

Sorensen Buffer—Table VI lists the literature and calculated values along with the experimentally determined values of pH for the 10 official phosphate buffer mixtures. It can be seen that the pH values reported by Sorensen (10) and cited by Goyan and Hind (4) in their formulation of isotonic phosphate buffer mixtures which have been transcribed into the USP (8) and NF (9) agree quite well with the experimental values obtained in this study at 25°. However, it should be pointed out that the pH values found in the USP (8) and NF (9) are somewhat ambiguous since they do not represent isotonic buffers' pH values as they might lead one to suspect; but instead represent the buffer mixtures' pH before the addition of the appropriate amounts of sodium chloride needed to render the solution isotonic. A rigorous approach involving all phosphate equilibria, mass balance, and charge balance was employed in calculating the pH. Because of the complexity of the relationship that results from such a rigorous approach, a computer (IBM-1130) was used to perform the required Newton-Raphson iteration. It can also be noted in Table VI that tonicity values calculated from freezing point depression data of the buffer mixtures are somewhat lower than those determined experimentally with the osmometer at 37°. This seems to indicate that at higher temperatures the ability of phosphate species to associate is slightly diminished. This was found to be true when the phosphate salts' *E* values were reviewed. Table II illustrates that the *E* values of both phosphate salts are 5 to 10% higher at 37° than at 0°. The pH values of the buffer mixtures at 37° are also included in Table VI.

The compilation of the data obtained in the re-evaluation of the official isotonic phosphate buffer found in Table VII demonstrates that the 10 buffer mixtures that were calculated to be isotonic at 0° are slightly hypertonic at 37°. The resulting solutions were hypertonic due to the low tonicity values assigned to the buffer mixtures which dictated the quantities of sodium chloride that would be necessary to render the buffers isotonic. The pH values for these buffer mixtures at 25 and 37° are listed in Table VII. The USP (8) and NF

(9) do not list such values; however, it was thought more important to know the pH of the resulting mixtures than the pH of the buffer mixture itself.

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Determination of Micellar Weights for Di-Alkyl Sodium Sulfosuccinates in Anhydrous and Hydrated Hydrocarbon Solutions

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Abstract □ Previous studies have demonstrated that di-(2-ethylhexyl) sodium sulfosuccinate, dissolved in various hydrocarbon solvents, is capable of solubilizing large amounts of water, whereas closely related compounds such as the di-*n*-octyl and di-*n*-hexyl derivatives exhibit negligible solubilizing capacity. In view of these observations the micellar size of these three compounds in *n*-octane was measured by light scattering. Large differences in micelle weight between di-(2-ethylhexyl) sodium sulfosuccinate in *n*-octane (13,000) and the other compounds (about 200,000) suggested a significant role for the 2-ethyl side chain. The active participation of water in the organization of these micelles is suggested by significant changes in micellar weight, well in excess of that accounted for by the added amount of water. The influence of different hydrocarbon solvents on micellar weight also was found to be quite significant.

Keyphrases □ Di-Alkyl Na sulfosuccinates—micellar weights □ Micellar weight determination—*n*-anhydrous, hydrated hydrocarbon systems □ Cohesive energy—micellar size □ Light scattering spectrometry—micellar weights □ Refractive index—micellar solutions

when relatively large amounts of water and lipids or oils are dispersed in the presence of surface-active micelle-forming molecules. Of particular concern, presently, is the ability of surface-active agents to solubilize water in nonpolar solvents. Pharmaceutical situations where this may be important include the formulation of clear oil-soluble liquids or gels to be applied to the skin, or the formulation of nonaqueous solutions for the depot injection of water-soluble allergenic extracts and vaccines. More basic still is the application of such knowledge toward an understanding of the properties of water at interfaces, particularly biological interfaces such as membranes.

Previous studies have demonstrated that di(2-ethylhexyl) sodium sulfosuccinate¹ dissolved in various hydrocarbon solvents is capable of solubilizing relatively large amounts of water (1-4), comparable to that solubilized by lecithin (5) and the more complex micro-

The present study is part of an overall effort to gain an understanding of the complex equilibria produced

¹ Supplied commercially as Aerosol OT by the American Cyanamid Co.

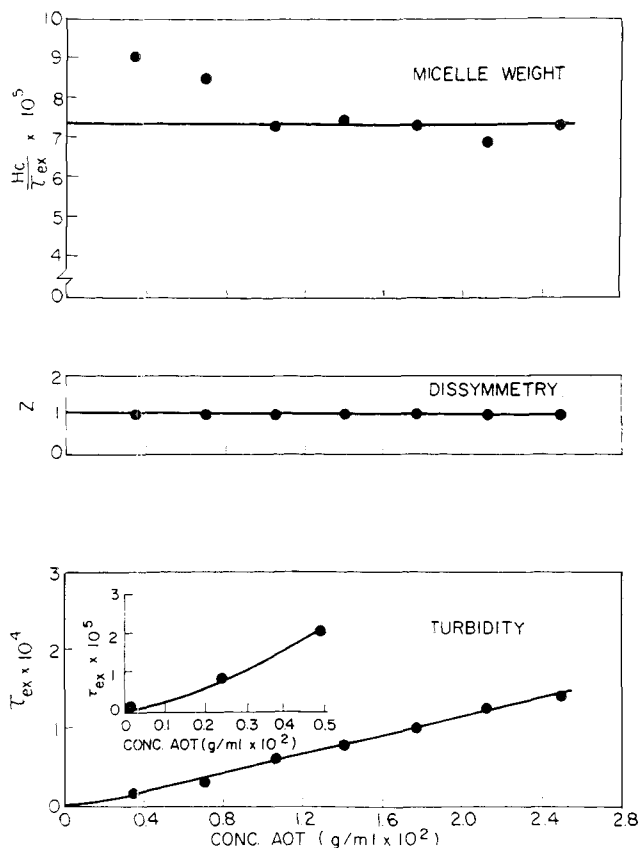


Figure 1—Light-scattering study of a di-(2-ethylhexyl) sodium sulfosuccinate (AOT)-*n*-octane system at 25°.

emulsion systems (6). In general the longer the chain length of the aliphatic hydrocarbon solvent the lower is the amount of water solubilized (1, 4). In contrast to this behavior, closely related compounds, di-(*n*-octyl) sodium sulfosuccinate and di-(*n*-hexyl) sodium sulfosuccinate, exhibit little ability to solubilize water in any hydrocarbon solvent (4).

In view of these observations, a light-scattering study was conducted in order to determine the effect of (a) increasing amounts of water and (b) hydrocarbon solvent chain length and structure on the micellar weight of di-(2-ethylhexyl) sodium sulfosuccinate. Studies with this compound in the absence of water also were carried out in a number of hydrocarbon solvents. Since appreciable amounts of the *n*-hexyl and *n*-octyl derivatives are not soluble except in *n*-octane, comparisons among the three alkyl sulfosuccinates were possible only in this solvent.

EXPERIMENTAL

Materials—Di-(2-ethylhexyl) sodium sulfosuccinate (AOT), di-(*n*-hexyl) sodium sulfosuccinate (AMA), and di-(*n*-octyl) sodium sulfosuccinate (OOT) were synthesized and purified according to procedures described previously (7, 8). Surface tension measurements indicated no minima at the critical micelle concentration (CMC) and values of CMC in good agreement with previously reported values (9, 10).

The hydrocarbon solvents, *n*-octane, dodecane, and hexadecane (Aldrich Chemical Co.), and *n*-decane and tetradecane (Eastman Organic Chemicals) were treated according to the method of Gillap *et al.* (11). Cyclohexane (Matheson, Coleman and Bell) was spectroquality and was twice distilled. Specific gravities deter-

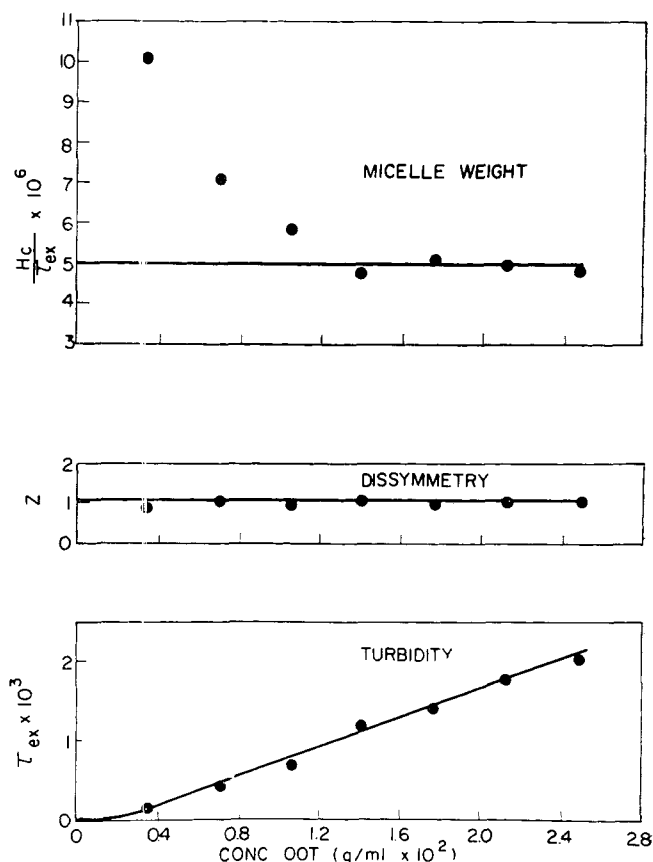


Figure 2—Light-scattering study of a di-(*n*-octyl) sodium sulfosuccinate (OOT)-*n*-octane system at 25°.

mined for all solvents were in excellent agreement with previously reported values (12, 13). The water used was twice distilled.

Instrumentation—Light-scattering measurements were made with a light-scattering photometer (Brice-Phoenix Universal, model series 2000, Phoenix Precision Instrument Co.), equipped with a cored cell jacket and cell table for temperature control at 25 ± 1°. An electrometer (Keithley model 610B) was substituted for the usual galvanometer as suggested by Abramson (14), to provide greater stability and faster readings. All measurements were made using incident light having a wavelength of 546 m μ . Differential refractive index measurements were made with a differential refractometer (Brice-Phoenix model BP 2000V) with a closed cell for volatile solvents. As above, a wavelength of 546 m μ was utilized.

Procedure—Samples for light-scattering measurements were prepared by a procedure described previously (4), and equilibrated with agitation at 25 ± 0.1° for 24 hr. to 2 weeks before use. All extraneous scattering elements were removed by positive pressure filtration through a vinyl fluoride membrane filter (Gelman Instrument Co., VF-6, 0.45- μ pore size) contained in a stainless steel filtration apparatus (Millipore Corp.). Filtration was made directly into the light-scattering cell; the cell was rinsed twice with filtrate prior to collection of a sample for measurement. Turbidity was measured in a cell (Phoenix Precision Instrument Co., T-101), while the dissymmetry measurements, at 45 and 135° to the incident beam, were made in a Zimm-type cell (15). A diaphragm (Phoenix Precision Instrument Co., K-342) was required to reduce the incident beam width for the dissymmetry measurements.

RESULTS

Anhydrous Surfactant-Solvent Systems—The light-scattering results for AOT, AMA, and OOT in *n*-octane are given in Figs. 1-3. The bottom plot in each figure depicts the excess turbidity, τ_{ex} , of each solution as a function of surfactant concentration, where τ_{ex} is the portion of total turbidity in excess of that due to pure solvent. The middle plot in each figure depicts the dissymmetry values which in all cases were very close to one. The top plot in

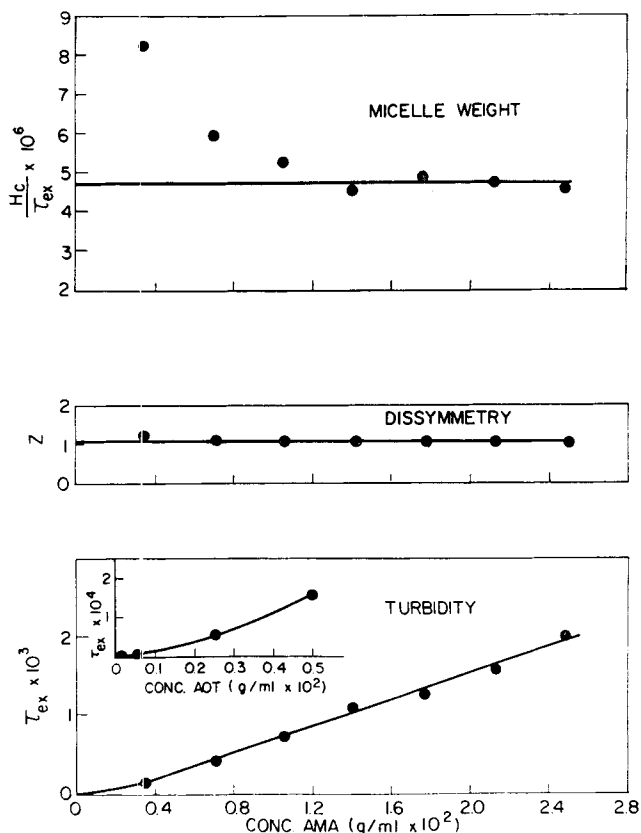


Figure 3—Light-scattering study of a di-(*n*-hexyl) sodium sulfosuccinate (AMA)-*n*-octane system at 25°.

each figure is used to obtain the micellar weight, M , by application of the Debye equation (16)² the intercept of this plot being equal to $1/M$. Since the concentration range where an apparent CMC may occur is negligible compared to concentrations exhibiting significant turbidity, extrapolations to obtain $1/M$ have been made to zero concentration. Due to the uncertainty of turbidity values and the marked curvature upward in the Hc/τ_{ex} versus concentration plots in this region, extrapolations were made utilizing only the more concentrated solutions (25).

Table I lists the apparent micellar weight for the three surfactants in *n*-octane while the values for AOT in other hydrocarbon solvents are given in the first line of Table II. In view of the inherent error associated with light-scattering measurements of small micelles and the uncertainty of extrapolation to $1/M$, the agreement of these results with other studies utilizing light-scattering and ultracentrifugal techniques is quite good. Based on light-scattering measurements, Ko-no *et al.* (17) have reported a value of $25,000 \pm 15\%$ for AOT in cyclohexane, and Peri (18) has reported $11,500 \pm 10\%$ for AOT in *n*-nonane. Using the ultracentrifuge, Mathews and Hirschorn (2) have obtained a value of 14,000 for AOT in dodecane, while Peri (18) obtained a value of 12,600 with the same system. As in the present case (Table II), Peri observed small increases in micellar weight with increasing hydrocarbon solvent chain length (18). No values for OOT and AMA have been reported previously.

Water-AOT-Solvent Systems—The results obtained with the various hydrous systems are given in Table II, with typical light-scattering data being given in Fig. 4. Calculations of micellar weight were made according to the method of Elworthy and McIntosh (19), who concluded that the Debye equation, which is defined for binary systems, can be applied to ternary systems if it is assumed that all of the water is associated with the surfactant. In view of the very low solubility of water in hydrocarbon solvents

² $Hc/\tau_{ex} = 1/M + 2BC$, where $H = [(32\pi^3 n_0^2)/(3N\lambda^4)](dn/dc)^2$, n_0 is the refractive index, λ is the wavelength of incident light, N is Avogadro's number, dn/dc is the differential refractive index between solvent and a solution of concentration, c , and B is the second virial coefficient.

Table I—Micelle Weights of Di-Alkyl Sodium Sulfosuccinates in *n*-Octane at 25°

Surfactant	Micelle Weight	Aggregation Number	Dissymmetry
AOT	13,500	31	1.00
AMA	211,900	546	1.05
OOT	201,200	453	1.05

(20) and the low apparent CMC of AOT in hydrocarbon solvents, it is quite reasonable to expect little free water and AOT to be present in this particular system. The values obtained in this manner are in reasonable agreement with ultracentrifugal studies utilizing AOT-water-dodecane (2), with large micelles occurring as the point of maximum water solubilization is approached. The large values obtained at higher molar ratios of water to AOT are subject to some error due to possible polydispersity in the size of micelles, which weights the micellar weight in favor of the larger micelles, and to the possibility of critical opalescence which produces high intensities of scattered light as a system nears phase separation (21). Unfortunately, the Debye equation is not valid under these conditions and quantitative interpretations of micellar size near the point of phase separation is not possible.

DISCUSSION

Comparison of AOT, OOT, and AMA—The major driving force for micelle formation in surfactant-hydrocarbon systems is the lack of affinity between the polar portion of the surfactant and the solvent molecules. In such systems the chain length of the surfactant plays a minor role, in contrast to aqueous systems where the major factor is the lack of affinity between water and the alkyl groups. The lack of any significant difference in micelle weight between OOT and AMA in *n*-octane is in keeping with this concept since their polar portions are identical and their hydrocarbon chain lengths differ by only two methylene groups. The marked difference noted for AOT micelles, however, suggests that another factor, the presence of a branched alkyl group, plays a significant role in these systems.

Since the cross-sectional area of the hydrocarbon portion of the dialkyl sodium sulfosuccinates exceeds that of the polar sulfonate group, the most sterically favored arrangement of these molecules in a nonpolar solvent is the clustering of polar groups into an inverted aggregate or micelle, having spherical or near spherical shape. Based upon the micellar weights reported for various AOT-hydrocarbon systems and hydrodynamic data from viscosity measurements (2, 18), a slightly asymmetric shape is more likely than an exactly spherical shape. Any factor which will increase the cross-sectional area of the hydrocarbon portion of the surfactant will greatly facilitate the formation of smaller micelles having a high degree of curvature, while still retaining closest packing of the oriented molecules. The significant difference in molecular configuration between AOT and OOT is shown in Fig. 5 by the use of space-filling molecular models, and indeed, the AOT molecule appears to have a bulkier hydrocarbon portion than OOT. The significance of the branched chain of AOT on molecular organization is further emphasized when one realizes that AOT is amorphous

Table II—Micelle Weights in Water-AOT-Hydrocarbon Solvent Systems at 25°

Moles water/mole AOT	<i>n</i> -Octane	<i>n</i> -Decane	Dodecane	Hexadecane	Cyclohexane
0	13,500	16,500	19,400	24,200	17,400
2.5	25,500	22,600	30,200	31,800	21,000
5.0	37,600	43,000	53,600	57,100	33,900
10.6	105,000	125,000	133,000	^a	Turbid
15.0	133,000	303,000	833,000	Turbid	Turbid
22.6	Turbid	Turbid	Turbid	Turbid	Turbid

^a At 7.5 moles of water/mole of AOT; micelle weight = 154,000.

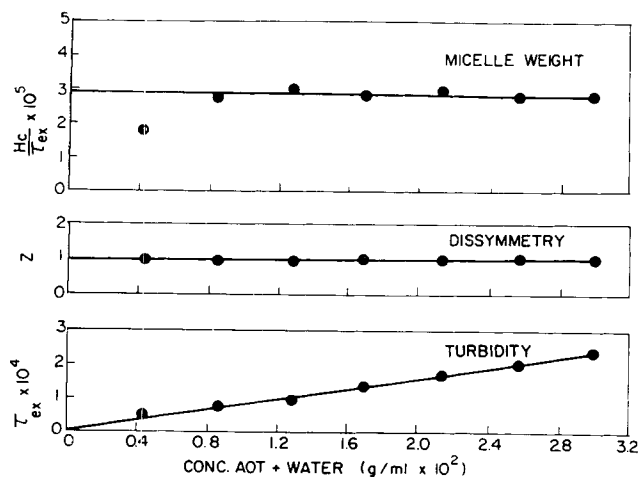


Figure 4—Light-scattering study of a water-AOT-n-octane system at 25°, with 5 moles of water/mole of AOT.

in the solid state and capable of exhibiting liquid crystalline behavior (22). In contrast, OOT and AMA are crystalline and do not exhibit such behavior. It appears, therefore, that OOT and AMA form relatively large micelles in *n*-octane because strong chain-chain interactions prevent a high degree of curvature in the micelle. The insolubility of OOT and AMA in the higher molecular weight *n*-aliphatic solvents suggests an even greater ability to form large aggregates which easily precipitate. On the other hand, significant chain-chain interactions between AOT molecules appear to be more restricted resulting in the smaller micelles.

Hydrous Systems and the Effects of Solvent—Ordinarily in surfactant-water-hydrocarbon solvent systems one would think that water should be solubilized in the polar portion of a micelle by interaction with the polar groups of the surfactant molecules. If the increase in micellar weight due to solubilized water reflects the addition of water to the original anhydrous micelle, it should be accounted for quantitatively by the weight of added water (19). That this is not the case in the present study is shown in Table III, where values calculated on the basis of an anhydrous micelle weight plus the weight of added water are compared with experimental values. In all calculations a spherical shape was assumed, which is in agreement with the results of Mathews and Hirschorn (2) for the water-AOT-dodecane system. The assumption made in these calculations is that closest packing of surfactant monomers is retained when water is incorporated into the micelle. This assumption is supported by X-ray-scattering studies on concentrated AOT solutions in hydrocarbon solvents, where despite the addition of water, the lateral distance between surfactant monomers in the micelle remains the same (23). It would appear, therefore, that in order to obtain such micellar weights and retain closest packing of monomers, a reorganization of micelles must occur with each

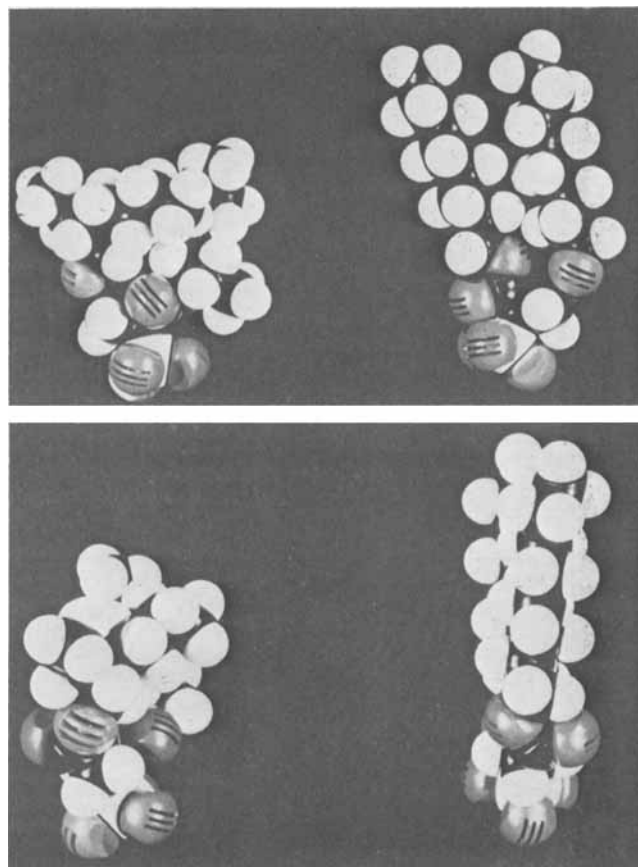


Figure 5—Comparison of AOT (left) and OOT (right) molecular structure from two directions, using space-filling molecular models.

addition of water. Such reorganization should lead to fewer and larger micelles, as the concentration of AOT remains constant. It is suggested that the presence of the ethyl side chain provides the flexibility required to reorganize the micelles just as it allows AOT to exhibit various lyotropic liquid crystalline phases (22). On the other hand, the lack of such flexibility limits any tendency for such reorganization in the OOT and AMA systems.

One can gain some insight into the effects noted for the different solvents by assuming, in part, that those factors influencing anhydrous micellar systems are also involved in the formation of hydrous micelles. The tendency to form such micelles will depend on the affinity between water and surfactant polar groups, and the hydrocarbon solvent, as well as the cohesive energy of the solvent. For hydrocarbon solvents with little affinity for polar groups, the

Table III—Micelle Weights in Water-AOT-Hydrocarbon Solvent Systems at 25°

Moles water/ Mole AOT	<i>n</i> -Octane		<i>n</i> -Decane		Dodecane	
	Predicted	Expt.	Predicted	Expt.	Predicted	Expt.
0	—	13,500	—	16,500	—	19,400
2.5	14,945	25,500	18,170	22,600	21,380	30,200
5.0	16,340	37,600	19,830	43,000	23,360	53,600
10.6	19,470	105,200	23,560	125,000	27,790	133,000
15.0	21,920	133,000	26,700	303,000	31,300	833,000
22.6	Turbid		Turbid		37,300	
Moles water/ Mole AOT	Hexadecane		Cyclohexane			
	Predicted	Expt.	Predicted	Expt.		
0	—	24,200	—	17,400		
2.5	26,680	31,800	19,160	21,000		
5.0	29,150	57,100	20,910	33,900		
10.6	^a	^a	Turbid			

^a Turbid at 10.6, at 7.5 moles water/mole AOT. Predicted, 31,620; expt. = 154,000.

stronger the cohesive energy or intermolecular attraction of the hydrocarbon solvent, the greater the tendency for polar groups to be "pushed" out of solution, and to aggregate into micelles. On this basis alone one would expect larger micelles to be produced with increasing chain length of the *n*-aliphatic solvents, as is the case for anhydrous and hydrous AOT micelles in this study. Such behavior could also explain the formation of smaller micelles seen in cyclohexane since its cohesive energy is lower than most of the *n*-aliphatic solvents.

Once the micelle forms, other factors to be considered are the hydrocarbon chain-chain interactions within the micelle, and the chain interactions between the micelle and solvent. One might expect solvent to penetrate into the micelle monolayer to some extent, if the state of the monolayer is not too highly condensed, thus producing a tendency for smaller micelles. This might be the case for the less condensed AOT monolayer (because of the bulky side chains), whereas less solvent penetration would be expected for the more tightly packed AMA and OOT molecules. Cooke and Schulman (24) in an attempt to demonstrate the effect of hydrocarbon solvents on microemulsion systems, measured solvent penetration into monolayers. They concluded, as one might anticipate, that at high surface pressures solvent penetration will not act as a determining factor in the area per molecule at the interface, but rather, solvent will be ejected from the monolayer. However, they did not exclude the possibility of partial solvent penetration at more moderate surface pressures, producing a slight solvation of the micelle. This suggestion also has been made by Peri for anhydrous AOT micelles (18). All solvents should be able to solvate micelles to some extent, but from a steric point of view perhaps the shorter chain solvents and cyclohexane may be favored as they are similar in length to the hydrocarbon chains of the surfactant and can align themselves more easily than can the longer higher molecular weight hydrocarbons.

Whatever the exact mechanism may be, it is clear that relatively small changes in the amount of water solubilized and the nature of the hydrocarbon solvent exert significant effects on the size of AOT micelles. In addition there appears to be a correlation between factors influencing micelle size and those influencing water solubilization; the smaller the micelle at any water-AOT ratio the less the chance for phase separation. The one exception to a simple explanation of size *versus* solubilization capacity is the fact that AOT in cyclohexane has limited water solubilization yet its micelle remains quite small upon the addition of water. This, perhaps, suggests a different mechanism for the limit on solubilization in the cyclohexane system, or an additional factor, not solely related to micelle size, operating for all solvents but more obvious with cyclohexane. Further studies designed to elucidate the mechanisms involved in the solubilization process are currently being carried out to test these ideas.

SUMMARY

The micellar weights of di-(2-ethylhexyl) sodium sulfosuccinate (AOT), di-(*n*-octyl) sodium sulfosuccinate (OOT), and di-(*n*-hexyl) sodium sulfosuccinate (AMA) in *n*-octane have been measured by light scattering and found to be 13,500, 201,200, and 211,900, respectively. Differences in the latter two values and that of AOT have been attributed to steric factors associated with the bulky ethyl side chain of AOT.

The micellar weight of AOT in various hydrocarbon solvents in the absence and presence of water has been measured. Increasing the chain length of the *n*-aliphatic hydrocarbon solvents increases the micellar weight for a given ratio of water to AOT. Correlation of micellar size with the cohesive energy of these solvents and pos-

sible solvent penetration into the micellar structure has been discussed.

The active participation of water in the organization of the AOT micelle is suggested by significant changes in size, well in excess of that accounted for by the added amount of water.

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