These *s*-triazine to pyrimidine transformation reactions probably proceed, as shown in Scheme II, by a somewhat different mechanism than that proposed for other ring transformations.[7,8] Attack of a carbon nucleophile at C_6 would occur to form σ complex C. Proton transfer from the exocyclic α-position of structure C to N_5 would give rise to carbanion D which could then undergo scission of the N_1–C_6 bond to give the open-chain intermediate E. Intramolecular nucleophilic attack of the terminal nitrogen on C_4 with simultaneous elimination of 1,3-dimethylurea results in the formation of pyrimidine **3**.

Experimental Section

General Methods. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Melting points were determined on a Thomas-Hoover capillary apparatus. UV spectra were recorded on a Unicam SP800 spectrophotometer and IR spectra on a Perkin-Elmer Infracord Model 221.

1,3-Dimethyl-*s*-triazine-2,4(1*H*,3*H*)-dione (1; 1,3-Dimethyl-5-azauracil). A mixture of 5-azauracil[12] (5.6 g, 0.05 mol) and dimethylformamide dimethyl acetal (70 mL) was refluxed gently for 1 h and stirred overnight at room temperature. The product was collected by filtration and recrystallized from ethyl acetate: 3.38 g (48%), mp 162–164 °C (lit.[13] mp 164 °C).

Conversion of 1 into 5-Azacytosine (2a). Guanidine monohydrochloride (1.9 g, 0.02 mol) was stirred in 0.7 M ethanolic sodium ethoxide (30 mL) for 10 min, and insoluble NaCl was removed by filtration. To the filtrate was added **1** (1.4 g, 0.01 mol), and the mixture was refluxed for 2 h. The mixture was concentrated to dryness in vacuo. The residue was dissolved in water (10 mL) and neutralized with acetic acid. The crystals were collected by filtration and recrystallized from water: 667 mg (59%), mp >350 °C dec. The IR spectrum of this sample was identical with that of an authentic sample.[14]

Conversion of 1 into 5-Azauracil (2b). To a solution of ethanolic sodium ethoxide (prepared by dissolving 230 mg of Na in 30 mL of ethanol) was added **1** (700 mg, 0.005 mol) and urea (600 mg, 0.01 mol). The mixture was refluxed for 2 h and then concentrated to dryness in vacuo. The residue was dissolved in water (10 mL), and the solution was neutralized with acetic acid to precipitate 5-azauracil (**2b**) which was recrystallized from water: 270 mg (48%), mp 270–272 °C dec (lit. mp 268–270 °C dec[12a], 284–285 °C dec[12b]). The IR spectrum of this sample was identical with that of an authentic sample.[12]

Uracil-5-carboxamide (3a). A solution of malonamide (1.02 g, 0.01 mol) in 0.33 M ethanolic sodium ethoxide was treated with **1** (700 g, 0.005 mol), and the mixture was refluxed for 3 h. The solvent was removed by evaporation in vacuo. The residue was dissolved in water (10 mL), and the solution was neutralized with acetic acid. Crystals were collected by filtration and recrystallized from water: 325 mg (42%), mp >300 °C (lit.[15] mp >300 °C). The IR spectrum of this sample was identical with that of an authentic sample prepared by ammonolysis of 5-(methoxycarbonyl)uracil.

Compound **3a** (100 mg) was dissolved in concentrated HCl (5 mL), and the solution was refluxed for 20 h and then was evaporated in vacuo. The residue was recrystallized from water to give 21 mg of uracil, mp 320–331 °C dec. The UV and IR spectra of this sample were identical with those of uracil.

5-Cyanouracil (3b). A mixture of cyanoacetamide (840 mg, 0.01 mol) and **1** (700 mg, 0.005 mol) in ethanolic sodium ethoxide (prepared by dissolving 230 mg of Na in 30 mL of ethanol) was stirred at room temperature for 48 h, and then the mixture was concentrated to dryness in vacuo. The residue was dissolved in water (10 mL), and the solution was neutralized with acetic acid. The precipitate, which was collected by filtration, did not absorb UV light and was discarded. The filtrate was concentrated in vacuo, and the residue was crystallized from water: 260 mg (38%), mp 289–296 °C dec (lit.[15] mp 295 °C dec). UV and IR spectral characteristics of this sample were identical with those of an authentic sample.

Registry No. **1**, 824-28-2; **2a**, 931-86-2; **2b**, 71-33-0; **3a**, 1074-97-1; **3b**, 4425-56-3; guanidine monohydrochloride, 50-01-1; sodium ethoxide, 141-52-6; malonamide, 108-13-4; cyanoacetamide, 107-91-5.

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Specific Effect of Micellar Microenvironment on an Intramolecular Nucleophilic Anionic Reaction

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Cationic micelles catalyze many nucleophilic anionic reactions,[1] and the exaltation of reactivity, usually 2–100-fold and very often <10,[2] is anion[3-5]—and reaction mechanism[6,7]—dependent. Usually two types of factors can be distinguished as responsible for this catalysis:[2] (1) the substrate and the anion association with cationic micelles through hydrophobic and electrostatic interactions which bring together the reagents in the micelles and lead to an increase of their local concentration and (2) the specific effect of micellar microenvironment, the physical properties of which differ from the rest of the solution.[2] In particular, the hydrogen bond solvating power,[7] as well as the polarity[9] of the micellar medium, is lower than that in water. Electrostatic interactions between positive cationic micelles and negatively charged species they might meet on the reaction path cannot be excluded.[2,8]

It now appears that one of the important obstacles to the better understanding of micellar catalysis is that it is difficult to evaluate the relative importance of concentration and medium effects. Though the role of micellar microenvironment has been demonstrated through the study of unimolecular[8,11] and bimolecular competitive reactions[7] where the same substrate and reagent react by two different mechanisms, there is at present only very little information concerning the specific effect of this medium.

We wanted to elucidate this point, and so we examined the influence of CTAB cationic micelles on a nucleophilic anionic intramolecular reaction. Our choice was the cyclization reaction of salicylaldoximacetate **2** into benzisoxazole **3** in basic medium (Scheme I). For such a model, the structure of **2** first is rigid and second has both nucleophilic and electrophilic centers, which has the advantage of eliminating the proximity and orientation factors. So any observed catalytic effect will be attributed

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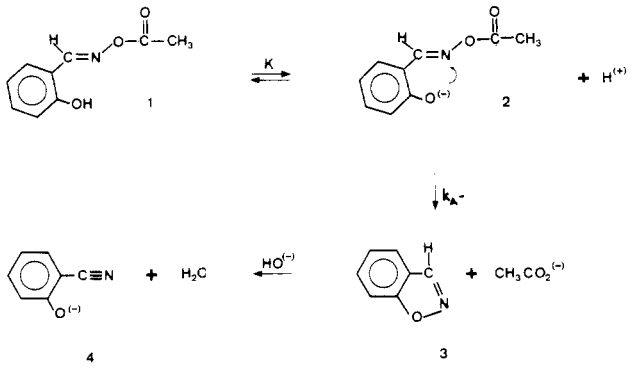
Scheme I



without ambiguity to the micellar microenvironment.

We used 2×10^{-2} M carbonate–bicarbonate buffer at pH 10.15 (20 °C). In these conditions, the observed pH is the same in water and in the presence of 10^{-2} M CTAB, and we verified that the salicylaldoximacetate is fully ionized: so the observed rate constant $k_{obsd} = k_{A^-}$, at which benzisoxazole **3** is produced from **2**.

The disappearance of **2** ($c = 2.10^{-4}$ M) is followed by UV spectrophotometry at 362 nm.

It is likely that **2** is strongly bonded to CTAB micelles owing to electrostatic interactions between the acetate anion of **2** and the quaternary ammonium cations, as well as hydrophobic interactions between hydrocarbon chains of the surfactant and the aromatic ring of **2**, as it has been shown for similar compounds.[2,10] The plot of the observed rate constant in the surfactant solution k_{mobsd} vs. [CTAB] shows that the plateau is reached at [CTAB] $< 10^{-2}$ M: k_{mobsd} is then equal to the one in the micellar phase.

The following chemical and kinetic arguments are in favor of the proposed mechanism. (1) The reaction scheme agrees with the one accepted for the cyclization of some ortho-substituted benzaldoximes[12] and particularly for salicylaldoxime-*O*-sulfonate in basic medium.[13] (2) Though **3**, which is produced in the first step, was not isolated from the reaction medium (because it gives **4**), we nonetheless identified it: we synthesized **3** independently, and we checked that **3** (as does **2**) leads to the same final product **4**, which was identified by its UV, IR, and NMR spectra. (3) The rate constant for the formation of **4**, $k = 3.1 \times 10^{-2}$ min^{-1} ([CTAB] = 10^{-2} M), can be spectrophotometrically determined by following the appearance of the cyanophenate's peak at 335 nm; it is lower than k_{A^-} (vide infra), so we can follow the two consecutive reactions **2** → **3** and **3** → **4**. We checked that this rate constant for the formation of **4** is the same whether we put **2** or **3** into the solution.

The intramolecular rate constant k_{A^-} increases when the reagents are transferred from water into the micellar medium for from 0.35 to 0.85 min^{-1}.

The specific effect of the micellar microenvironment on an intramolecular nucleophilic anionic reaction could be demonstrated in this study. For this reaction, when the products are transferred from water to a micellar medium, the reactivity enhancement is 2.4, which could be considered to be weak.

This enhancement can, in fact, be appreciated by comparison with a bimolecular reaction in which the structure and the reactivity of the nucleophile are as close as possible to those of the monomolecular reaction. We chose the intermolecular attack on *p*-nitrophenyl acetate of the dichlorophenate ion. The nucleophilic centers are in both cases phenate functions which have similar pK values (pK_m = 7.5 ± 0.1 for the dichlorophenate[3] and pK_m = 7.7 ± 0.1 for **2**). Thus the nucleophilic reactivities must be comparable since they are related to the basicity of the reacting species. For the intermolecular reaction, the total maximum micellar effect is about 7. This data takes into account, at the same time, the increase in the local concentration of the reagents in the micellar phase and the influence of the medium on reactivity. It is reasonable to conclude that in this last case, these two factors are of comparable importance. Furthermore, the sensitivity to the solvent effect is larger for intermolecular than for intramolecular reactions.[16]

If the generally observed catalytic effects of CTAB for bimolecular reactions are taken into account, it seems clear that, in addition to the important factor of the proximity of the reagents, micromicellar environment is far from negligible.

In a case such as our model where the negative charge in the initial state is delocalized in the transition state, two interpretations can be proposed for the micellar catalysis: either a better desolvation of the anionic group in the initial state than in the transition state or an electrostatic stabilization of the transition state by the positive charge of the micelle.[1,2] These interpretations were proposed especially for the monomolecular decarboxylation of the 6-nitrobenzisoxazole-3-carboxylate ion[8,15] which is strongly catalyzed by micelles of cationic surfactants.

Experimental Section

The NMR spectra were obtained on a Varian T-60 apparatus with Me_4Si as internal standard. UV spectra and kinetics were recorded on a Beckman ACTA III spectrophotometer in a thermostated cell, the temperature of which was controlled by a thermocouple.

Salicylaldoximacetate **1** was prepared by a standard method.[17] Benzisoxazole **3** was redistilled before use. Cyanophenol **4** was a commercial Aldrich reagent. CTAB was the Merck AR product.

Identification of the Products of the Reaction. A solution of 250 mL of 10^{-3} M salicylaldoximacetate **1**, 10^{-1} M CTAB and 2×10^{-1} M carbonate–bicarbonate solution was left 1 day at room temperature. A saturated solution of KI was then added to eliminate most of the surfactant. The precipitate was filtered, and the aqueous solution was extracted with ether. The ether layer was washed (H_2O), dried ($MgSO_4$), and evaporated to give the product.

The same procedure as above was followed with the omission of CTAB and KI. The product obtained was identified as cyanophenol **4** by NMR, UV, and IR spectrophotometry.

Determination of k_{A^-} and K_m. The pK of **2** was only estimated by a kinetic method since **2** is rapidly transformed into **3**. The following equations were used for the micellar solution.

$$v_m = k_{A^-_m}[A^-]_m = k_{mobsd}[A_T]_m \qquad K_m = [A^-]_m[H^+]_m/[AH]_m$$

$$[A^-]_m = [2]_m \qquad [A_T]_m = [1]_m + [2]_m$$

We obtained then $1/k_{mobsd} = 1/k_{A^-_m} + [H^+]/k_{A^-_m}K_m$. The plot of $1/k_{mobsd}$ vs. $[H^+]_m$ gives $k_{A^-_m}$ and K_m.

The different values of $[H^+]_m$ were obtained by working in several carbonate and "Tris" buffers.

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Registry No. **1**, 59417-52-6; **3**, 271-95-4; **4**, 611-20-1.

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