

FORMAMIDE, A WATER SUBSTITUTE IN MICELLES AND MICROEMULSIONS =  
STRUCTURAL ANALYSIS USING A DIELS-ALDER REACTION AS A CHEMICAL PROBE

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ABSTRACT

We recently demonstrated that it is possible to prepare waterless microemulsions by replacing water with formamide. Using the Diels-Alder reaction between methyl acrylate and cyclopentadiene as a chemical probe, we were able to explore the monophasic areas of both ionic and non-ionic surfactant solutions in formamide. Discontinuities in reaction selectivity indicate the presence of structured phases.

Organized aqueous media (micelles, microemulsions) are being increasingly employed for synthetic purposes. Various chemical, photochemical and enzymatic reactions can be carried out in such media. They offer greater potential for solubilization of the reactants, and can favor particular molecular arrangements (orientation, proximity), conferring various degrees of stereospecificity.

In general, direct micellization of amphiphilic molecules is carried out in the presence of water, even if only in trace amounts for the formation of inverse micelles. The unique properties of water (polarity, protic and highly structured) have led to the widespread use of aqueous systems. Hydrophobic interactions and internal pressure effects have been used to stabilize these systems.

However, many organic reactants are not easily solubilized in water. Moreover, dielectric constants in microenvironments with their localized interfacial properties are lower than in water, and are closer to those found in salt solutions or in methanol.

These considerations have led to a requirement for non-aqueous solvents which will enhance solubility and reactivity in such non-homogeneous media.

### I. Specification for a water substitute

Two approaches can be employed, one based on theoretical consideration of the physico-chemical properties of water, and the other based empirically on the results of experiments.

#### 1. Physicochemical properties

The hydrophobic interactions observed in aqueous systems are in fact a particular example of solvophobic interactions in general. The ability of some ionic amphiphilic molecules to form micelles in non-aqueous media indicates that a water replacement would have the following properties :

- i) High polarity: the dielectric constant must be sufficiently high to dissociate ions of amphiphilic molecules and hinder self-association.
- ii) High solvating power: this, in combination with the high dielectric constant, favors dipole interactions over associations between opposite charged ions.
- iii) Highly structured: the notion of structure is based on the strength of intermolecular bonds and the geometry of the molecules. Both chemical (hydrogen bonds) and non-chemical (polar and non-polar) interactions must be taken into account (1). The structural nature of a solvent can be evaluated from two main parameters:

- the internal pressure  $P_i$
- the density of the cohesion energy  $D_{ce}$ .

Initially, solvents forming hydrogen bonds were chosen, although this is not an absolute requirement if aprotic molecules could be found of sufficient polarity (dipole) to structure the medium.

Tables 1 and 2 show physicochemical parameters for various potential solvents (1).

	$D_{ce}^a$ J.cm <sup>-3</sup>	$P_i^b$ J.cm <sup>-3</sup>	$\epsilon/\epsilon_0^c$	$\mu^d$	$E_T^e$
Water	2302	150.6	78.5	1.8	63.1
Formamide	1574.9	554.4	109.5	3.4	56.6
Ethylene glycol	892.0	502.1	37.7	2.0	56.3
Methanol	873.6	288.3	32.6	1.65	55.5
N-methyl formamide			182.4	3.8	54.1
N-methyl acetamide			175.7	4.3	52.0

Table 1: Physicochemical characteristics of various solvents. a) density of cohesion energy, b) internal pressure, c) dielectric constant, d) charge dipole moment, e) Kosswar's parameter

	$\gamma$ $\text{mN.m}^{-1}$ ( $^{\circ}\text{C}$ )		$\gamma$ $\text{mN.m}^{-1}$ ( $^{\circ}\text{C}$ )
Water	70 (20 $^{\circ}\text{C}$ )	Methanol	22.55 (20 $^{\circ}\text{C}$ )
Formamide	58.5 (20 $^{\circ}\text{C}$ )	N-methyl formamide	37.96 (30 $^{\circ}\text{C}$ )
Ethylene glycol	48.9 (20 $^{\circ}\text{C}$ )	N-methyl acetamide	33.67 (30 $^{\circ}\text{C}$ )
$\text{Et}_3\text{NH}^+\text{NO}_3^-$	46.3 (50 $^{\circ}\text{C}$ )		

Table 2: Surface tension  $\gamma$  of various solvents

Examination of these parameters suggested that formamide would be suitably structured.

## 2. Empirical observations

These are based on the presence of molecular associations in different solvents.

O. Sinanoglu and S. Abdunur (2) established the following order of solvophobicity: water > glycol, formamide >> ethylene glycol > n-butanol, methanol, n-propanol, ethanol > t-butanol. This order is also found for the stability of DNA double helices in the same solvents (3). It can be seen that formamide stands out from the other non-aqueous solvents. This has also been confirmed by X-ray diffraction, showing the highly structured nature of liquid formamide (4).

## II. Formamide a water substitute

We therefore carried out a comparison between water and formamide in various situations:

1 - In a structural investigation of molecular associations (micellization; formation of microemulsions) (5).

2 - In various reactions in phase transfer or in microemulsions (6).

### 1. Self-association in formamide

Several studies on micellization in this solvent have been carried out (7) although for the SDS/formamide system, Almgren et al. (8) report that they have been unable to detect SDS micelles in formamide at 25 $^{\circ}\text{C}$ .

#### 1.1. Micellization

At the Krafft temperature, a surfactant coexists in the three states: unassociated micellar and hydrated solid. We showed that micellization only takes place above the Krafft temperature for ionic surfactants, and that the Krafft temperature itself depends both on the nature of the surfactant and the medium (Table 3).

Surfactant	Formamide		Water	
	Krafft temp. (°C)	CMC mole.l <sup>-1</sup>	Krafft temp. (°C)	CMC mole.l <sup>-1</sup>
CTAB	43	9 × 10 <sup>-2</sup> (60°C)	26	1.03 × 10 <sup>-3</sup> (45°C)
SDS	55	2.2 × 10 <sup>-1</sup> (60°C)	16	9.7 × 10 <sup>-3</sup> (45°C)

Table 3: Krafft temperatures and CMC in water and formamide for two ionic surfactants (9).

Micelles of ionic surfactants in formamide can only be formed above the Krafft temperature (higher in formamide than in water). Under these conditions, the CMC values are also higher in formamide than in water (for both ionic and non-ionic surfactants). Formamide would seem to confer the properties of a low melting anhydrous salt similar to triethylammonium nitrate (10).

### 1.2. Microemulsion formation

The rather strict conditions for micellization described above can be reduced by addition of a cosurfactant and an oil. We have previously reported studies of four component systems using formamide and ionic surfactants using both perhydrogenated and perfluorinated compounds (5). In all cases we found that the microemulsions were stable for many months.

### 2. Waterless microemulsions as reaction media

Various studies have shown the value of aqueous microemulsions as reaction media (11), although their scope has been limited by the lack of solubility of many reagents in water. Formamide would appear particularly useful in such situations, and we have carried out various Diels-Alder reactions in such media (6a). This reaction is interesting not only for synthetic purposes but also because it can be used as a probe to study the nature of the reaction medium itself.

#### 2.1. Choice of probe reaction

Among the empirical parameters of polarity, the parameter  $\mu$  of Berson has been employed (12). It is an index of the proportions of the isomers obtained in the reaction of methyl acrylate with cyclopentadiene:



The two isomers (endo and exo) are obtained via two different transition states of different polarity. Berson defined the parameter  $\mu$  from the ratios of the

two isomers:

$$\log |\text{endo}|/|\text{exo}| = \rho$$

We carried out this reaction in various solvents. The calculated values of  $\rho$  are as follows:

Solvent	Et <sub>3</sub> N	CH <sub>3</sub> CN	HCONH <sub>2</sub>	N-methyl acetamide	Water
$\rho$	0.0445	0.692	0.825	0.672	0.869

In N-methyl acetamide the selectivity was less than in water or formamide. As suggested by Breslow "solvophobic type interactions would seem to play an important role" in this system (13). From these considerations it can be seen that  $\rho$  cannot be used as the criterion of polarity alone, but that it provides a measure of both polarity and structure (or solvophobicity) of the environment. This reaction is thus suitable as a chemical probe for investigation of the relationship between reactivity and structure of the medium. We have used it to study microemulsions using both ionic and non-ionic surfactants.

## 2.2. Diels-Alder reactions in formamide

### Microemulsions with ionic surfactants

#### a) Phase behavior: experimental evidence for organized media

We used isooctane as the oil, cetyltrimethylammonium bromide (CTAB) as surfactant and 1-butanol as cosurfactant. As for aqueous systems, we kept the mass ratio of isooctane/formamide at unity. Figure 1 shows a diagram of the various Winsor systems for these microemulsions. It represents the percentage of surface active components as a function of salt concentration in formamide, and closely resembles the appearance of the aqueous system.

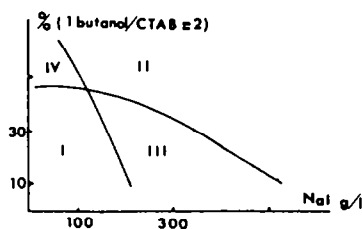


Fig.1: Phase behavior for the system formamide, isooctane, 1-butanol and CTAB and NaI.

Macroscopically, a Winsor IV (W IV) system is a single phased medium resulting from the complete mutual solubilization of all the constituents of the original mixture. If the water and oil content is high enough, a W IV system can be considered to be a microemulsion. Also at the macroscopic level, Winsor I (W I) and Winsor II (W II) systems are diphasic media in which one of the phases is a

microemulsion. In a W I system the microemulsion forms the lower phase, and is in equilibrium with an excess organic phase. In a W II system, the microemulsion forms the upper phase, and is in equilibrium with an excess aqueous phase. A Winsor III (W III) system is a triphasic medium in which the microemulsion forms the middle phase in simultaneous equilibrium with an excess organic and an excess aqueous phase.

The phase behavior of the system described above is consistent with the presence of an organized microemulsion, and is not a simple cosolubilization. However, it should be noted that high surfactant concentrations (30-40%) are required to obtain W IV microemulsions. This is probably due to the fact that formamide is less structured than water, and so more surface active components are required to solubilize the oil. A large W III zone, in the electrolyte-rich medium can be observed, which is only stable above 80°C. It was found that if the electrolyte concentration is over 100 g/l, the constituents tend to separate out below this temperature.

#### b) Monophasic area of formamide microemulsions

##### Reactivity, density and conductivity

The monophasic zones (W IV) were investigated in this system. The high solubility of the substrates in formamide enabled us to study the complete microemulsion phase diagram (figure 2). Good agreement between changes in conductivity and endo/exo selectivity can be seen in the plot of conductivity versus formamide volumic fraction  $\phi$ .

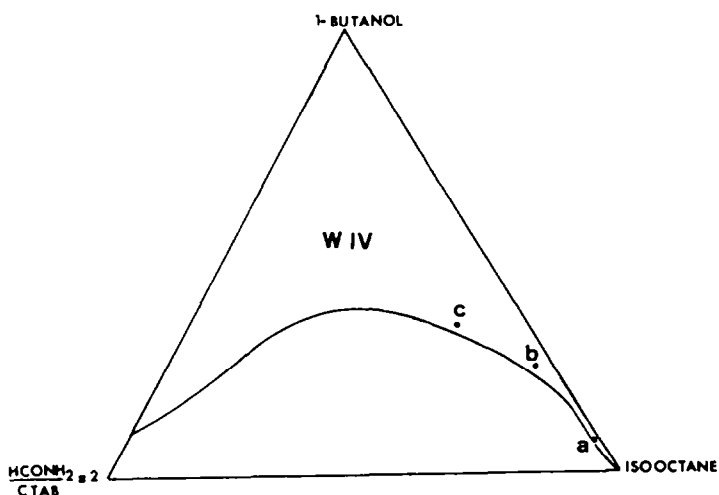


Fig.2: Pseudo ternary phase diagram of the system formamide/CTAB = 2, 1-butanol, isooctane

Along the demixion line (fig.2), the abrupt changes in selectivity and conductivity (fig.3) can be attributed to phase inversion from reverse micelles (formamide in oil) to direct micelles (oil in formamide).

It can also be seen that there are discontinuities in density, indicating structural rearrangements.

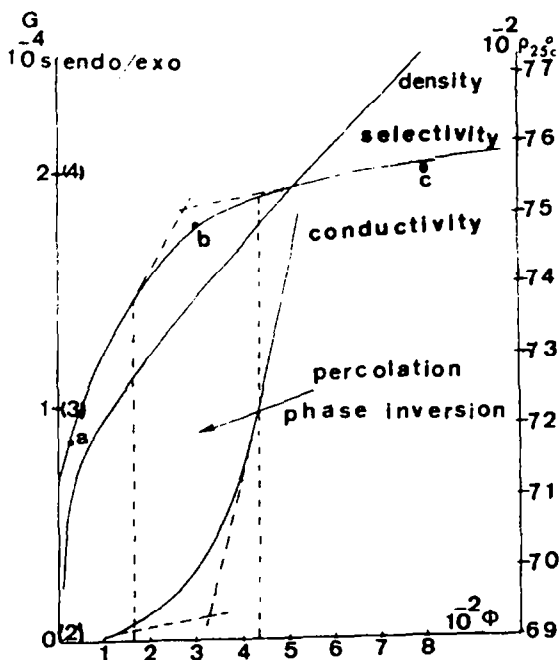


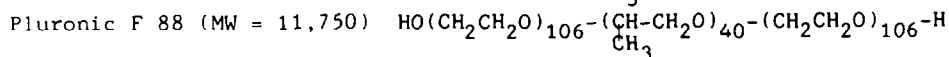
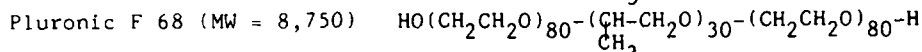
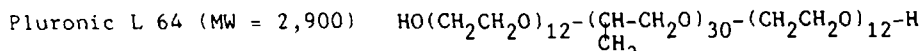
Fig. 3: density, conductivity and selectivity (endo/exo) versus volumic fraction of formamide.

### 2.3. Diels-Alder reactions in formamide

#### Microemulsions using non-ionic surfactants

The absence of charged products with non-ionic surfactants makes the investigation of the physicochemical characteristics of the monophasic area more difficult. The chemical probe reaction is thus particularly suited for this type of analysis.

We used the following non-ionic surfactants:



These agents are trisequenced polymers of ethylene oxide and propylene oxide which readily form aqueous microemulsions.

The monophasic zones were determined on the following systems:

A - Formamide/L 64 = 2, toluene (oil), isopropanol (cosurfactant) (fig. 4a)

B - Formamide/F 68 = 2, toluene (oil), isopropanol (cosurfactant) (fig. 5a)

C - Formamide/F 68 = 2, toluene (oil), isopropanol (cosurfactant) (fig. 6a)

D - Formamide/F 88 = 0.5, toluene (oil), isopropanol (cosurfactant) (fig. 7a)

We used a solvent/surfactant ratio of 2 as this gave larger microemulsion zones than those with isopropanol/surfactant = 2. With F 88, a solvent/surfactant ratio of 0.5 was chosen to enable a molar comparison with L 64 (25% MW).

Inspection of values of density in the figures 4b-7b shows that, in contrast to that found for ionic surfactants, no structural alterations could be observed in these systems. Density changed monotonically from one end of the diagram to the other as the continuous phase changed from toluene to formamide.

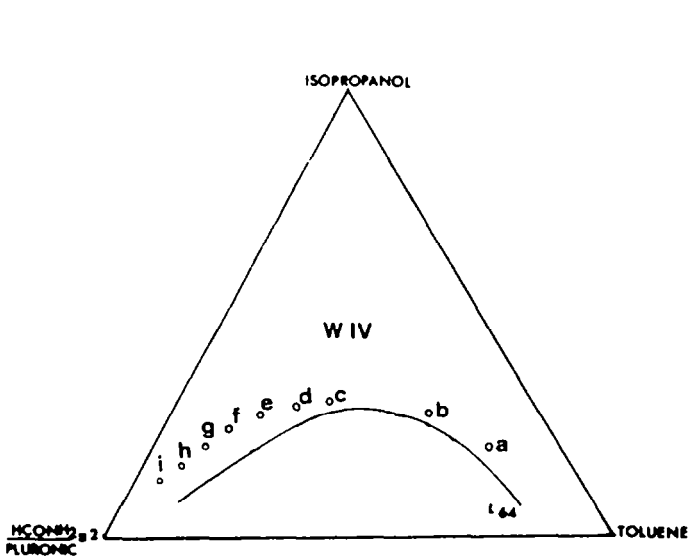


Fig.4a Pseudo ternary phase diagram of the system: formamide/Pluronic L 64 = 2, toluene, isopropanol

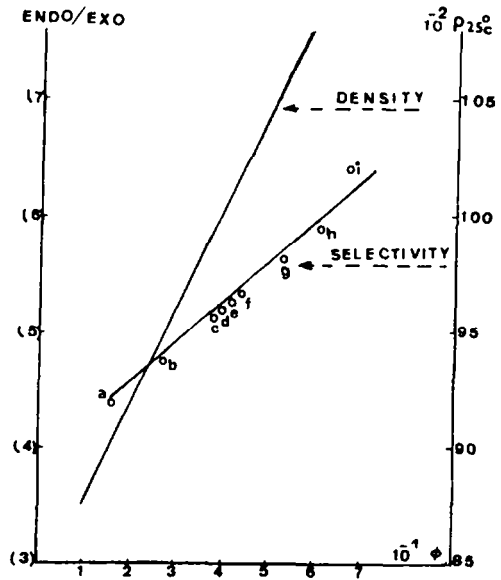


Fig.4b Density and selectivity versus volumic fraction of formamide

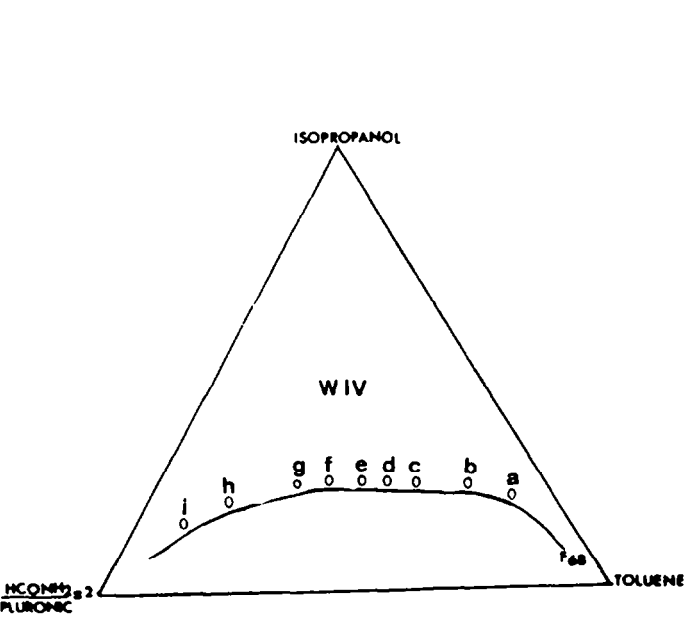


Fig.5a Pseudo ternary phase diagram of the system: formamide/Pluronic F 68 = 2, toluene, isopropanol

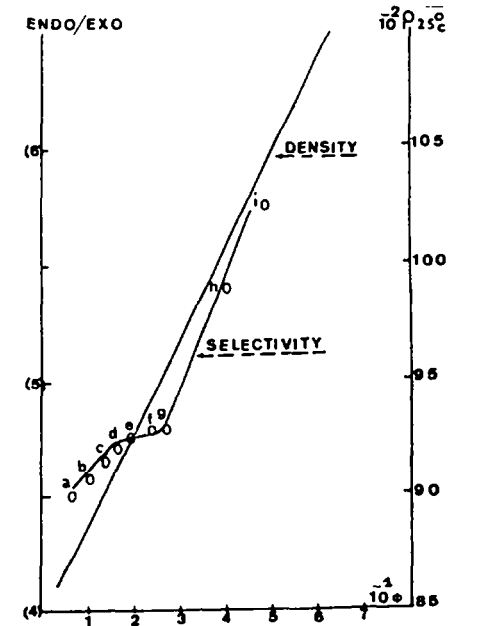


Fig.5b Density and selectivity versus volumic fraction of formamide



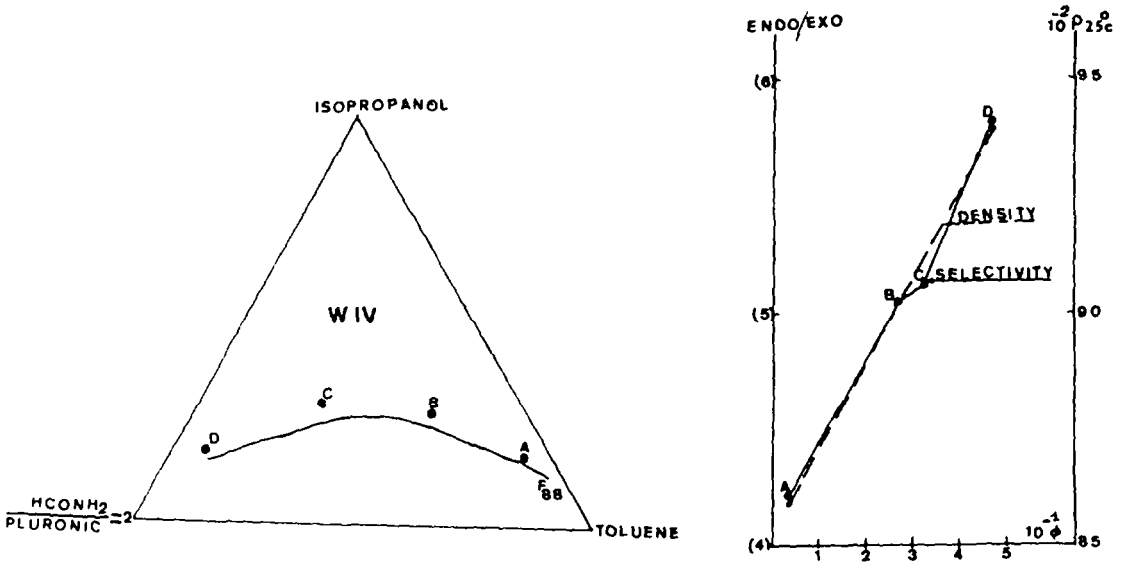


Fig. 6a Pseudo ternary phase diagram of the system: formamide/Pluronic F 88 = 2, toluene, isopropanol

Fig. 6b Density and selectivity versus volumic fraction of formamide

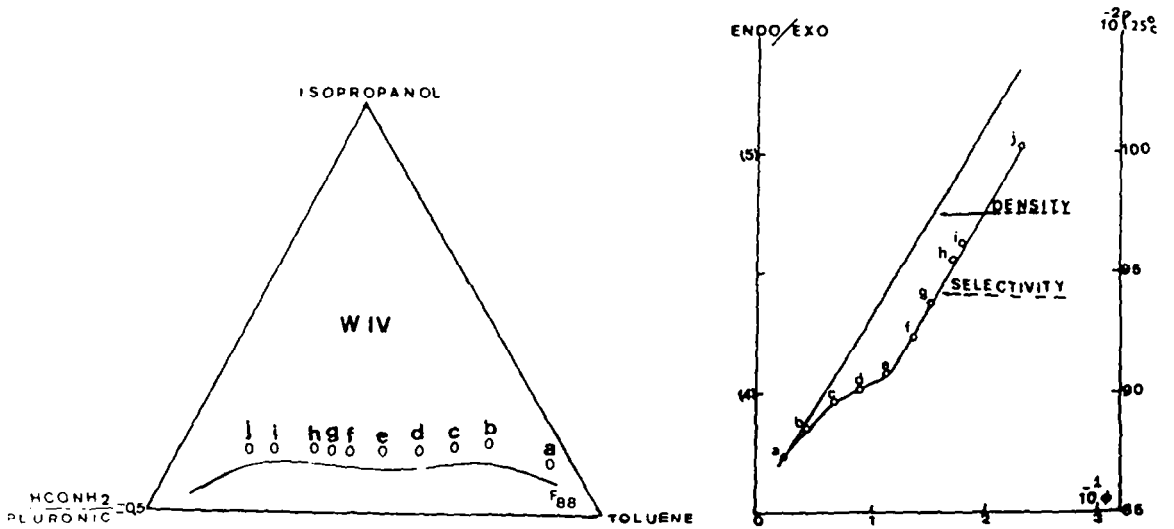


Fig. 7a Pseudo ternary phase diagram of the system: formamide/Pluronic F 88 = 0.5, toluene, isopropanol

Fig. 7b Density and selectivity versus volumic fraction of formamide

From the values of the endo/exo ratios observed, it can be seen that:

1. As for ionic surfactants, there is a discontinuity in reaction selectivity (for Pluronic F 68 and F 88). Monophasic systems with discontinuities could not be obtained with the L 64 polymer, which was attributed to the difference in molecular weight.
2. The greatest range of selectivity ( $\Delta(\text{endo/exo}) = 2.05$ ) as well as the highest selectivity was found with Pluronic L 64 (6.47 for  $\phi = 0.66$ ). In pure formamide, the selectivity at these concentrations is close to 7.

These results suggest that different types of mixture are involved. The polymers with more hydrophilic moieties (ethylene oxide) lead to micelle formation in formamide. Pluronic F 68 and F 88 with similar behavior have a similar ratio of number of hydrophilic groups/total hydrophilic + hydrophobic groups:

$$\text{F 68} \quad \text{EO}/(\text{EO} + \text{PO}) = 160/190 = 0.81$$

$$\text{F 88} \quad \text{EO}/(\text{EO} + \text{PO}) = 212/252 = 0.84$$

whereas Pluronic L 64 has a higher proportion of hydrophobic groups:

$$\text{L 64} \quad \text{EO}/(\text{EO} + \text{PO}) = 24/54 = 0.44$$

These figures suggest that the balance between hydrophilic and hydrophobic (or solvophobic) regions is crucial to the formation of organized structures. For Pluronic L 64, only cosolubilization could be obtained. In this case there were no discontinuities from the pure toluene to the pure formamide end of the diagram, and no organized structures could be detected.

Barker and Vincent (14) have recently determined the structure of polymeric microemulsions obtained from polystyrene/polyethylene oxide in mixtures of toluene, water and 2-propanol. For a molar fraction of ethylene oxide above 0.7, and for a suitable mass ratio of alcohol/toluene, micelles could be detected in the continuous toluene phase with a very low water content.

In formamide, Pluronic F 68 and F 88 and a molar fraction of ethylene oxide of 0.8, similar behavior should be observed, while for Pluronic L 64 micelles would not be produced.

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In conclusion, these results demonstrate that non-aqueous microemulsions can be produced by substituting formamide for water. The use of a Diels-Alder reaction as a chemical probe has also enabled investigation of the structure of the various zones in these media with both ionic and non-ionic surfactants.

Further studies on these non-aqueous systems from both the structural and

synthetic points of view (photoamidation, reactions catalyzed by transition metals etc) are in progress.

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