

EFFECT OF THE NATURE OF SURFACTANT ON THE REACTIVITY OF *C,N*-DIPHENYLNITRONE TOWARDS ACRYLONITRILE IN DIFFERENT MICROEMULSION SYSTEMS

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Abstract. The reactivity of the 1,3-dipolar cycloadditions of *C,N*-diphenylnitron with acrylonitrile in different microemulsion systems has been investigated. The effect of the nature of surfactant (cationic, anionic), a component of water- and oil-borne microemulsions, on the rate of this reaction has been studied. The electrostatically attractive character of cetyltrimethylammonium bromide, a cationic surfactant, would bring the reactants closer to each other; hence, a rate enhancement would ensue, particularly within the water-rich zone. Besides, the fact that acrylonitrile played a dual role, as a component of the microemulsion and a dipolarophile in the cycloaddition reaction, made the work-up advantageously sound. Additionally, the increase in reagents molar ratio was found to promote higher reactivity.

Keywords: acrylonitrile, cycloaddition, isoxazolidine, microemulsion, nitron.

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Introduction

Microemulsion is a dispersed state of one-in-the-other mixture of two immiscible liquids in the form of microdroplets [1-3]. As per the nature of substrate added to a microemulsion, three solubilisation sites for this substrate are plausible: the micellar core, the interface created between the polar heads, and the dispersing medium [4,5]. A myriad of reports, endorsed the fact that microemulsions are favourable media for organic reactions, which are usually hampered in conventional ones. Such macroscopically isotropic and microscopically structured media allow the reactants to draw near each other, to concentrate, and to induce their organization, hence, a better reactivity coupled with a better regio- and stereoselectivity [6-11].

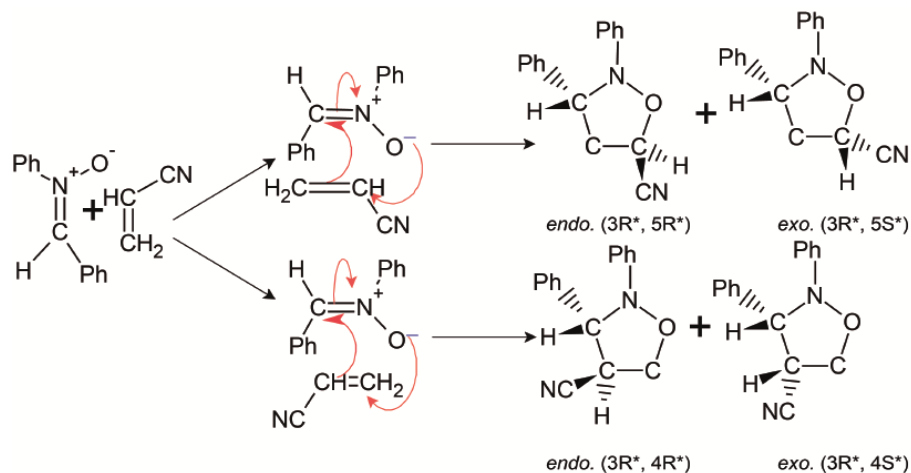
Heterocyclic chemistry remains indubitably a weighty chapter of organic chemistry. Its role and benefits increasingly gain a giant foothold in several industries, including pharmaceuticals, dyes, plastics, and agrochemicals [12-14]. One of our ongoing researches is synthesis of isoxazolidines and study of their biological

activities. Apart from this biological property, they are known for the anti-inflammatory activity and others [15-19]. The common procedure to make them has been through the 1,3-dipolar cycloaddition of nitrones with alkenes [20,21]. This reaction is also known as the Huisgen cycloaddition or Huisgen reaction that proceeds by concerted mechanism. Generally, 5-substituted isoxazolidines are obtained starting from mono-substituted and 1, 1-disubstituted alkenes. The formation of 4-substituted products is observed only for strong electron-withdrawing groups [22]. This cycloaddition has been extensively studied both computationally [23-26] and experimentally [27-28], in a variety of media: aqueous media [29-31], solid state [22,32-34], ionic liquids [35-38], emulsions and microemulsions [39,40].

In the present paper, we wish to report the results of the effects of the type of the microemulsion (water- and oil-borne ones, O/W and W/O) and the electrical charge of the polar head of the surfactant (cationic, anionic), a basic constituent of the microemulsion, on the reaction rate of 1,3-dipolar cycloaddition of

C,N-diphenylnitron (DPN) with acrylonitrile (ACN) when run in the microemulsion medium. Scheme 1 recalls the mechanism illustrating the

two possible sites of attack, giving rise to two pairs of isoxazolidine isomers, (3*R*, 4*R*; 3*R*, 4*S*) and (3*R*, 5*R*; 3*R*, 5*S*).



Scheme 1. Mechanism of 1,3-dipolar cycloaddition between DPN and ACN.

Experimental

Chemicals and equipment

Chemicals and solvents (purity > 95%) were purchased from either Fluka or Prolabo. *C,N*-Diphenylnitron was prepared as previously described [41]. Acrylonitrile was purified by distillation before use. UV-visible spectra were recorded on a Shimadzu 160 double beam spectrophotometer.

Pseudo-ternary phase diagrams

Establishment of pseudo-ternary phase diagrams was deemed to be an inevitable step for confining the existent domains of the studied microemulsions. For a matter of comparison herein dealt with, sodium dodecylsulphate (SDS) and cetyltrimethylammonium bromide (CTAB) were chosen as anionic and cationic surfactants, respectively. *n*-Butanol was used as co-surfactant in this study and the mixture surfactant/co-surfactant was thus taken as a pseudo-component of the microemulsion. The choice for *n*-butanol as co-surfactant was not arbitrary; but was based on its chemical inertness towards ACN and its ability to take part in the stability of the microemulsion. Based on our previous work [41] and others [4], the [surfactant]/[co-surfactant] weight ratio was set to 1/2, allowing a broad domain of microemulsion existence. The cycloaddition was first examined with toluene as an oily constituent of the microemulsion to provide an insight into the course and outcome of the reaction under these conditions. Then, toluene was substituted by ACN, acting as oily constituent of the microemulsion and dipolarophile in the proposed cycloaddition. Accordingly, the

following four phase diagrams were drawn to represent four pseudo-ternary systems:

System I: Water/(SDS/*n*-Butanol=1/2)/Toluene.

System II: Water/(CTAB/*n*-Butanol=1/2)/Toluene.

System III: Water/(SDS/*n*-Butanol=1/2)/ACN.

System IV: Water/(CTAB/*n*-Butanol=1/2)/ACN.

To realize the pseudo-ternary phase diagrams, demixion curves that delimit the existence domain of microemulsions ought to be established as follows:

Downward demixion curve

1. Titration of *water/oil* binary mixtures of different compositions (from water-rich compositions to oil-rich ones) at 25°C, with a solution made of 75% of water and 25% of surfactant and *n*-butanol (*surfactant/n-butanol*= 1/2) until a transparency occurred.
2. Titration of pseudo-binary mixtures of *oil/(surfactant/n-butanol*= 1/2) with pure water until a cloudy appearance was observed.
3. Titration of pseudo-binary mixtures of *water/(surfactant/n-butanol*= 1/2) with oil until a cloudy appearance was observed.

Upward demixion curve

1. Titration of pseudo-binary mixtures of *oil/(surfactant/n-butanol*= 1/2) with pure water until a transparency occurred.
2. Titration of pseudo-binary mixtures of *water/(surfactant/n-butanol*= 1/2) with oil until a cloudy appearance was observed.

The employed microemulsions were selected from the drawn phase diagrams, one water-borne micromulsion W/O (A) and one

oil-borne one O/W (**B**). The microemulsions were made according to the data shown in Table 1.

Table 1

Composition (wt.%) of the microemulsions.

| Microemulsion | Water | SDS or CTAB | <i>n</i> -Butanol | Toluene or ACN |
|---------------|-------|-------------------|-------------------|----------------------|
| A | 50 | 12.5 | 25 | 12.5 |
| B | 20 | 12.5 | 25 | 42.5 |

1,3-Dipolar cycloaddition in microemulsion

In a 25 mL flask, 0.294 g (1.5 mmoles) of DPN was dissolved in 3 mL of microemulsion, followed by addition of the required amount of ACN. The mixture was vigorously stirred at 25°C. The follow-up of the reaction was through UV-visible analysis at a given reaction time. To do so, a 5 μ L sample of the mixture was diluted with 4 mL of ethanol and the unreacted DPN was quantified by measuring the UV-visible

absorbance at λ_{\max} = 313 nm of the diluted sample [11].

Calibration curve

A mother solution DPN/microemulsion was prepared by dissolving 0.294 g of DPN in 3 mL of microemulsion. Aliquots of 1, 2, 3, 4, 6, 8, 10 and 12 μ L were then sampled and diluted in 8 mL of ethanol. Absorbance of each diluted sample was measured at λ_{\max} = 313 nm and the curve $Abs = f(C)$ was drawn.

Results and discussion

Figure 1 present the phase diagrams delineating the areas of the existence of microemulsions. It can be noticed the vast domains of the existence of microemulsion for the four systems *I-IV* in the vicinity of water- and oil-rich sides. However, the choice was focused on surfactant-rich ones as per the superposition of the four diagrams.

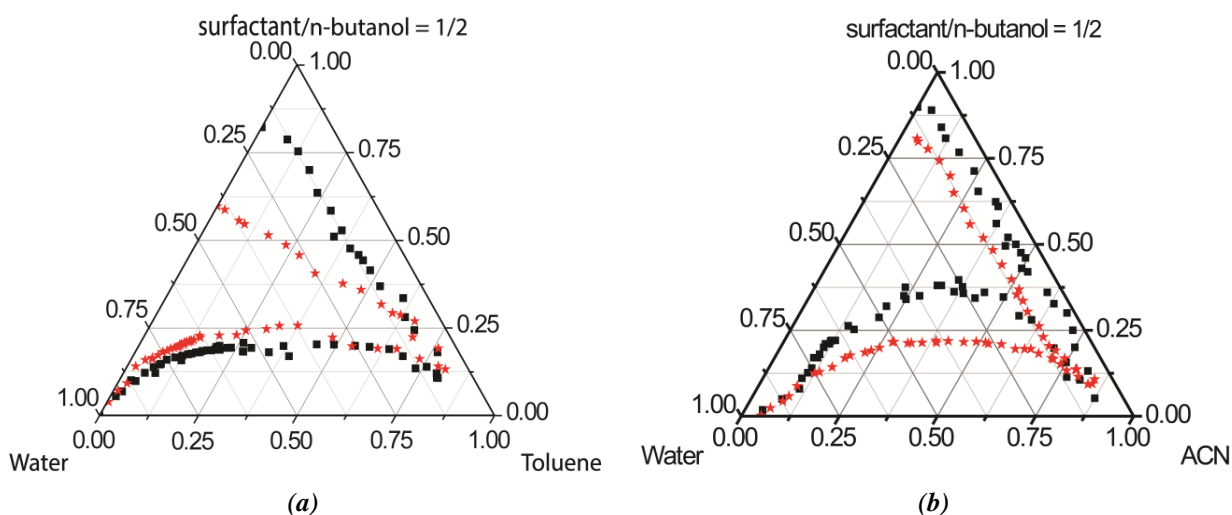


Figure 1. Pseudo-ternary phase diagrams for:
 (a) ★ water/(SDS/*n*-butanol)= 1/2)/toluene; ■ water/(CTAB/*n*-butanol)= 1/2)/toluene,
 (b) ★ water/(SDS/*n*-butanol)= 1/2)/ACN; ■ water/(CTAB/*n*-butanol)= 1/2)/ACN.

The kinetics of the cycloaddition reaction was monitored by UV-visible analysis of the residual DPN. It is worth mentioning that whatever the location of the dissolved substrate within the microemulsion, either in its interior or at the interface of microaggregates, would not distort the overall interpretation of the spectra. The evolution of the intensity of the absorbance band of DPN with reaction time for microemulsion **B** of system *I* is illustrated in Figure 2. The increasingly fading of the absorbance band at 313 nm and the rising one at 238 nm, a characteristic band of the isoxazolidine, was an evidence of the success of the cycloaddition in microemulsion medium.

The appearance of an isosbestic point at 253 nm proves the existence of equilibrium between the two species without intermediates. From this analysis, the rate constants k of the cycloaddition in different microemulsions were computed and are gathered in Table 2.

Needless is to recall that the microenvironment of the reactants affects their reactivity. Hence, reaction outcome in oil-borne microemulsion will differ from that in water-borne one, as confirmed by many reports [42-46]. In the present work, isoxazolidines were synthesized in both O/W and W/O microemulsions, **A** and **B**. The latter one consists of water microdroplets dispersed in toluene,

separated by a film made of surfactant and co-surfactant; DPN and ACN ended up in an environment similar to conventional medium, with slight nitrene content at the water-toluene interface as illustrated in Figure 3(b). On the contrary, the former microemulsion one consists of oil microdroplets dispersed in water, separated by a film made of surfactant and co-surfactant.

Both organic substrates, DPN and ACN, tended to move towards the interface where to react. While the formed isoxazolidine migrated to the hydrophobic core of the microemulsion, the reactants tended to concentrate once again at the mentioned interface, promoting a reaction rate enhancement (Figure 3(a)).

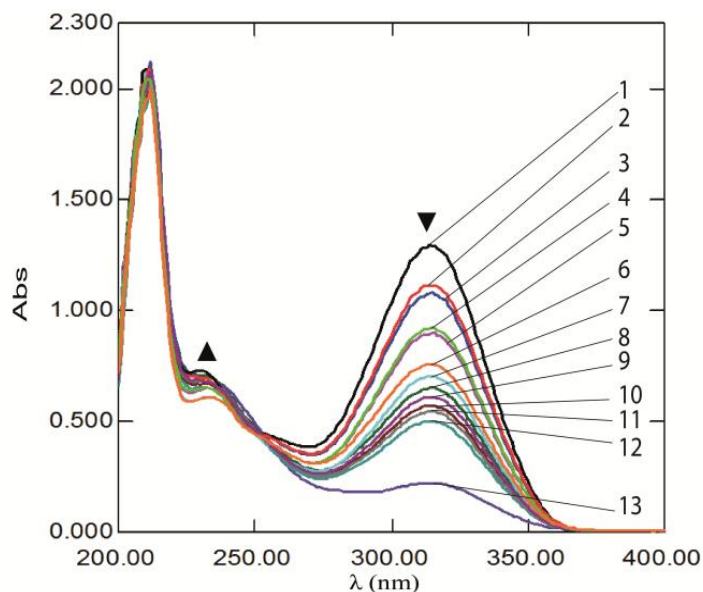


Figure 2. UV-visible spectra evolution with reaction time, for DPN-microemulsion IB, at 25°C, in ethanol.

Table 2

Rate constants of 1,3-dipolar cycloaddition between DPN and ACN for different DPN/ACN molar ratios in microemulsion systems at 25°C.

| Run | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|--|---------|---------|---------|---------|--------|--------|-------|-------|
| Microemulsion | (IB) | (IA) | (IIB) | (IIA) | (IIIB) | (IIIA) | (IVB) | (IVA) |
| Surfactant | SDS | SDS | CTAB | CTAB | SDS | SDS | CTAB | CTAB |
| Oil | toluene | toluene | toluene | toluene | ACN | ACN | ACN | ACN |
| DPN/ACN | 1/20 | 1/20 | 1/20 | 1/20 | 1/80 | 1/24 | 1/80 | 1/24 |
| $k \times 10^3 \text{ (M} \cdot \text{s}^{-1}\text{)}$ | 1.2 | 1.3 | 1.9 | 2.3 | 4.4 | 2.1 | 7.4 | 3.2 |

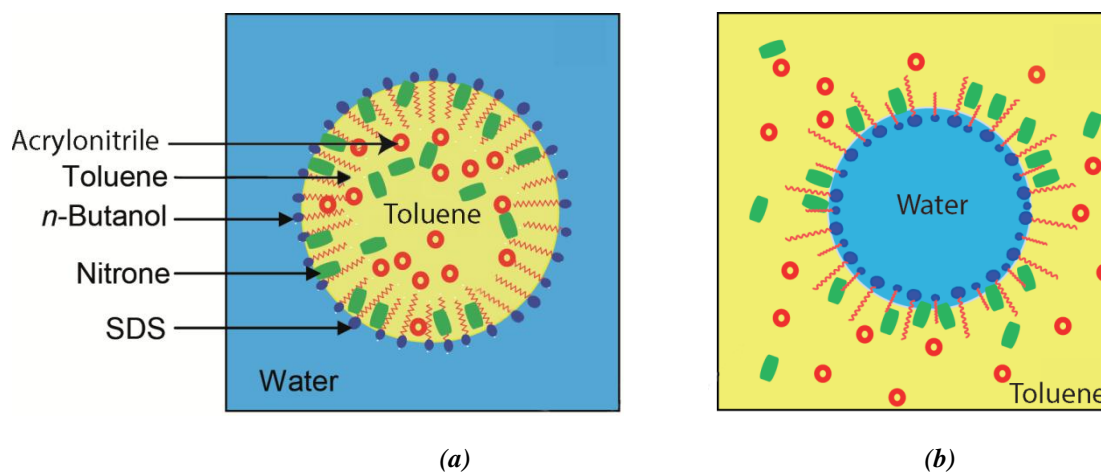


Figure 3. Illustration of location sites of DPN and ACN in: (a) a direct microemulsion, IA; (b) a reverse microemulsion, IB.

The results shown in Table 2 for runs 1 and 2 suggest that the rate constant of the cycloaddition remained nearly unchanged on going from oil-rich zone to water-rich one. Reversing the shape of the micelles in water-borne microemulsion **A** and re-concentrating the reactants in the microdroplets did not improve the reaction rate.

The type of charge of the surface active agent may affect the microemulsion characteristics, thus, the reaction course. The double layer, comprised of the polar heads of surfactant and its counterions, created a local electrical field, giving rise to another kind of interfacial environment which influenced the position of the reactants. In fact, the ensued repulsive electrostatic interactions would have allowed the reactants to stand either close to the interface or far from it. Moreover, this created field may have either reduced the stability of the reactants, provoking an acceleration of the reaction, or enhanced their stability, inducing a reaction rate drop.

A rate acceleration can be noted when the kinetic results for the microemulsions **IA** and **IIA** (SDS as surfactant) were compared with those for **IB** and **IIB** (CTAB as surfactant) (Table 2); the rate constant increased from $1.2 \times 10^{-3} \text{ M}\cdot\text{s}^{-1}$ to $1.9 \times 10^{-3} \text{ M}\cdot\text{s}^{-1}$ in the case of oil-borne microemulsions (**B**) and from $1.3 \times 10^{-3} \text{ M}\cdot\text{s}^{-1}$ to $2.3 \times 10^{-3} \text{ M}\cdot\text{s}^{-1}$ in the case of water-borne ones (**A**). These results are in agreement with those reported by Chatterjee, A. *et al.* [47]. Their report indicates that excellent yields of the 1,3-dipolar cycloaddition reactions between *C*-aryl-*N*-phenyl nitrones and alkenes were observed when run in microemulsion with CTAB

as surfactant, as compared with microemulsion consisting of SDS surfactant.

On the other hand, the effect of microemulsion as medium for organic reactions was supported by the work of Engberts, J. *et al.* [48]. In their investigation, they observed that the reaction rates of 1,3-dipolar cycloaddition between benzonitrile oxide and *N*-ethylmaleimide at 25°C were 35 and 150 times greater in AOT/isooctane/water microemulsion than in water and isooctane, respectively. The rationale of this rate improvement was the increase of reactants concentrations at the interface and the destabilization of benzonitrile oxide by the electrical field induced by the anionic polar heads of AOT surfactant. This reaction was also studied in SDS- and CTAB-based micellar media and the result was a reactivity decline as compared to the reaction outcome in water [39]. The relatively better reactivity in water was reasoned as due to the undisturbed ‘solvated state’ of benzonitrile oxide, hence becoming more stable and less reactive. However, the reactivity depression that occurred in microemulsion was explained as due to ‘solvation power lowering’, ensuring higher reactivity.

In the light of the above results, an explanation for the difference in chemical reactivity of DPN towards ACN when CTAB and SDS were used (Figure 4), lies on the electrostatic force exerted by the dodecylsulphate ion on the negative charge of the nitron molecule; the latter species will end up in the aqueous superficial layer, full of cationic counterions (Na^+), to become more stable by solvation. A chemical reactivity reduction ensues regardless the type of microemulsion used (O/W or W/O) (Figure 4(a)).

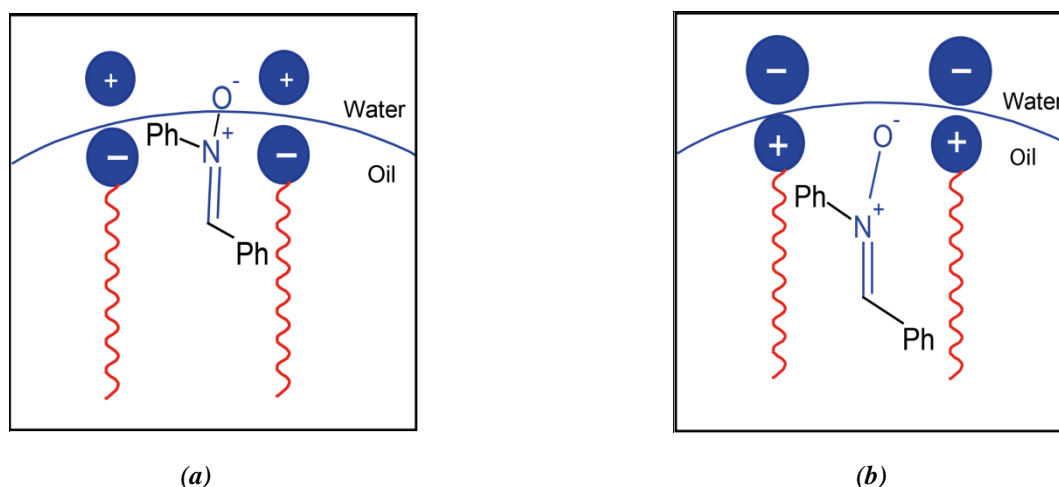


Figure 4. Positioning of DPN molecule at the W/O interface in the presence of surfactant: (a) SDS, (b) CTAB.

In the case of the positively charged polar heads of CTAB, attractive electrostatic forces stimulated the migration of DPN molecules towards the interface zone. The high concentration of anionic counterions (Br^-) within the superficial layer that is close to the interface, would keep DPN molecules far from the aqueous environment, impeding their solvation. In this fashion, the interface, acting as a microreactor, would allow nitron molecules to concentrate near ACN ones, and therefore the reactivity increases (Figure 4(b)).

It is worthwhile to point out to the positive role of the cationic surfactants in the microemulsion as far as the cycloaddition course was important. So, as observed for systems *III* and *IV*, the increase in DPN/ACN molar ratio was found to promote higher reactivity. For example, the rate constant rose from $1.9 \times 10^{-3} \text{ M}\cdot\text{s}^{-1}$ to $7.4 \times 10^{-3} \text{ M}\cdot\text{s}^{-1}$, on going from microemulsion *IIB* to microemulsion *IVB*.

Conclusions

The use of oil-borne microemulsions (O/W) in the synthesis of isoxazolidine is in tune with green chemistry. The dual employment of ACN, as microemulsion component and reactant, makes the water-borne microemulsions (W/O) environmentally-friendly by excluding the use of another organic component.

SDS-based W/O or O/W microemulsions with an ACN/DPN molar ratio of 20 showed no difference of chemical reactivity. On the contrary, the O/W CTAB-based microemulsions allowed higher reactivity.

Another important issue is the impact of solvation (hydration) of reactants on the course of the cycloaddition reaction in microemulsion. The negative charge of the counterion of a cationic surfactant will contribute to hydration lowering of nitron, favouring its increased reactivity.

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