Cyclization and Molecular Rearrangement Under Micellar and Microemulsion Conditions

Brajesh K. Jha, Ajay S. Chhatre and Bhaskar D. Kulkarni*
Chemical Engineering Division, National Chemical Laboratory,† Pune-411 008, India

Reaction procedures for Beckmann rearrangement and cyclization can be improved substantially if carried out under micellar/microemulsion conditions. This mode of operation allows the use of dilute acids as against the conventional highly acidic medium with ease of product recovery and yield. Experimental results for a case example of D-(−)-*N*-carbamoyl phenyl glycine to phenyl hydantoin are presented and analysed.

Surfactants are known to play a definite role in the process of self-organization leading to the formation of aggregates known as micelles. A microemulsion is one such assembly composed of at least four components, namely oil, water, the surfactant and a co-surfactant, which supports the interfacial activity of the surfactant. The presence of co-surfactant may be critical since it determines the level of the interfacial tension between the oil and water components. The collective behaviour of each of the above mentioned components can be best described by a pseudo-ternary or a quaternary phase diagram, which shows various distinct regions: single phase; two phase; bicontinuous; lamellar; and the three phase domains. These domains often reveal some unusual but interesting properties that are specific to them and can be gainfully exploited.

Thus micellar and reversed micellar systems have been used as media for conducting numerous organic and inorganic reactions.[1] Solubilization in such pseudo-phases brings about variation in the rates that can be attributed to electrostatic, hydrophobic, electrophilic and/or nucleophilic interactions, resulting in changing the free energy of activation of the process.[2,3] The microemulsions, by virtue of their large interfacial area, enhance transport and therefore the rates of chemical reaction. The microdroplet acts as a microreactor and has been exploited in obtaining uniform particle distribution in polymerization reactions, the formation of ultrafine semiconductor[4] and theoretical-density microhomogeneous superconducting materials[5] and development of new methods in organic synthesis.[6] In addition to its use as a medium for reactions, other properties such as ease of preparation, stability, low viscosity and interfacial tension and molecularly ordered interface have proven to be useful in technological applications.

Chemical reactions in micellar/microemulsion media have been extensively investigated and it is generally recognized that micelles can catalyse the reaction by concentrating the reagents in the region occupied by the surfactant head group. This region is referred to as Stern layer.[1,7] The rate constants of the catalysed reactions generally depend on the surfactant concentration and vary with it to exhibit maxima. Such maxima occur due to two opposing effects: a higher concentration of surfactants draws more reagent into the micelle, but also leads to an increasing total volume of the Stern layer, thereby diluting the concentration at the micellar surface. A few reactions such as rearrangement of the benzidine molecule,[8] binding of hydrogen ions to anionic micelles[9] and cyclization of terpenoids[10] have shown significant improvements in the rate of reaction in micellar media. In general it is anticipated that all those reactions which involve the participation of hydrogen ions, either as a reactant or as a catalytic species, can benefit substantially in such media.

We herein report the reaction of the D-(−)-*N*-carbamoyl derivative of phenyl glycine with sulfuric acid and the advantages of having a micellar/microemulsion solution as a reaction medium. We concentrate on exploiting one very important property of microemulsion solutions for carrying out this reaction. The particular property of interest to us concerns the anomalous H^+ ion concentration experienced in certain regions of the phase space. The lack of accurate information about the hydrogen ion concentration in such systems has often hindered interpretation of many experimental results.[11] The question of determining the strength of an acid or a base in microemulsion systems has been vigorously pursued in the past years and the problem is complicated due to changes in the acid dissociation constants.[12] Notwithstanding the developments and the difficulties in the accurate determination of acid concentration, the fact remains that anomalous changes in acid strengths do occur in certain phase volumes of the system.

Experimental

Sodium dodecyl sulfate obtained from Loba Chemicals (AR grade) was used as a surfactant. Fluka guaranteed pentan-1-ol (AR grade) was used as a co-surfactant. Concentrated H_2SO_4 was obtained from SD chemicals and was diluted to the required strength using distilled water. The exact concentration of H_2SO_4 was determined by titration with standardized 0.5 mol dm^{-3} sodium hydroxide solution. The D-(−)-*N*-carbamoyl derivative of phenyl glycine was chemically synthesized in the laboratory and was purified by recrystallization.

We have recently reported the phase behaviour of the micellar/microemulsion system comprising sodium dodecyl sulfate (SDS), pentan-1-ol and aqueous sulfuric acid.[13] The aqueous sulfuric acid vertices of each of these triangular phase diagrams are of interest to us in the present investigation, and these have been shown in Fig. 1 As can be appreciated from these figures, in a region close to the transition from a single phase to a two phase to a three phase region (marked as A in the figure) the local concentration of the reactants are relatively high in some of the colloidal assemblies. We carried out the cyclization of the D-(−)-*N*-carbamoyl derivative of phenyl glycine to phenyl hydantoin in this region. It may be noted that the conventional D-(−)-*N*-carbamoyl derivative of phenyl glycine is usually obtained from phenyl hydantoin using a microbial route.[14] The present system accomplishes the reverse step using a non-enzymatic route. In addition, we have exploited this region for carrying out the rearrangement of cyclohexanone oxime to caprolactam. It may be noted that

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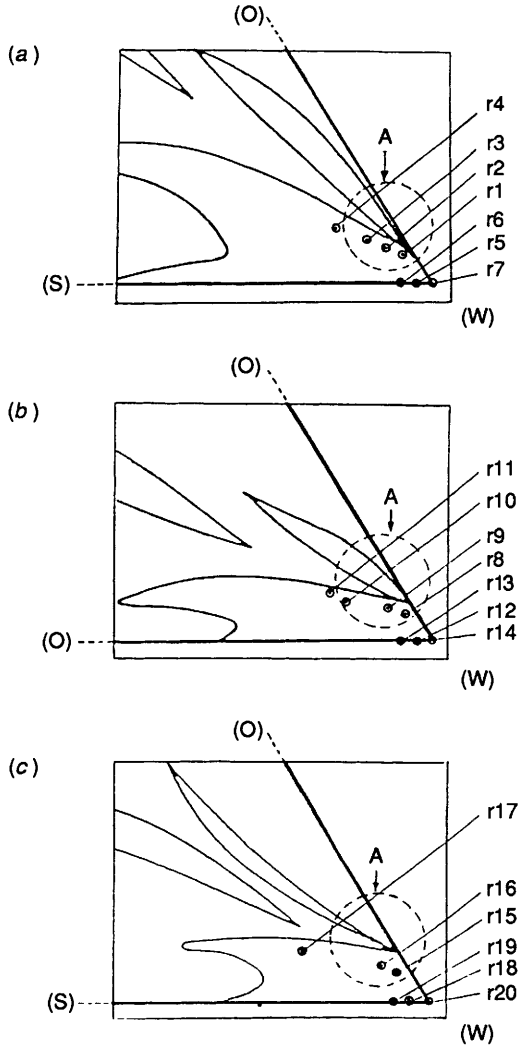

Fig. 1 Sulfuric acid apex of the pseudoternary phase diagram of the micellar/microemulsion system comprising SDS (S), aqueous H_2SO_4 (W) and pentan-1-ol (O). Experimental points r1 through r20 represent the compositions used in Runs 1 through 20 respectively. Strength of aqueous H_2SO_4 (*a*) 0.27, (*b*) 0.54, (*c*) 1.08 mol dm^{-3}.

the conventional method for this reaction requires highly concentrated sulfuric acid.[15]

We have selected a set of compositions of various micellar or microemulsion solutions from the above mentioned phase diagrams, for carrying out the cyclization of D-(−)-*N*-carbamoyl phenyl glycine to phenyl hydantoin (Runs 1–20) in the first part of the experiments. The different micellar/microemulsion systems studied and the percentage composition of various media used in the present work are reported in Table 1. Runs 1–6, 8–13 and 15–19 correspond to micellar/microemulsion solutions containing SDS and pentan-1-ol in 0.27, 0.54 and 1.08 mol dm^{-3} H_2SO_4 respectively. Runs 7, 14 and 20 correspond to aqueous solutions of 0.27, 0.54 and 1.08 mol dm^{-3} H_2SO_4 containing no surfactant or co-surfactant. Taking into consideration the solubility data reported earlier,[13] 4.00 g of D-(−)-*N*-carbamoyl phenyl glycine was added to 100 cm^3 of each of the above mentioned solutions so that the reaction mixture in most of the runs was always saturated with respect to D-(−)-*N*-carbamoyl phenyl glycine. The reaction mixture was maintained at 25 °C with stirring for 24 h after which the solution was vacuum filtered to remove the solid undissolved D-(−)-*N*-carbamoyl phenyl glycine. The filtrate was analysed quantitatively by HPLC technique as described elsewhere.[13]

Results and Discussions

The analysis of 100 cm^3 of the filtrate of the product mixture is reported in Table 1. The percent conversions are calculated on the basis of net D-(−)-*N*-carbamoyl phenyl glycine solubilized at the end of 24 h. It can be seen from Table 1 that the conversion of D-(−)-*N*-carbamoyl phenyl glycine to phenyl hydantoin after 24 h of the reaction is much better in the case of microemulsions (Runs 1–4, 8–11 and 15–17) than those in the cases of micellar solutions (Runs 5 and 6, 12 and 13, 18 and 19) or pure aqueous sulfuric acid (Runs 7, 14 and 20). The analysis also indicates selective formation of phenyl hydantoin, besides unreacted solubilized D-(−)-*N*-carbamoyl phenyl glycine in the product filtrate.

All of the above micellar/microemulsions are of oil-in-water type. Monomeric surfactant SDS and added solutes D-(−)-*N*-carbamoyl phenyl glycine diffuse into the micelles or microemulsion droplets, and in view of their large interfacial

Table 1 Composition of reaction medium[a] and analysis of 100 cm^3 of the filtrate of the product mixture after 24 h reaction time

Conc. H_2SO_4/ mol dm^{-3}	Run No.	S (%)	W (%)	O (%)	*N*-Carbamoyl phenyl glycine unreacted/g	Net phenyl hydantoin formed/g	Conversion (%)
0.27	1	0.67	97.10	2.23	0.601	2.843	83.9
	2	1.40	96.10	2.50	0.924	2.610	75.7
	3	2.00	95.00	3.00	1.426	2.183	62.8
	4	4.00	92.00	4.00	1.988	1.089	37.6
	5	1.00	99.00	0.00	0.988	traces	—
	6	2.00	98.00	0.00	1.349	traces	—
	7	0.00	100.0	0.00	0.132	nil	—
0.54	8	0.67	97.10	2.23	0.680	2.547	80.5
	9	1.40	96.10	2.50	1.381	1.966	61.1
	10	4.00	93.00	3.00	2.792	1.091	30.1
	11	4.50	91.00	4.50	2.808	1.077	29.7
	12	1.00	99.00	0.00	0.728	0.063	8.7
	13	2.00	98.00	0.00	1.538	0.084	5.7
	14	0.00	100.0	0.00	0.116	traces	—
1.08	15	0.67	97.10	2.23	0.344	2.903	90.3
	16	1.40	96.10	2.50	0.791	2.891	80.1
	17	6.00	90.00	4.00	2.240	1.588	43.8
	18	1.00	99.00	0.00	0.441	0.079	16.5
	19	2.00	98.00	0.00	1.116	0.086	7.8
	20	0.00	100.00	0.00	0.056	0.031	37.8

[a] At 25.0 °C; percentage by weight: SDS (S); H_2SO_4 (W); pentan-1-ol (O).

area it is anticipated that the transfer of material between water micelles or microemulsion droplets is much faster than the activated thermal reactions. Reaction typically occurs at the micellar surface in the Stern layer which contain specially bound counterions. The underlying mechanism in obtaining such an improvement depends on the concentration of micellar bound hydrogen ions rather than on the total H^+ concentrations.[16,17] D-(−)-*N*-Carbamoyl phenyl glycine molecules at the interface orient themselves with their carbamoyl groups and the acid groups extended into the Stern layer of the droplet, where the reaction proceeds more efficiently, and then favours the cyclization.[18,19] The product phenyl hydantoin may partition itself between the droplet interface and the bulk aqueous phase. Enhancement of the conversion can also be attributed to the increased concentration of reactant at interface. The results for the reaction reported here are generic in character and other similar reactions and typically those involving Beckmann rearrangement can substantially benefit from this mode of operation. Preliminary results on rearrangement of cyclohexanone oxime to caprolactam have shown very promising results.

Conclusions

Cyclization reactions as carried out conventionally require highly acidic conditions and operation and handling, especially on larger scales, often prove to be difficult. In addition, product purification and recovery from such systems is problematic. The results obtained in the present studies suggest that micellar or microemulsion solutions of anionic surfactants in dilute acids can be looked upon as an alternative medium for these reactions which otherwise required drastic conditions. Also those reactions which require H^+ as a catalytic species can benefit substantially in such micellar/microemulsion media.

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