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Elucidating chemical reactivity and transition state of mononuclear rearrangement of heterocycles through the use of compartimentalized micellar media

Susanna Guernelli[a], Romina Zappacosta[b], Gabriella Siani[b], Domenico Spinelli[c], Antonella Fontana[b,*]

[a] Dipartimento di Chimica "Giacomo Ciamician", Università degli Studi di Bologna, Via S. Giacomo 11, 40126 Bologna, Italy
[b] Dipartimento di Farmacia, Università "G. d'Annunzio", Via dei Vestini, 66100 Chieti, Italy
[c] Dipartimento di Chimica "Giacomo Ciamician", Università degli Studi di Bologna, Via F. Selmi 2, 40126 Bologna, Italy

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ABSTRACT

The present comprehensive kinetic investigation in micellar systems deepens and broadens the knowledge of mononuclear rearrangement of heterocycles (MRH) of *Z*-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole, reaction already carried out in different reaction media. As a matter of fact the use of four types of micelles different for charge, shape and polarity has allowed us to evaluate the role of micellar systems, as reaction media, on the rate of MRH and to quantify their catalytic effect. Moreover, the data obtained have enabled us to draw some intriguing conclusions on the localization of the substrate in the micelles, the transition state structure and the driving force of the reaction.

1. Introduction

The chemistry of heterocyclic compounds represents a crucial segment of the today's chemistry, with at least 55% of organic chemistry papers devoted to this field. Heterocycles, especially five and six-membered rings containing nitrogen, play a key role in life processes such as the transfer of hereditary information from DNA to proteins, enzyme activity, storage and transfer of bioenergy, oxygen transport by haemoglobin, chlorophyllian synthesis, and so on [1].

Beside organic chemistry and biochemistry, many other sciences, from medicinal to agricultural and from material science to technology, are in debt to heterocycles. Indeed, several drugs (antibiotics, neurotropics, cardiovascular and anticarcinogenic agents), plant development regulators, pesticides, thermostable polymers, highly durable fibres exploit nitrogen containing heterocyclic systems [1–21].

For these reasons we have addressed our interest to synthetic applications and mechanistic studies of the mononuclear rearrangements of heterocycles (MRHs, Scheme 1) [22–26]. This type of reaction, involving an azole five-membered aromatic heterocycle generally linked to a side chain through a continuous π-electron system, leads to the synthesis of several different heteroaromatic azoles. MRHs are S_{Ni} processes occurring *via* a quasi-aromatic transition state (10 π electrons in a bicyclic structure) characterized by structure and solvent-dependent pathways [2,27–38].

We have previously studied the interconversion of several *Z*-arylhydrazones of 5-substituted-3-benzoyl-1,2,4-oxadiazoles into the relevant 4-acylammino-2-aryl-5-phenyl-1,2,3-triazoles in order to clarify the mechanistic aspects of the reaction by collecting both kinetic [2,27–29] and computational data [30]. More recently the use of micelles (Triton X-100 and C_{14}DMAO) [39,40] and cyclodextrin (β-cyclodextrin) [41,42] as well as ionic liquids [35,36,43] has allowed us to obtain detailed information concerning both the reaction mechanism and the effects of substrate structure on the MRH reaction rates.

The micelles provide interfaces able to modify physico-chemical properties of the investigated compounds [44–49].

The incorporation of 1,2,4-oxadiazoles derivatives in non-pre-organized (micelles) [39,40] or in pre-organized (β-cyclodextrin) [41,42] systems has allowed to overcome their poor solubility in

* Corresponding author. Tel.: +39 0871 3554790; fax: +39 0871 3554911.
E-mail address: fontana@unich.it (A. Fontana).

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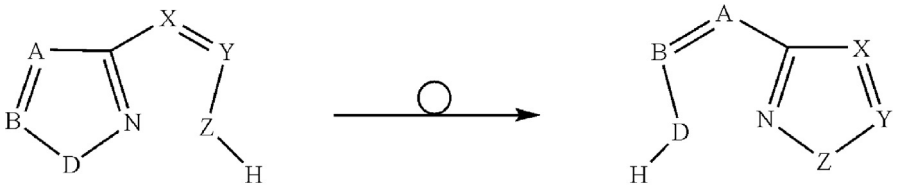


Scheme 1. Azole-into-azole interconversion.

water and, in order to determine proton concentration, to avoid the use of operational scales such as the pS^+ scale [50,51], established by interpolation from known pK_a data in aqueous dioxane.

Moreover the use of an inherently microheterogeneous solvent such as the aqueous micellar solution may offer different advantages over the continuous media. For example reactants in a continuous solvent undergo desolvation in order to approach close enough to react to each other. On the other hand, two reactants of a bimolecular reaction solubilized in the same micelle are forced in close proximity, thereby increasing the rate of reaction at the expense of a substantial loss of freedom of translational motions of the reactant molecules. Indeed, the dimension of the micelles could be critical for the molecular reciprocal orientation in the transition state formation [52].

Besides, in a previous paper, a concerted process was suggested for this MRH, where the magnitude of the activation barrier was determined by the interplay of two opposite factors, that is, the nucleophilicity of the nitrogen atom and the acidity of the nitrogen-bonded proton [30]. Nevertheless, while the former plays a significant role in the micellar aprotic region, the acidity of the nitrogen-bonded proton preferentially manifests itself in the aqueous compartment. Thus, the prevalence of one factor over the other in different micellar systems may highlight their relevant contribution to the MRH process.

Therefore, in order to complete and integrate the results obtained with non-ionic (Triton X-100, polyethylene glycol *tert*-octylphenyl ether) [39] and zwitterionic (C_{14}DMAO, *N*-tetradecyl-*N*,*N*-dimethylamine oxide) [40] micellar systems we have now undertaken a kinetic study in the presence of a wide variety of surfactants (*i.e.* SDS, sodium dodecyl sulfate; CTABr, cetyltrimethyl ammonium bromide; C_{14}DMAO; Triton X-100) in the presence of phosphate buffers at different pH values and temperatures. The S_{Ni} reaction of the *Z*-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**1**) into the relevant 4-benzoylamino-2,5-diphenyl-1,2,3-triazole (**2**) was chosen as a model reaction to elucidate mechanistic aspects such as, to name a few, the charge dispersion and timing of chemical bond formation-and-breaking in the transition state (Scheme 2).

The experimental data were fitted into the classical equation based upon Berezin's model [53], *i.e.* the so called pseudophase model, and allowed us to obtain both the reaction rate constants in aqueous and in micellar pseudophase, k_W and k_M respectively, as well as the relevant binding constants (K_S). These results have proven particularly useful and have shown that the four investigated surfactants exhibit some significant differences in catalytic activity due to the prevailing contribution of nitrogen nucleophilicity or of nitrogen-bonded proton acidity in the process.

2. Experimental

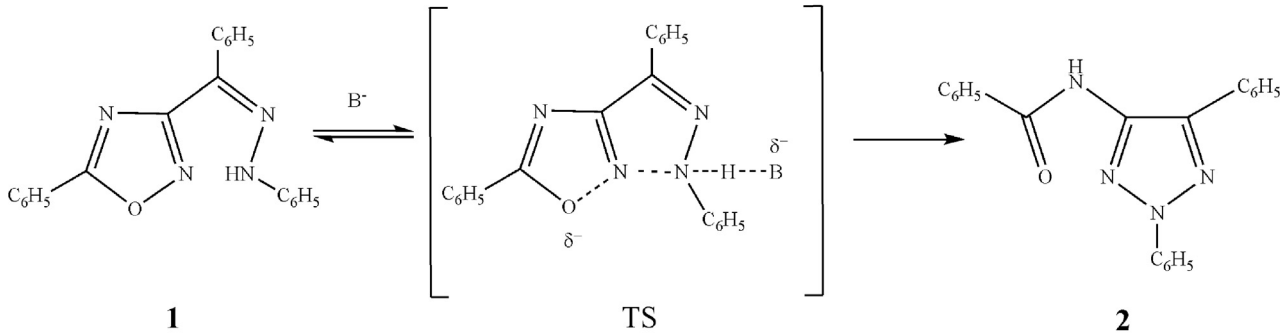
2.1. General

The *Z*-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazoles (**1**) was prepared according to literature methods [55]. The zwitterionic surfactant, C_{14}DMAO, was used as received from Prof. Hoffmann (Bayreuth Centre for Colloids & Interfaces). All other surfactants obtained from commercial suppliers were used without further purification.

Aqueous stock solutions in doubly distilled water of surfactants and phosphate buffer solutions at pH 7.4 ($[H_2PO_4^-] = [HPO_4^{2-}]$) and 11.7 ($[HPO_4^{2-}] = [PO_4^{3-}]$) were prepared by weight and used within few days. The pH measurements were carried out by using a Radiometer PHM 84, calibrated at pH 7.0 and 12.0 (±0.05). The ionic strength of the buffered solutions was kept constant at the value of 0.2 mol dm^{-3} through addition of KCl.

2.2. Critical micellar concentration measurements (c.m.c.)

The surface tensions of the investigated surfactant (SDS, CTABr, C_{14}DMAO and Triton X-100) in the presence and in the absence of **1** (5.0×10^{-5} mol dm^{-3}) were measured with a SensaDyne QC6000 Surface Tensiometer by the maximum bubble pressure method [56]. Dry nitrogen flows into a capillary immersed into the surfactant solution. On gradually increasing the pressure in the capillary, the bubble increases in size and curvature until it becomes hemispherical. Beyond this point the bubble



Scheme 2. MRH of the *Z*-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**1**) into the relevant 4-benzoylamino-2,5-diphenyl-1,2,3-triazole (**2**). B^- is an added base or the solvent.