, obtained by adding every component in a glass tube and gently shaking, or by autoemulsification too, were tested for stability as previously described (Gallarate et al. 1987; Hansrani, 1980).

Experimental cells. 'Measure' and 'reference' cells were identical, composed of a cylindrical body in which a lower vessel was screwed on: the 'measure' cell's lower vessel was filled with the emulsified system (or simply with a mixture of components) and then closed with a cover; the component to be added was placed upon the cover; on the other hand, the 'reference' cell contained the same mixture present in the lower vessel of the 'measure' one, but no further component was added onto the cover. In both cases, a thin mercury film on the cover guaranteed the airtight closure. In this way, only the heat involved in the addition of the reactant to the mixture was effectively measured. Both cells were placed into the calorimeter, and when the equilibrium was obtained, an automatic mechanism for continuous alternative reversing of the calorimeter allowed the mixing of the reactants initially separated in the cells. The calorimeter used being a completely closed system, no continuous addition of reactants was possible in the same measurement, but a new calorimetric measurement had to be performed for any addition of a dose of co-surfactant or water.

Examined systems. In the description of the systems studied, the amount of any component was indicated in the following way: using molar fractions (x^*), considered equal to one, the sum of molar fractions only in the microemulsions (this method was used for all systems in which, after the mixing of the components, the final composition was identical or still defecting in respect of the microemulsion). In contrast to this, when the additions were performed to a microemulsion already formed or diluted with excesses of co-surfactant, the molar fractions x were calculated as usual, referring to the effective amount of each component in that particular system, and considering the sum of the molar fractions in the examined systems equal to one.

Microemulsion no. 1

(A) Addition of butanol to the mixture: ISM ($x_1^* = 0.02011$), water ($x_2^* = 0.92518$), AOT ($x_3^* = 0.00644$): (1) in the amount exactly required to obtain the microemulsion ($x_4^* = 0.04827$); (2) in defect (x_4^* from 0.01429 to 0.03297).

(B) Addition of butanol to some final systems obtained at point (2) ($x_4^* = 0.01429$ and 0.02528) in the amount exactly required to obtain the microemulsion.

(C) Addition of different amounts of butanol to the microemulsions obtained with the minimum required or more butanol; the molar fractions of butanol in the initial and final systems were respectively: $x_{4\text{in}} = 0.04827$; 0.07614; $x_{4\text{fin}} = 0.08737$; 0.09539; 0.10072.

Microemulsion no. 2

– *Addition of butanol*

(A) Addition of butanol to the mixture: ISM ($x_1^* = 0.00863$), water ($x_2^* = 0.92715$), lecithin ($x_3^* = 0.01137$), butanol ($x_4^* = 0.01590$):

(As can be noted, water, ISM and lecithin were present in the ratios exactly required for the microemulsion; the presence of one-third of the total amount of butanol was required to obtain the microemulsion directly in the calorimeter, because of the lowering of the viscosity of the system.)

(1) in the amount exactly required to obtain the microemulsion ($x_4^* = 0.05295$).

(2) in defect (x_4^* from 0.02332 to 0.04027).

(B) Addition of butanol to the final systems obtained at point (2) in the amount exactly required to obtain the microemulsion.

(C) Addition of butanol to the microemulsion already formed; the molar fractions of butanol was $x_4 = 0.05295$ in the initial system and varied from 0.06024 to 0.07834 in the final ones.

(D) Addition of butanol to the microemulsion already broken with excesses of butanol; the molar fractions of butanol in the initial and final systems were, respectively: $x_{4\text{in}} = 0.06920$ and 0.07834; $x_{4\text{fin}} = 0.08815$ and 0.10240.

– *Addition of water*

Water was added to a mixture of ISM ($x_1^* = 0.00863$), water ($x_2^* = 0.60344$), lecithin ($x_3^* = 0.01137$), 1-butanol ($x_4^* = 0.05295$) in the amount exactly required to obtain the microemulsion ($x_2^* = 0.92715$). The identical amount of water was added to a mixture of ISM ($x_1^* = 0.00863$), water ($x_2^* = 0.28017$), lecithin ($x_3^* = 0.01137$), butanol ($x_4^* = 0.05295$); molar fraction of water in the final system = $x_2^* = 0.60344$; the same amount of water was also added to the microemulsion previously obtained. (Molar fraction of water in the final system $x_2 = 0.94493$.)

– *A system without surfactant*

To separate the thermal effects due to the partition of butanol between isopropylmyristate and water from the phenomena involved in the process of formation of a microemulsion, a mixture formed by ISM, water and butanol, having the composition described for (A) for microemulsion no. 2, but in the absence of any surfactant, was added with different amounts of butanol (x_4^* from 0.02657 to 0.10067).

N.B. In this case, molar fractions were always calculated by considering the sum of the molar fractions equal to one in the microemulsion no. 2, also encompassing lecithin.

Results

It was possible to obtain microemulsion no. 1 directly in the calorimetric cell by adding the butanol required, all at once, to the emulsion placed in the lower vessel; the calorimetric stirring was then sufficient to allow microemulsification. In the case of microemulsion no. 2, the formation of the microemulsion was possible only by introducing an aliquot of butanol already in the lower vessel.

The addition of butanol to the examined mixtures was an endothermic process for both the microemulsions studied and also for the system in the absence of surfactant, i.e. the partial molar enthalpy, always referred to as the added moles of butanol, was above zero.

Microemulsion no. 1

The partial enthalpies obtained by the addition of increasing amounts of butanol to the system no. 1 (water–ISM–AOT) as a function of the moles of butanol are reported in Fig. 1: the relationship between the measured ΔH and the moles of butanol added was almost linear up to the concentration of alcohol corresponding to the formation of the microemulsion. The partial molar heat, obtained from the slope of the straight line, was 1.35 kJ · mol^{-1}.

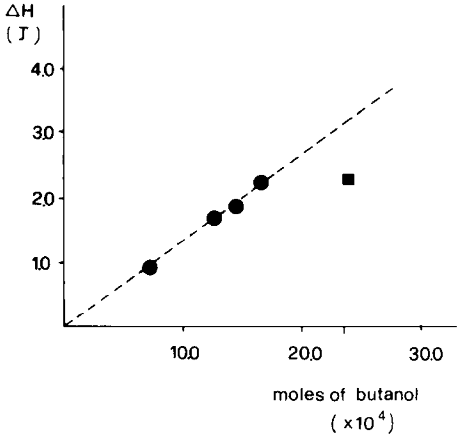

Fig. 1. Enthalpies of addition of butanol to a system of water–ISM–AOT. Abscissa: moles of butanol. Ordinate: enthalpies of addition. ●, additions in defect; ■, formation of the microemulsion.

TABLE 1

(A) Partial molar enthalpies of addition of butanol to a system AOT–water–ISM: formation of the microemulsion

Moles butOH ($\times 10^4$)	$\Delta H_{m_{form}}$ (kJ · mol^{-1} ±0.05)
10.9 (a)	0.95
16.4 (b)	0.96
23.5 (c)	0.96

x_4^* in the microemulsion = 0.04827.

(a) Moles of butanol in the initial mixture: 12.6×10^{-4} $x_4^* = 0.02528$.

(b) Moles of butanol in the initial mixture: 7.1×10^{-4} $x_4^* = 0.01429$.

(c) No moles of butanol in the initial mixture.

(B) Partial molar enthalpies of dilution of microemulsion no. 1 by addition of butanol

Moles butOH ($\times 10^4$)	$\Delta H_{m_{dilution}}$ (kJ · mol^{-1} ±0.05)
8.2 (a)	0.45
10.9 (b)	0.89
21.3 (c)	1.21

Molar fractions of butanol in the initial and final systems:

(a) $x_{4_{in}} = 0.08649$; $x_{4_{fin}} = 0.10072$.

(b) $x_{4_{in}} = 0.07614$; $x_{4_{fin}} = 0.09539$.

(c) $x_{4_{in}} = 0.04827$; $x_{4_{fin}} = 0.08737$.

The ΔH relative to the addition of the amount of butanol exactly required for the achievement of the microemulsion deviated from the slope of the straight line towards a lower endothermicity: the heat measured in this case was 29% lower than in the preceding ones.

The molar enthalpies obtained in the case of the formation of the microemulsion are reported in Table 1A: they were quite identical, despite the different amounts of butanol already in the initial mixture. The additions of butanol to microemulsion no. 1 and to the same microemulsion previously diluted with an excess of butanol, further diluted the system without provoking its clouding; the molar ΔH relative to these additions are reported in Table 1B: they were not constant, always being endothermic, and varied with the volume of butanol already present in the microemulsions.

Microemulsion no. 2

TABLE 2

Partial molar enthalpies of addition of butanol to a system of water – ISM – lecithin – butanol: formation of the microemulsion and breaking of the microemulsion

Moles butOH ($\times 10^4$)	$\Delta H_{\mathrm{m}_{\mathrm{form}}}$ (kJ·mol^{-1} ±0.05)	$\Delta H_{\mathrm{m}_{\mathrm{break}}}$ (kJ·mol^{-1} ±0.05)
4.0	1.16 (a)	1.61 (a′)
8.1	1.18 (b)	1.34 (b′)
10.4	1.17 (c)	1.41 (c′)
12.2	1.14 (d)	1.29 (d′)
14.2	1.14 (e)	1.30 (e′)
19.1	1.12 (f)	–

Moles of butanol in the microemulsion = 27.3×10^{-4} ($x_4 = 0.05295$)

Molar fractions of butanol in the initial system:
(a) $x_4^* = 0.04519$; (b) $x_4^* = 0.03724$; (c) $x_4^* = 0.03278$; (d) $x_4^* = 0.02929$; (e) $x_4^* = 0.02541$; (f) $x_4^* = 0.01590$.

Molar fraction of butanol in the final systems:
(a′) $x_4 = 0.06024$; (b′) $x_4 = 0.06760$; (c′) $x_4 = 0.07168$; (d′) $x_4 = 0.07484$; (e′) $x_4 = 0.07834$.

Addition of butanol. The partial enthalpies obtained by addition of different amounts of butanol to the emulsified system (water, ISM, lecithin, butanol), to obtain the microemulsion are reported in Fig. 2: the partial enthalpies of the addition of butanol to the formed microemulsion, causing breaking of the microemulsion itself, are also reported in the same figure. The relationship between the measured ΔH and the moles of butanol added was linear up to the concentration of butanol required to form the microemulsion (partial molar heat, from the slope of the straight line in Fig. 2 = 1.39 kJ · mol^{-1}). The partial molar heat relative to the formation of the microemulsion was again below the value obtained in the case of the addition of butanol in defect: the deviation was 17%. The partial molar enthalpies relative to the formation of the microemulsion by addition of different amounts of butanol are reported in Table 2(first column); they were constant, independent of the molar fraction already present in the initial mixture. In Table 2(second column) the partial molar enthalpies obtained by breaking the microemulsion with an excess of butanol are also reported. The ΔH of breaking was always endothermic, it had a value of 1.34 kJ · mol^{-1}, quite similar to the one compared to the additions of butanol yielding concentrations below those for microemulsion formation; only the ΔH corresponding to the addition of the minimum amount of butanol required to break the microemulsion was more endothermic (16%) than that value.

The addition of butanol to the microemulsion already broken with an excess of alcohol always showed an endothermic behaviour, but the partial molar ΔH was not constant, varying with the molar fraction of butanol already present in the initial system (Table 3).

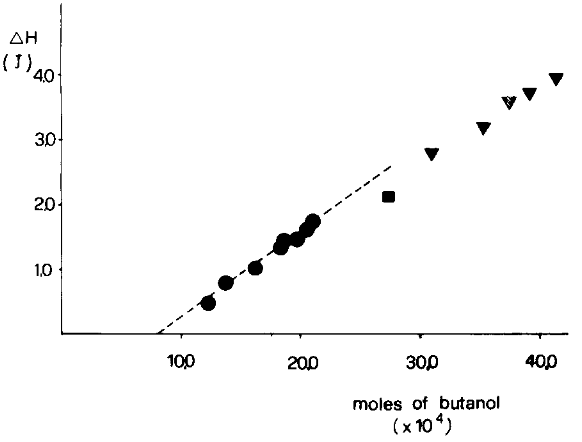

Fig. 2. Enthalpies of addition of butanol to a system of water–ISM–lecithin–butanol. Abscissa: moles of butanol. Ordinate: enthalpies of addition. ●, additions in defect; ■, formation of the microemulsion; ▼, breaking of the microemulsion.

TABLE 3

Partial molar enthalpies of addition of butanol to a broken microemulsion no. 2

Moles butOH ($\times 10^4$)	ΔH_{mol} (kJ·mol^{-1} ±0.05)
10.9 (a)	0.28
14.2 (b)	0.16

(a) Moles of butanol in the initial system: 36.3×10^{-4}; $x_{4_{\mathrm{fin}}} = 0.08815$.

(b) Moles of butanol in the initial system: 41.5×10^{-4}; $x_{4_{\mathrm{fin}}} = 0.10240$.

TABLE 4

Partial molar enthalpies of addition of butanol to a mixture of water–ISM–butanol in the absence of any surfactant

Moles butOH ($\times 10^4$)	ΔH_{mol} (kJ·mol^{-1} ±0.05)
5.5	1.34 (a)
10.1	0.73 (b)
16.4	0.63 (c)
19.1	0.93 (d)
21.9	0.92 (e)
27.3	1.09 (f)
43.7	0.84 (g)

N.B. Every ΔH value is an average of at least 3 values.

Molar fractions x_4^* of butanol in the final systems: a = 0.02657; b = 0.03550; c = 0.04772; d = 0.05295; e = 0.05838; f = 0.06886; g = 0.10067.

Addition of water. The addition of water to the mixture ISM–butanol–lecithin, defecting in water, and to the microemulsion was an exothermic phenomenon. The partial molar ΔH (always referred to the added moles of water) relative to the formation of the microemulsion was more exothermic than the one relative to the addition of water yielding concentrations below those for microemulsion formation. The partial molar enthalpy of addition of water to the microemulsion, in order to break it, was lower (absolute value) than the partial molar ΔH of formation. The obtained ΔH were respectively:

$$\Delta H_{mol\,(form)} = 0.12 \text{ kJ} \cdot \text{mol}^{-1}$$

$$\Delta H_{mol\,(defect)} = -0.03 \text{ kJ} \cdot \text{mol}^{-1}$$

$$\Delta H_{mol\,(breaking)} = -0.08 \text{ kJ} \cdot \text{mol}^{-1}$$

A system without surfactant. The partial molar enthalpy of addition of butanol to the system water–ISM–butanol in the absence of any surfactant, always being endothermic, was not constant, but varied with the different molar fractions of butanol in the system (Table 4).

Discussion

The main result obtained from the evaluation of the enthalpies evolved when different amounts of butanol were added to the two considered microemulsion systems (only differing in the surfactant and in the molar fractions of the components) was that the process occurring in the presence of the surfactant seemed to be completely different from the one occurring in its absence. Whereas the molar enthalpy change upon addition of butanol to a system water–ISM–butanol varied probably owing to its concentrations and partitioning in the system (Table 4), this was not the case in the microemulsion systems. In fact, in both the cases examined (with two different surfactants) addition of different amounts of butanol yielded constant molar enthalpy changes up to the critical microemulsion concentration; besides, the molar ΔH of addition of butanol in defect (obtained by the straight line in Figs. 1 and 2) were quite similar in both cases, assuming that the differences between the two surfactants did not markedly influence the values of ΔH. The constancy of the partial molar enthalpy has been confirmed throughout the possible measurable concentrations of butanol added. The values of the partial molar enthalpy of butanol added, measured upon formation of the microemulsion, have been confirmed by adding different amounts of butanol to various water–oil–surfactant–butanol mixtures in order to obtain the same concentration required for the microemulsion; as the values obtained were the same, there was no dependence on the amount of butanol added (Table 2). The constancy of the partial molar enthalpy of addition of butanol in defect to the emulsified systems could be explained assuming that butanol distributed itself in a constant ratio among continuous, disperse phase and interphase. The role of interphase might be particularly interesting, as progressive additions of co-surfactant could involve a continuous increase in the extension of the interphase-specific surface (increase in the number of nanodroplets and decrease in their dimensions) and consequent more or less invariable concentration of butanol at the interphase, along with its increasing concentration, determining the constancy of the partial enthalpy. As previously reported by some authors (e.g. Ruckenstein, 1981), the formation of the microemulsion could be accompanied by a series of phenomena (maximum entropy of dispersion and maximum dilution of surfactant and co-surfactant in the continuous and disperse phase) which provoked a dramatic modification in the system. The minimum in endothermicity measured at the formation of the microemulsion was probably due to a superposition of similar phenomena (dispersion of nanodroplets, maximum adsorption of both surfactant and co-surfactant at the interphase, abrupt production of a large interfacial area), some of which are exothermic, some endothermic, thus involving, on average, a lesser endothermicity. The formation of the microemulsion should be accompanied by an exothermic heat. The exothermic component of microemulsion formation was also evidenced in the experiment in which water was added to the appropriate mixture of water/ oil/ butanol/ surfactant. Any addition of water was accompanied by an exothermic evolution of heat; when the addition of an appropriate amount of water caused the formation of the microemulsion, the exothermic heat realized was higher than in the case in which the addition of water only diluted the external phase. The behaviour of both systems upon addition of butanol to the already-formed microemulsions was more complex. Two different experiments, due to the differences in stability of the two microemulsion systems, were performed. As the microemulsion with AOT as surfactant was very stable in a rather wide butanol concentration range it was possible to add butanol to a formed microemulsion without "breaking" it; in this case the partial molar enthalpy of addition was no longer constant (Table 1B) but decreased upon increasing butanol added. It was not possible to perform an identical experiment with the lecithin microemulsion, because the butanol concentration range, in which it was stable, was very narrow. It was in this case possible to disrupt the microemulsion by adding slight excesses of butanol and diluting with butanol a microemulsion already broken with excesses of co-surfactant.

The heat measured when butanol was added to the lecithin provoking its disruption was 1.6 $\mathrm{kJ} \cdot \mathrm{mol}^{-1}$ (Table 2, second column); it was noteworthy that this value exceeded the values obtained from the slope of the straight line (Fig. 2) of 0.22 $\mathrm{kJ} \cdot \mathrm{mol}^{-1}$, whereas the microemulsion formation heat was below that value of 0.24 $\mathrm{kJ} \cdot \mathrm{mol}^{-1}$. Perhaps it could suggest that the exothermic part of the heat evolved upon microemulsion formation was measurable as an excess in endothermicity when the microemulsion was disrupted. The "disruption" heat was measured for different butanol additions (Table 2, second column) and in all cases the values obtained were higher than those measured when the same amount of butanol was used for forming, instead of disrupting, the microemulsion. These breaking heats, apart from the first one which was probably connected with the disruption, did not seem to vary significantly with butanol concentration and the molar heat was not far from the constant partial molar enthalpy of addition observed at butanol concentration below the microemulsion.

On the other hand, the addition of butanol either to the microemulsion with AOT – in order to dilute it – or to an already broken microemulsion with lecithin was accompanied by a molar heat varying with the concentration of the co-surfactant. The ΔH measured upon addition of butanol in the absence of any surfactant was likely to be the result of a partition of butanol in water (ΔH_m of dilution $= -9\ \mathrm{kJ} \cdot \mathrm{mol}^{-1}$) and ISM ($\Delta H > 0$) (Arnett et al., 1969). The resulting endothermicity could indicate that the concentration of butanol in ISM prevailed upon the one in water, according to the different solubilities in the two phases. In conclusion, the minimum in endothermicity, measured at the formation of both microemulsions, suggested that their achievement was an anomalous situation, characterized by a negative enthalpy change of the emulsified system. A parallel study of the behaviour of the examined systems in the presence of drugs will be the object of a future paper.

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