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Photoreactions of Charged Benzophenone with Amphiphiles in Micelles and Multicomponent Aggregates as Conformational Probes

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Abstract: Photolysis of mixed micelles composed of sodium dodecyl sulfates (SDS) and benzophenone-4-carboxylate leads to insertion of the benzophenone carbonyl into the SDS chain. Degradative methods are described by which the distribution of functionalization positions can be determined. The data show that attack occurs over almost the entire chain, from C-5 to C-11; with the same benzophenone probe and sodium hexadecyl sulfate attack occurs from C-5 to C-15. The random distribution suggests extensive coiling and folding of the detergent chains. Photolysis of hexadecyltrimethylammonium bromide (CTAB) with benzophenone-4-trimethylenetrimethylammonium bromide confirms this picture. Photolysis of CTAB with benzophenone-4-butyrate below the critical micelle concentration leads to highly selective attack at C-15 ascribed to ion pairs or clusters, while in the concentration region for micelle formation it becomes more random. The reaction of CTAB at micellar concentrations with benzophenone-4-carboxylate, -propionate, -butyrate, and -pentanoate shows that attack on C-15 of CTAB, at the end of the chain, *decreases* as the probe is lengthened. This remarkable finding also suggests folding of the detergent chain. The distribution is characterized by a new parameter, R_f. Studies of this parameter as a function of concentration and with added sterol or dodecanol confirm many of the previous pictures of micellar structures, but show that these structures are not rigid enough to lead to synthetically useful selective reaction.

Introduction

Some years ago we developed the use of benzophenone photochemistry for the selective functionalization of steroids.[1] This then led to the selective halogenation of steroids by the use of rigid free-radical reagents or templates.[2] Although such processes can be quite attractive and synthetically useful, they depend on the rigidity of both the reagent and the steroid substrate in order that significant geometric control of the chemistry ensue. With flexible substrates the attack by the attached benzophenone or phenyliodine dichloride reagents is quite nonspecific.[3] Conformational information, but not useful synthetic transformations, can be obtained.

We decided to explore the selectivity of such reactions for flexible substrates incorporated in micelles. In simple micelles physical studies[4] indicate that the chains are "liquid-like", but this could still allow some ordering relative to flexible chains in solution. Furthermore, at high concentrations amphiphiles can undergo transitions to new phases with considerable ordering of the chains, resembling bilayers.[5] Thus our studies promised to supply information on the amount of ordering attained. It was also possible that synthetically useful selectivity could be achieved if sufficient orientation were present.

As flexible substrates which can form micelles, we have studied cetyltrimethylammonium bromide (CTAB, **1**), sodium cetyl sulfate (CTS, **2**), and sodium dodecyl sulfate (SDS, **3**). The critical micelle concentrations[6] of **1**, **2**, and **3** in H_2O at 25°C are respectively 0.001, 0.0004 (at 35°C), and 0.008 M. As probes or reagents we have used a series of benzophenone carboxylates, including benzophenone-4-carboxylate (**4**), benzophenone-4-acetate (**5**), benzophenone-4-propionate (**6**), benzophenone-4-butyrate (**7**), and benzophenone-4-heptanoate (**8**). Cationic benzophenone-4-trimethylene-*N*-trimethylammonium (**9**) was also used. In addition, 4′-propylbenzophenone-4-carboxylate (**10**), 4′-cyclohexylbenzophenone-4-carboxylate (**11**), and the benzophenone derivative of cyclohex-

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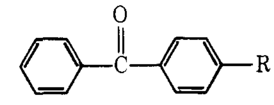
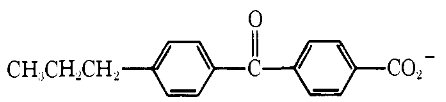
$CH_3(CH_2)_nX$

1: $n = 15$; $X = {}^+NMe_3Br^-$
2: $n = 15$; $X = OSO_3^-Na^+$
3: $n = 11$; $X = OSO_3^-Na^+$



4: R = CO_2^-
5: R = $CH_2CH_2CO_2^-$
6: R = $CH_2CH_2CH_2CO_2$
7: R = $CH_2CH_2CH_2CH_2CO_2^-$
8: R = $(CH_2)_6CO_2^-$
9: R = $CH_2CH_2CH_2{}^+NMe_3Br^-$



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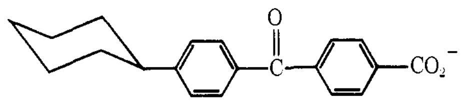

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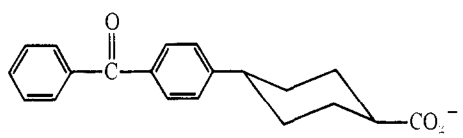

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anecarboxylic acid (**12**) were also involved in a few studies.

Since the interest in these systems was in part the possibility that synthetically useful selectivity might be found, many of the studies were performed with 2:1 molar ratios of substrate to reagent to maximize yields but minimize multiple attacks. Of course this leads to a significant perturbation of substrate micelle structures. In a few cases other ratios were examined to check this perturbing effect.

The reagent-substrate system was photolyzed until the benzophenone chromophore had disappeared. After freeze drying, the insertion products of the benzophenone probe into CTAB were characterized (Scheme I) by Hofmann elimination with KO-*t*-Bu in Me_2SO, dehydration with P_2O_5, and oxidation with RuO_2 and $NaIO_4$ to afford a mixture of ketopentadecanoic acids. These were esterified with diazomethane, converted to the thioketals with ethanedithiol, and analyzed by mass spectroscopy (fragmentation at the thioketal group). We have described elsewhere[3] some of the control studies which validate this analytical method. A further check here is that authentic mixtures of the thioketals of methyl 14-ketopentadecanoate and methyl 6-ketopentadecanoate were correctly analyzed (calcd 25.0%/75.0%, found 27.1%/79.9%; calcd 18.2%/81.8%, found 17.8%/82.1%). A few of the micellar reactions were run in duplicate, and were reproducible to within 1-2%.

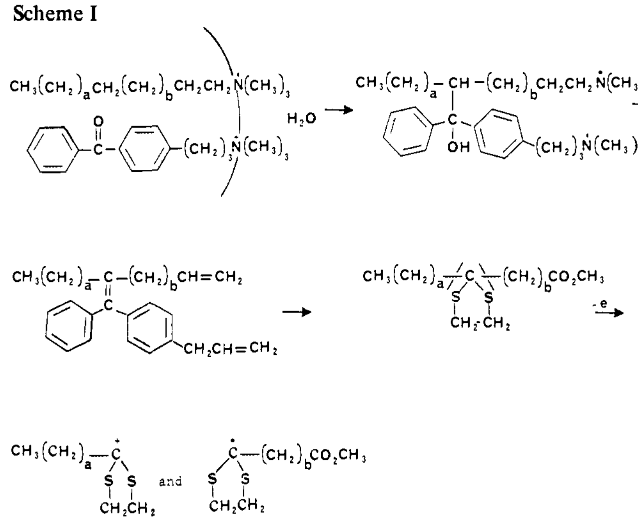
With CTS (**7**) and SDS (**8**) the crude photolysis products were hydrolyzed (dilute HCl) to remove the sulfate groups and acetylated. The acetates were then degraded to ketohexadecyl acetates and ketododecyl acetates and these were converted to thioketal acetates essentially as above and as we have described elsewhere.[3]

Results

The distribution of sites of attack is pictured in Figures 1 and 2. It should be noted that the degradative scheme for CTAB is such that information on carbons 1-4 will be lost or unreliable; for SDS and CTS the degradation should lose information only on C-1 and C-2.

Figure 1a shows that the pattern of functionalization of SDS by benzophenonecarboxylate, at a 2:1 ratio, depends on concentration. The critical micelle concentration (cmc) for SDS is 8×10^{-3} M, and we find by standard surface tension measurements that it decreases to ca 3×10^{-3} M (SDS component) for our mixture. Even so, the pattern at 2×10^{-3} M SDS resembles that at 1×10^{-2} M, and apparently does not reflect reaction in a micelle. A new pattern appears at 1×10^{-1} M, and persists at 1.0 M, indicating that these are the micellar results. Near the cmc the components are distributed between micellar and nonmicellar phases. Ohnishi et al.[7] have reported a study in which a spin label, partitioned between SDS and H_2O, only went completely into the micelle at 0.1 M SDS. This

Scheme I



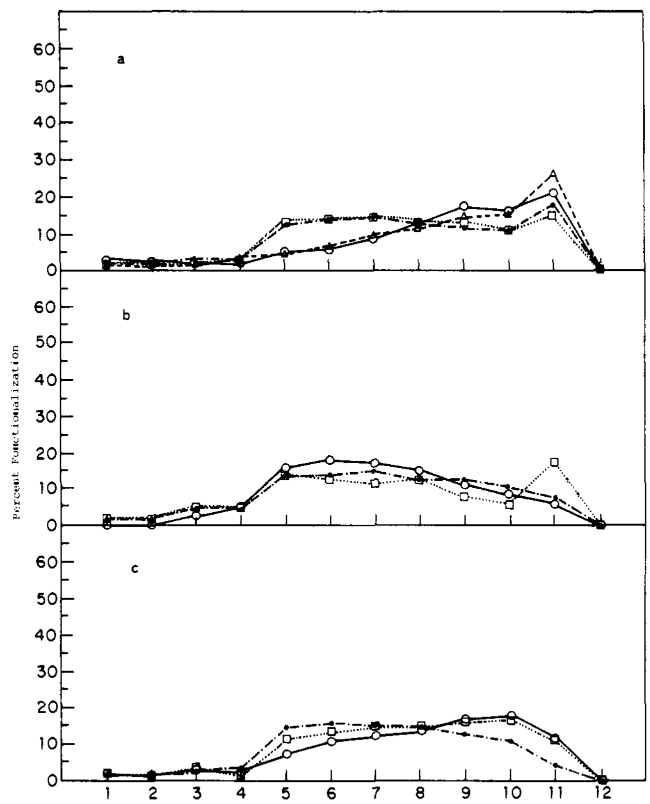


Figure 1. Percent functionalization of various dodecyl carbons. (a) A 2:1 ratio of SDS to benzophenone-4-carboxylate at SDS concentrations of 2×10^{-3} (○ — ○), 1×10^{-2} (△ - - △), 1×10^{-1} (□ .... □), and 1.0 M (● -·-·- ●). (b) A 2:1 ratio of SDS (10^{-2} M) to simple benzophenone (□ ···· □), a 1:1 ratio of SDS (10^{-2} M) to benzophenone-4-carboxylate (● - - - ●), and a 6:6:15:2 ratio of SDS: dodecanol:H_2O:4 (○ — ○). (c) A 2:1 ratio of SDS (10^{-2} M) to the dodecyl ester of benzophenone-4-carboxylic acid showing attack on the ester (○ — ○) and on the SDS (● - - - ●), and a 10^{-1} M solution of benzophenone-4-carboxylic acid in dodecanol (□ ···· □).

Table I. Absorption Spectra of Benzophenones in Various Solvents and in a CTAB Micelle

medium	λ_{max} for n-π^*, π-π^* benzophenone	4	6
1.37×10^{-2} M CTAB, H_2O	328, 254	336, 260	328, 267
H_2O	sh, 257	sh, 262	sh, 265
cyclohexane	347, 249	350, 254	345, 254
dioxane	342, 251	344, 255	342, 255
acetonitrile	338, 251	341, 255	337, 255
methanol	332, 252	336, 257	330, 258
95% ethanol, 5% H_2O	332, 253	337, 258	329, 262

is very similar to our finding. The distribution in Figure 1a shows that both inside and outside the micelle a similar product mixture is formed, with attack over carbons 5-11.

Figure 1b shows several systems. In one, SDS at 10^{-2} M was reacted with simple benzophenone, with no charged group to promote orientation at the micelle-H_2O interface. Of course the benzophenone could well be oriented so as to put its polar carbonyl group at the surface, and Fendler[8] has reported UV evidence that benzophenone in a CTAB micelle has an n-π^* transition characteristic of a very polar medium. We confirm this observation, as Table I shows. The spectra of our ketones in CTAB micelles resemble spectra in methanol, not in cyclohexane. Nonetheless, we find that benzophenone attacks widely over the SDS chain. Comparing it with benzophenonecarboxylate, Figure 1a, the major difference is that simple benzophenone gives somewhat more attack at C-3 and C-4, near the SDS polar head group. What is not revealed in the figure is that the *extent* of functionalization is much less with simple benzophenone (photolyzed to disappearance).

Figure 1b also shows the result when SDS and benzophenonecarboxylate react at 10^{-2} M and a 1:1 ratio. The comparison with the 2:1 ratio in Figure 1a shows that a major change in structure has occurred. In particular, there is much less attack at C-11 for the 1:1 ratio. The final curve in Figure 1b is a mixture of SDS, dodecanol, and H_2O with the benzophenonecarboxylate. It is known[9] that such mixtures approach the structure of bilayers, not micelles, in which the hydrocarbon chains are more extended and ordered. The product distribution reflects this, with extensive attack at C-5, 6, and 7 and little attack at C-11 of the combined dodecyl chains from SDS and dodecanol.

If a micelle were an ordered structure it might impose that order on a reagent-substrate molecule dissolved in the micelle. Figure 1c shows the product distribution for the dodecyl ester of benzophenonecarboxylic acid in SDS (10^{-2} M) at a 1:2 ratio. Both the attack on the dodecyl group and the attack on SDS are nonspecific, but both show interesting effects. The attack on SDS does not show the usual C-11 peak seen for many other probes, while the attack on the dodecyl group is more random than that we have reported[3] for this ester in organic solvents. In the present case the dodecyl functionalization probably includes *inter*molecular attack.

The other curve in Figure 1c shows the attack of benzophenonecarboxylic acid on liquid dodecanol. Although hydrogen bonding could have imposed some orientation, the product distribution is relatively random.

Since the cmc's of CTS and of CTAB are 0.004 and 0.001 M, respectively, results at 10^{-2} M should reflect principally the reactions in micellar systems. In Figure 2a are the results for CTS at 10^{-2} M at 2:1 ratio with benzophenonecarboxylate and with benzophenonebutyrate (at 60 °C, for solubility). The two curves are similar except that the longer probe has a little more tendency to attack at C-5 and a little less tendency to attack at C-15. That a *longer* probe should attack *less* at the far end of the CTS is contrary to simplest expectations. Figure

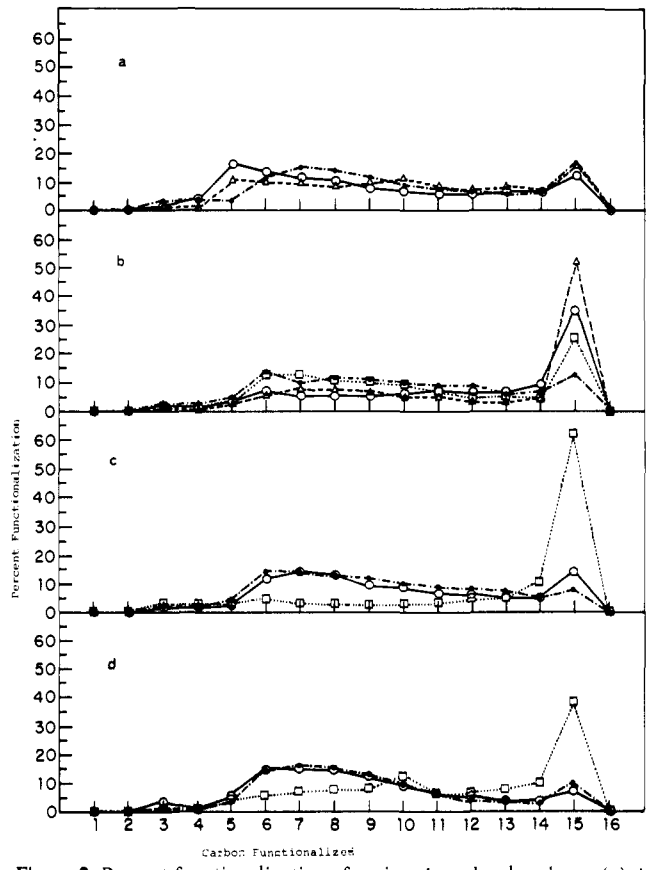


Figure 2, Percent functionalization of various hexadecyl carbons. (a) A 2:1 ratio of CTS (10^{-2} M) with benzophenone-4-carboxylate (△ - - △) and with benzophenone-4-butyrate (○ — ○), and a 2:1 ratio of CTAB (10^{-2} M) with cationic probe **9** (● - - - ●). (b) A 2:1 ratio of CTAB (10^{-2} M) with benzophenone-4-carboxylate (△ - - - △), benzophenone-4-propionate (○ — ○), benzophenone-4-butyrate (□ ‧ ‧ ‧ □), and benzophenone-4-pentanoate (● - ‧ - ●). (c) An. 8:1 ratio of CTAB (10^{-2} M) to benzophenone-4-carboxylate (○ — ○), a 20:1 ratio of CTAB (0.961 M) to benzophenone-4-butyrate (● - - - ●), and a 2:1 ratio of CTAB (1.0×10^{-4} M) to benzophenone-4-butyrate (□ ‧ ‧ ‧ □). (d) A 2:1:1 ratio of CTAB (10^{-2} M) to benzophenone-4-butyrate to cholesterol (● - - - ●), a 2:1 ratio of CTAB (10^{-2} M) to probe **11** (○ — ○), and a 2:1 ratio of CTAB (10^{-2} M) to probe **12** (□ ‧ ‧ ‧ □).

2a also shows that attack on cationic CTAB by a cationic probe gives a very similar pattern to that of anionic CTS with an anionic probe of related length. The shift of one carbon in the initiation position, C-6 vs. C-5, is expected since C-1 of CTAB is equivalent to the oxygen atom in CTS.

By contrast, when the reagent has an opposite charge to that of the micellar host strong perturbations can result.[5] A striking set of data is seen in Figure 2b. Here CTAB at 10^{-2} M reacts in a 2:1 ratio with benzophenonecarboxylate, -propionate, -butyrate, and -pentanoate. As the probe is lengthened there is progressively *less* attack on C-15, which is a more convincing version of the effect seen in Figure 2a.[10]

Some of the effect in Figure 2b is due to perturbation by the high concentration of the oppositely charged probe. Thus Figure 2c shows that using 10^{-2} M CTAB in 8:1 ratio with benzophenonecarboxylate abolishes much of the attack at penultimate C-15 seen for the 2:1 ratio. Furthermore, the product distribution can be affected strongly by total concentration. Figure 2c shows that with a 20:1 ratio of CTAB to anionic probe at a CTAB concentration of 0.961 M, there is a preference for attack at C-6 over attack at penultimate C-15. At this concentration CTAB is a hexagonal phase[5] gel with a structure resembling a bilayer, not a micelle. That is, the chains tend to be parallel, with less coiling. However, with a CTAB to probe ratio of 2:1 at a CTAB concentration of 10^{-4} M, below the cmc, the pattern in Figure 2c shows very great se-

lectivity for C-15. This specificity below the cmc was *not* seen in Figure 1a for an anion–anion pair.[11]

Figure 2d shows the results of three experiments to modify the selectivity and structure in the CTAB–reagent system. In one case, a 2:1 CTAB to anionic probe system at 10^{-2} M had cholesterol added. The results are similar to those for the gel in Figure 2c, suggesting that the cholesterol stiffens the structure.[12] In the other two experiments, a cyclohexane ring is incorporated in the reagents. When this is attached to the 4′ position of benzophenone-4-carboxylate it strongly diminishes attack on the penultimate C-15 carbon of CTAB. We also see a similar pattern for 4′-propyl substitution. However, when the cyclohexane is interpolated between the benzophenone and the carboxylate the penultimate C-15 is attacked, and a new local maximum at C-10 also appears. C-10 is the carbon which should be attacked if the probe forms an oriented ion-paired structure with a fully extended CTAB chain.

Discussion

The first point to be made is that whatever orientation is imposed by the structure of a micelle is insufficient to lead to synthetically useful selectivity. This is true even in gels or in "micelles" with added sterols or dodecanol in which much more rigidity is expected. We see evidence of such increased order, but not to the point of real positional selectivity. The only really selective reaction was that (Figure 2c) for an ion pair of CTAB and benzophenonebutyrate *below* the cmc. Apparently the resulting aqueous surroundings coil the chain to the point at which chiefly the penultimate C-15 is attached.

The charged groups on substrates and reagents are probably aligned at the surface of the micelle. This is most obvious when they have opposite charges and can ion pair, but even when they have the same charge they are expected to be located at the micelle–water interface. Thus the randomness of attack probably does not result from extensive misalignment of the charged ends. Two other sources of disorder are still present, however. One problem is that the reagents may not be oriented perpendicular to the micelle–water surface. If the benzophenone ketone group tended to lie in a polar region, as our UV data may suggest, the reagent would then be oriented parallel, not perpendicular, to the surface. However, our functionalization results do not really support this idea, at least in its entirety. Models show that with the perpendicular orientation reagent **4** should be able to initiate attack at C-5 or C-6, while probe **12** should initiate attack at C-9 or C-10. We do not see a large amount of attack on the first few carbons of the substrates, as the parallel orientation would predict. Of course there is some, so some randomness of reagent orientation may be involved.

The other source of disorder is randomness in the conformation and orientation of the substrate. Since visual impressions of distribution curves are not completely satisfactory, we propose a parameter R_r to characterize the distributions. This is defined as the ratio of the amount of functionalization at the penultimate carbon, characteristic of a coiled chain, to that at the carbon which would be attacked if the chains were parallel, fully extended, and alligned.

$$\text{randomness ratio} = R_r = \frac{\text{attack at penultimate carbon}}{\text{attack for perfect orientation}}$$

For example, in Figure 1a the R_r, ratio of attack at C-11 to attack at C-6, changes from 3.73 at 10^{-2} M to 1.0 at 0.1 M. This is expected as the extensive coiling in an aqueous environment gives way to less coiling in a micelle.

The response of R_r to changed conditions is sensible. Thus in the 1:1 reaction of SDS and benzophenonecarboxylate we are apparently dealing with a micelle, and a rather stiff one with such a high proportion of aromatic rings. Here the R_r falls to 0.5, reflecting little coiling of the SDS. In the SDS–dodecanol system R_r is down to 0.35. In a simple micelle the tendency of the hydrocarbon chains to line up parallel and fully extended is opposed by electrostatic repulsion between the head groups.[5] The result is a typical micellar structure: some of the chains are fully extended, but others must coil to fill the wedge-shaped spaces which would otherwise result from the construction of a circular cross section with rigid rods. With dodecanol present the head group repulsion is reduced since half the chains are uncharged, so a more typical bilayer structure can result with fewer coiled chains.

The results with CTS in Figure 2a add to this picture. R_r for the reaction with benzophenonecarboxylate is 1.50, but R_r for the reaction with benzophenonebutyrate is 0.90, showing that the longer probe has *less* tendency to attack C-15 relative to C-6. This suggests that we can say more than that some chains are coiled. They show a tendency to *fold back*, bringing the distant C-15 closer to the surface and thus within better reach of a *shorter* probe.[10]

The results in Figure 2b confirm this picture. R_r for the reaction of CTAB with probes of different lengths varies inversely with length: 9.0 for **4**, 6.27 for **5**, 2.55 for **6**, and 1.44 for **7**. The effect then dies out; we find that the curve with **8** is almost identical with that for **7**, with an R_r of 1.37. The striking results in Figure 2b reflect ion pairing of a reagent and substrate chain, and also the perturbation of structure associated with such heavy loading by counterions in the head-group layer. When this loading is decreased by using CTAB:**4** in an 8:1 ratio (Figure 2c), R_r drops from 9.0 to 1.0 (the C-15 to C-7 ratio).

Even less coiling is seen with a 20:1 ratio of CTAB to **7** in which the CTAB is at such a high concentration that it is a gel (Figure 2c). Here R_r is only 0.67 (referred to C-9). In such hexagonal phase gels polar head group repulsions are finally overcome by hydrophobic forces, and the structure resembles a bilayer with fewer coiled chains. The opposite effect is seen for very low concentration, below the cmc. Presumably CTAB and **7** are ion paired, and hydrophobic forces may also align them, but **7** is extensively coiled in its predominantly aqueous environment. The R_r is an astonishing 32.3.

The interstices in a micelle can be occupied by other molecules, rather than by coiled host chains. The result is seen in Figure 2d: incorporation of cholesterol along with 2:1 CTAB:**7** ratio at 10^{-2} M CTAB takes R_r from 9.0 down to 0.73. The curve is almost superimposable on that for the gel in Figure 2c.

The idea that much of the coiling seen in Figure 2b is the result of specific interactions between substrate–reagent paired molecules in the micelle is consistent with the results seen with CTAB and **11**. The extra cyclohexane ring at the end of the probe apparently interferes with coiling of CTAB around the end of the reagent, and R_r drops to 0.5. When the cyclohexane is instead used to lengthen the distance between head group and ketone, in **12**, the R_r is up to 3.9, and some preferred attack occurs at C-10 as expected with this length reagent.

Finally, it should be noted that for simplicity our discussion so far has focussed on the interpretation of R_r's, and other details of product distributions, in terms of the coiling of the substrate chains. However, we cannot exclude some contributions from the two other sources we have mentioned, viz., nonperpendicular orientations relative to the micellar surface and misalignment of head groups. Furthermore, we must reemphasize the fact that our probes introduce major perturbations of the structures, so the information obtained is valid only for our actual systems. It is also possible that some of our systems are in dynamic equilibrium among several phases, and that the data are thus averages for such phases. With such reservations, it should be said that our results in general confirm and amplify the current picture of micelle structure. We

see considerable disorder in simple micelles, but our results suggest that much of the disorder involves chains which are folded back, not simply coiled. Furthermore, we confirm the increased order in bilayers, and in binary systems including cholesterol or dodecanol. However, this increased order is not sufficient to be of interest in synthetic chemistry.

Experimental Section[13]

Materials. Sodium dodecyl sulfate (Aldrich) was washed with ether and recrystallized four times from 95% ethanol. Sodium hexadecyl sulfate was prepared from purified cetyl alcohol, and recrystallized three times from methanol–isopropyl alcohol (Anal. ($C_{16}H_{39}O_4SNa$) C, H, S). Cetyltrimethylammonium bromide (Aldrich) was washed with ether and recrystallized four times from ether–methanol to mp 247.6–248.4 °C.

The 4-benzophenonecarboxylic, 4-benzophenoneacetic, 4-benzophenonepropanoic, and 4-benzophenonebutyric acids were prepared and purified as described earlier,[1] as was the dodecyl ester of benzophenonecarboxylic acid.[3] 4-Benzophenoneheptanoic acid, mp 68–70 °C, was prepared by Friedel–Crafts acylation of phenylheptanoic ester with benzoyl chloride in the standard manner and characterized by NMR and mass spectra. Similarly, Friedel–Crafts acylation of *n*-propylbenzene and of cyclohexylbenzene with 4-carbethoxybenzoyl chloride was used to prepare 4′-propylbenzophenone-4-carboxylic acid, mp 174–176 °C, and 4′-cyclohexylbenzophenone-4-carboxylic acid. Friedel–Crafts acylation of *trans*-4-phenylcyclohexanecarboxylic ester[14] with benzoyl chloride was used to prepare **12**, mp 198–202 °C. Cationic probe **9**, known as the iodide,[15] was prepared as the bromide from 4-benzophenonepropionic acid by reduction to the primary alcohol with diborane, conversion to the bromide, and reaction with trimethylamine.

Photolyses. The solid reagent and substrate were placed in a photolysis vessel and water was distilled in to volume under N_2. Photolysis with a 450-W medium-pressure Hanovia lamp was performed with a quartz well and uranium glass filter until the benzophenone group had disappeared (infrared). The time required was a few hours for most systems, but longer for the dilute reaction or the gel, which scattered light.

Degradation of the Products from the SDS and the CTS Reactions. The reaction mixture was freeze dried and taken up in 300 mL of 0.5 M hydrochloric acid. After being heated at reflux for 15 h, the solution was cooled and extracted three times with ether. The residue, after ether evaporation, was acetylated with acetic anhydride–pyridine and chromatographed on silica gel to separate dodecyl acetate or cetyl acetate from the functionalized material. The product was then esterified with diazomethane, dehydrated with thionyl chloride and pyridine, and cleaved with RuO_2 and $NaIO_4$. The resulting ketododecyl acetate mixture was converted to the ethylene thioketal as we have described elsewhere,[3] and submitted to mass spectral analysis.

The reaction with an SDS and dodecanol mixture was treated as above; the HCl hydrolysis converts the SDS to dodecanol. The reaction product from photolysis of dodecyl *p*-benzoylbenzoate in SDS was first chromatographed on silica, after freeze drying. The neutral product was eluted with 10% ether in hexane, the charged product with 50% methanol–water. The charged product, from SDS, was degraded as above. The neutral product was analyzed as we have described previously.[3]

Degradation of the Products from the CTAB Reactions. The product was freeze dried and dissolved (ca. 7 g product mixture) in 500 mL of dimethyl sulfoxide. Under N_2, 5.0 g of potassium *tert*-butoxide was then added, and the mixture was stirred for 12 h under N_2. Cooling, neutralization with 5% hydrochloric acid, and four extractions with $CHCl_3$ afforded a crude product from which hexadecene was removed by rough chromatography on silica. The product was then dehydrated with P_2O_5 in benzene,[3] esterified with diazomethane (if the reagent had been an acid), and oxidized with RuO_2 and sodium metaperiodate. The crude keto acid product was esterified with diazomethane and converted to its ethylene thioketal as we have described.[3]

Mass Spectral Analysis. This followed the procedure we have described.[3] Data were acquired on a Finnigan Model 3300 mass spectrometer with a Finnigan Model 6000 data system in the electron impact mode at 15–19 eV. The percent functionalization at a given carbon was obtained from the sum of the integrated total intensities of the two fragments associated with the corresponding thioketal isomer. The $C_4H_7S_2$ peak for the reaction of CTAB with **6** below the cmc, indicating very high selectivity for attack at C-15, was checked by high-resolution mass spectroscopy, and had the correct *m/e* to six significant figures.

If attack had occurred in the terminal CH_3 of a substrate, the thioketal fragment $C_3H_5S_2$ would have had *m/e* 105. We found varying amounts of *m/e* 105 in our analyses, but controls showed that this was contributed by impurities and disappeared on careful purification. Accordingly, in our data of Figures 1 and 2 the percent attack at the terminal primary carbon, which must be very low, was set to zero.

The reproducibility of our data in different runs was generally within 1–2% on an absolute scale. Thus at a given carbon the percent attack may be 7 ± 2%, with a correspondingly large uncertainty in R_r.

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References and Notes

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