Supramolecular Assemblies as Promoters of Iodohydrin Formation

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Keywords: Synthesis design / Surfactants / Iodohydrins / Iodine / Green chemistry

Finding alternative reaction media to replace polluting organic solvents is one aim of green chemistry. The ultimate green solvent, water, is the cheapest, non-toxic and most readily available reaction medium: three properties which make it an environmentally and economically attractive solvent. However, a fundamental problem in performing reactions in water is that many organic substrates are hydrophobic and not soluble in water. Several approaches are possible in solubilizing these compounds in aqueous media, one of which is carrying out reactions in aqueous solutions of surfactants at concentrations above their critical micellar concentration (cmc). Reactions of iodine with cyclohexene, 1-octene and styrene in water or in the presence of cationic surfactants do not give useful amounts of iodohydrins, but reactions in anionic surfactants give good yields. Iodohydrins are important functionalizable compounds and are readily prepared in the presence of sodium dodecyl sulfate (SDS) or sodium *N*-dodecanoyl sarcosinate (SANa). The critical conditions for these reactions were optimized with a rigorous statistical approach, the experimental design method. Use of these newly optimized reaction conditions gave high yields in short times for all of the alkenes examined. The use of anionic surfactants in water to form iodohydrins is a valid alternative to methods previously described.

Introduction

Alkenes react readily across the double bond.[1] Electrophilic additions to unsaturated compounds, where the electrophile is a halogen molecule or derivative and the nucleophile is the alkene, are shown in the following scheme (Figure 1).

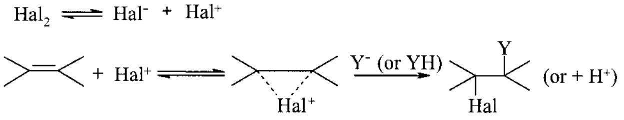

Figure 1. Scheme of halogenation of alkenes by iodine in water

The main importance of these processes is that they generate saturated compounds with the potential to have different vicinal substituents in a single-step reaction. For example, newly formed α-halohydrins are attractive as they can be used in further reactions because they are useful intermediates and are targets in organic syntheses.

Finding reaction media to replace polluting organic solvents is one of the principles of Green Chemistry.[2] Water is the cheapest, non-toxic and most readily available reaction medium, which makes it an environmental and economically attractive solvent. However, a fundamental problem in performing reactions in water is that many organic substrates are hydrophobic and sparingly soluble in water. Several approaches are useful in solubilizing organic compounds in aqueous media, one of which is carrying out reactions in the presence of amphiphiles, e.g. surfactants containing both apolar hydrophobic and polar hydrophilic groups on the same molecule. In water, this dual character leads to self-association or micellization.[3] Because of this self-association, micelles can control the course of organic reactions because they provide different local environments within a few Ångströms. Therefore, unlike homogeneous solvents, micelles provide a variety of microenvironments ranging from the hydrocarbon core to the polar interface to bulk water, allowing hydrophobic and hydrophilic molecules to be solubilized in local domains. Micelles may affect reaction rates and equilibria by bringing reactants together or keeping them apart,[4] e.g. they can incorporate both water-insoluble and ionic compounds at the micellar surface. Therefore they can also promote regio-selectivity in the products by orienting reactants.[5]

For both economic and environmental reasons recovery of surfactants is crucial. Separation of products from crude reaction mixtures containing surfactants can be difficult because these systems readily form emulsions during standard

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DOI: 10.1002/ejoc.200300085

extraction procedures. These problems have been faced and solved in different ways. As an example, Jaeger and co-workers[6] have developed a general approach involving the synthesis of a chemically labile surfactant, which can be readily hydrolyzed when the reaction is complete, which simplifies extraction of the products, although the surfactant is lost. Alternatively, ionic surfactants can be recovered by cooling the reaction mixture to below the Krafft point of the surfactant, leading to precipitation. Similarly non-ionic surfactants can be recovered by heating the reaction mixture above its cloud point. As a final example, surfactants can be recovered by ultrafiltration or by stripping products with supercritical CO_2.

Electrophilic alkene additions have been extensively studied and, particularly for bromination, the reaction mechanism in homogeneous solution is well understood.[7] Rates and products are extremely sensitive to the reaction conditions, which makes alkene halogenations useful probes of micellar structure. There are several examples in the literature of kinetic and synthetic investigations on alkene bromination aimed at analysis of the microenvironment at the micellar−water interface.[8]

Unlike syntheses of chloro- and bromohydrins,[9] formation of iodohydrins from alkenes and iodine in water is unsatisfactory owing to the reversibility of the addition of iodine to a double bond, where the equilibrium is very unfavorable[10] (Figure 2).

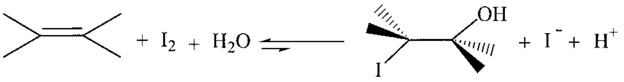

Figure 2. Scheme of iodination showing the ionic intermediates formed during the reaction and reversibility of iodination of alkenes

Therefore, iodohydrins are typically obtained by reaction of epoxides with hydriodic acid, elementary iodine[11] or metal iodides or from halide ion exchange of chlorohydrins or bromohydrins in acetone.[12] Other reported procedures carry out iodination in the presence of scavengers (e.g. mercuric oxide or silver oxide[10]), oxidizing agents of iodide ions (e.g. nitrous acid, oxygen, sodium nitrite,[10] pyridinium dichromate[13]), redox systems (e.g. periodic acid/sodium hydrogen sulfite systems[14]), or by using agents such as NIS (*N*-iodosuccinimide[15]) in DME/H_2O (DME = 1,2-dimethoxyethane) at −20 °C.

Because micelles can modify rates and equilibria of many organic reactions and there is extensive literature data on brominations in micellar solutions,[8,16] aqueous surfactant solutions have been used for syntheses of iodohydrins from simple alkene molecules and iodine. The aim of this study was to develop a simple preparative procedure to obtain iodohydrins. Although we did not have a homogeneous system, because of a large excess of reactants over surfactant, we considered the reaction mixture to be a normal micellar system, using the pseudophase treatment.[19] The absence of organic solvents and harsh reagents, the use of water as a reaction medium and the possibility of recovering the surfactant make this procedure environmentally friendly and consistent with the principles of sustainable chemistry.[2] Therefore we undertook a rigorous study of the effects of surfactants on the iodination reaction of alkenes.

Both cationic and anionic surfactants, at different concentrations, but always above their critical micellar concentration (cmc), were tested with the purpose of optimizing formation of the iodohydrins. Cationic surfactants were cetyltrimethyl ammonium compounds: $CTAI_3$ [$C_{16}H_{33}N^+(CH_3)_3I_3^-$], $CTAIBr_2$ [$C_{16}H_{33}N^+(CH_3)_3IBr_2^-$], obtained by addition of cetyltrimethyl ammonium iodide (CTAI) to a solution of I_2 or Br_2, respectively, and $CTAI_2Br$ [$C_{16}H_{33}N^+(CH_3)_3I_2Br^-$], obtained by addition of I_2 to a solution of cetyltrimethyl ammonium bromide (CTABr). Anionic surfactants were sodium dodecylsulfate (SDS, $C_{12}H_{25}OSO_3^-Na^+$), and sodium *N*-dodecanoyl sarcosinate [SANa, $C_{11}H_{23}CON(CH_3)CH_2COONa$].

Reactions were carried out in aqueous solution using I_2 or I_3^- as the iodine source with cyclohexene, 1-octene and styrene. Reactions were carried out in the dark and easily followed visually until the end, monitoring the disappearance of the red iodine color. (The use of UV/Vis apparatus was ruled out because of the strong absorbance of turbid solutions.) Synthetic processes and yields were optimized using a mathematical chemometric method. A full-factorial design for the four variables (temperature, concentration of iodine, concentration of surfactant and solution pH) was generated with the Spectre program.[17] Reaction yields were regressed on the data matrix and the importance of each reaction parameter was calculated, in order to optimize the reaction yields.

Results and Discussion

Iodinations in Water and Iodine (I_2 or I_3^-) Without Surfactant

In order to establish the baseline reactivity of each substrate, iodination was performed in water in the absence of surfactant. Under these conditions, only cyclohexene yielded a significant amount of product (Table 1). The *trans*-2-iodocyclohexanol, which was obtained in 60% yield with respect to the iodine source, was recovered after three hours of reaction. For the other alkenes, the equilibrium was always toward reactants and undesired by-products, and only a very small amount of iodooctanol was isolated after long reaction times (Table 1). The intense red color of residual iodine did not disappear during reaction. Neither the yields nor the reaction times for cyclohexene depended on the iodinating agent, and I_2 or I_3^- reacted equally well. Similar results were observed previously, where in aqueous solution there was no observable difference between the reactivities of Br_2 and Br_3^- [8b,18] in alkene brominations. Therefore, it seems reasonable to conclude that reactions of bromine and iodine with alkenes follow similar mechanisms.

Table 1. Iodination in water

Alkene[a]	X[b]	Time (h)	Products	Yield (mol %)[c]
Cyclohexene	I_3^-	3	*trans*-2-iodocyclohexanol	60
Cyclohexene	I_2	3	*trans*-2-iodocyclohexanol	60
Styrene[d]	I_2	24	polymers	–
Styrene[d]	I_3^-	24	polymers	–
1-Octene	I_3^-	100	1-iodooctan-2-ol 2-iodooctan-1-ol	5[e]

[a] Temperature 60 °C, 0.06 M alkene. [b] The molar concentration of iodine or I_3^- is always 0.03 M. [c] With respect to $[I_2]$ or $[I_3^-]$. [d] 0.03 M styrene. [e] Sum of both regioisomers; ratio [1-iodooctan-2-ol]/[2-iodooctan-1-ol] 9:1.

Iodinations in Micellar Systems

Micellar effects on reaction rates have been analyzed with pseudophase models, which separate the contributions of reactant concentration at the interface and reactivity in that region and include transfer equilibria of reactants between water and micelles.[19] In these models, micelles are regarded as a separate phase from water, and the overall reaction rate is the sum of the rates in each pseudophase. In the present work, we do not attempt to analyze reaction rates quantitatively, but instead try to gain a qualitative understanding of the iodination reaction in these terms. All the alkenes have extremely low water solubility, and we assume that reactions occur only at the micelle−water interface. We note that the pseudophase kinetic treatments were developed largely for reactions of very dilute organic substrates and may not be applicable to reactions in preparative conditions, where treatment of transfer equilibria is complicated. However, the general concepts provide a useful guide for these reactions even though they cannot be applied quantitatively.

Iodinations in Water, Iodine (I_2 or I_3^-) and Cationic Surfactants

Additions of I_2 or Br_2 to a solution of CTABr or CTAI form $CTAI_2Br$, $CTAIBr_2$ or $CTAI_3$, depending on the relative initial conditions that were used in the iodinating reactions. There was no productive reaction in the presence of these cetyltrimethylammonium surfactants, even though reaction times were at least 10 times longer than those for reactions in water, and there were many side products (such as diiodo compounds and oligomers). Moreover, with both $CTAIBr_2$ and $CTAI_2Br$ bromo-iodinated products were also recovered.

Owing to the lower polarity of the micellar surface compared to the water, micelles reduce the rate of reactions that involve polar intermediates and charge separations at the interface.[8] For bromination, we consider the equilibrium:

$$\mathrm{Br_3^-} \overset{K_d}{\leftrightarrows} \mathrm{Br_2} + \mathrm{Br^-}$$

which is medium dependent and K_d decreases with decreasing solvent polarity.[8b,20]

Thus in surfactant assemblies, the ratio Br^-/Br_3^- is affected, favoring Br_3^-. In homogeneous conditions this anion is generally less reactive than Br_2 by approximately one order of magnitude;[10,21] moreover in a cationic surfactant Br_3^- interacts very strongly with the micellar head group. For these reasons, alkene brominations in CTABr were slower by a factor of 10^5-10^6 than in water.[8b,16]

We believe that, because of the greater polarizability of iodine than bromine, similar or larger effects are involved in alkene iodination in the presence of cationic surfactants, resulting in a very low iodinating power, slow reactions and formation of undesirable by-products. Iodide ions should be concentrated at the cationic interface of the micelles, interfering with the halogenation equilibrium. For these reasons we believe that cationic surfactants will not be useful in syntheses of iodohydrins.

Iodinations in Water, Iodine (I_2 or I_3^-) and Anionic Surfactants

The effect of anionic surfactants on iodination was then studied. We assumed that the negative charge of the micellar surface would exclude the iodide anion from that region and protect micellar-bound products from I^-, eliminating the need for scavengers or oxidizing agents of the iodide. Furthermore, a carbocationoid transition state should interact favorably with the anionic head groups.

Both SDS and SANa affected reaction rates and products. Relative to halogenation in water, the anionic surfactants increased yields and shortened reaction times for all substrates, with strongly reduced by-product formation. All results are shown in Table 2 and 3.

Cyclohexene gave similar yields of iodohydrins in the absence or presence of surfactants, but the reaction time was approximately one-third as long with the micelles. Although the local second-order rate constants in the micelles might be expected to be lower than in water, owing to the lower polarity at the micellar interface,[8c] both reactants, I_2 and the alkene, are concentrated at the water−micelle interface, where these ionic reactions take place,[22−24] thus overcoming any kinetic inhibiting effect. Therefore, the overall reaction rate is accelerated.

There are small differences in reaction times observed in SDS and SANa, but no obvious trend. The reaction times

Table 2. Iodination in aqueous solutions of SDS

Alkene[a]	[S], (M)[b]	X [c]	Time (h)	Products	Regioisomers ratio ([a]/[b])	Yield (mol %)[d]
Cyclohexene	0.025	I_3^-	1.5	*trans*-2-iodocyclohexanol		62
Cyclohexene	0.05	I_2	0.5	*trans*-2-iodocyclohexanol		60
Styrene [e]	0.1	I_2	24	2-iodo-1-phenylethan-1-ol		42
1-Octene	0.025	I_3^-	16	1-iodooctan-2-ol (a) 2-iodooctan-1-ol (b)	2	43
1-Octene	0.05	I_2	7	1-iodooctan-2-ol (a) 2-iodooctan-1-ol (b)	2	57

[a] Temperature 60 °C, 0.06 M alkene. [b] [S] is surfactant concentration. [c] The molar concentration of iodine or I_3^- is always 0.03 M. [d] With respect to [I_2] or [I_3^-]. [e] 0.03 M styrene.

Table 3. Iodination in aqueous solutions of SANa

Alkene[a]	[S], (M)[b]	X[c]	Time (h)	Products	Regioisomers ratio ([a]/[b])	Yield (mol %)[d]
Cyclohexene	0.025	I_3^-(0.03)	1	*trans*-2-iodocyclohexanol		60
Cyclohexene	0.05	I_2 (0.04)	0.5	*trans*-2-iodocyclohexanol		50
Styrene [e]	0.15	I_2 (0.03)	24	2-iodo-1-phenylethan-1-ol		47
Styrene [e]	0.05	I_2 (0.03)	24	2-iodo-1-phenylethan-1-ol		22
1-Octene	0.025	I_3^-(0.03)	24	1-iodooctan-2-ol (a) 2-iodooctan-1-ol (b)	3	51
1-Octene	0.05	I_2 (0.04)	24	1-iodooctan-2-ol (a) 2-iodooctan-1-ol (b)	3	45

[a] Temperature 60 °C and 0.06 M alkene. [b] [S] is surfactant concentration. [c] In parenthesis the molar concentration of iodine or I_3^-. [d] With respect to [I_2] or [I_3^-]. [e] 0.03 M styrene.

shown in Table 2 and 3, demonstrate, as expected, that I_2 is more reactive than I_3^-, while the yields of iodinated products are similar. This result fits the proposed exclusion of the anions from the negatively charged micellar surface.

Styrene and 1-octene gave the desired products only when the reaction was carried out in the presence of anionic surfactants. When halogenations were carried out in water, the polymerization of styrene took place much more rapidly than halogen addition and the linear octene was recovered mostly unchanged, together with a few oligomers.

With anionic surfactants, styrene formed 2-iodo-1-phenylethanol with yields of 47% (SANa) and 42% (SDS) for the two anionic surfactants studied. The behavior was similar for cyclization of 2-(ω-bromoalkoxy)phenoxide in dicationic surfactants,[25] where intermolecular reactions were precluded by the positioning of the reactant in a well-structured substrate−surfactant aggregate. As a first approximation, it is reasonable to assume that this effect is independent of micellar charge and depends only on the presence of large well-organized assemblies with the substrate at the surface. A recent study of benzene solubilization in aqueous CTABr demonstrated that the aromatic molecule lies in clefts at the micellar surface replacing water molecules in that surface.[26] Similarly, a study on the chemical trapping of water at the surfaces of cationic micelles showed that cyclohexene lies at the surface and that its bromination takes place in a water-rich area of the surface,[27] although evidence on micellar structure in water may not apply in the presence of apolar solutes.[26] On the other hand, in some aqueous cetyltrimethyl ammonium surfactants, benzene NMR signals suggest that solute mobility at the aggregate surface is not affected by the size of the aggregate.[26] In a number of micellar models, water was believed to penetrate the micelle. Menger used space-filling models[28] to conclude that there should be deep voids in the micelle, which accommodate water molecules extensively. Fromherz,[29] Butcher and Lamb,[30]and Dill and Flory[31] postulated different structural organizations with partial exposure of alkyl groups to water. These micellar models are independent of surfactant charge, and should be valid for cationic, anionic, zwitterionic and non-ionic micelles. Therefore, it is reasonable to believe that styrene molecules are separately located in clefts of the micellar pseudophase, so that styrene polymerization is slowed down with respect to the halogenation reaction. Such a picture does not contradict the well-established dynamic nature of micelles. In the fast amphiphilic exchange of molecules between micelles and bulk water, solubilization of substrates is a dynamic exchange equilibrium. Because of the very low alkene solubility in water, this equilibrium is strongly shifted in favor of micelles, just as if a styrene droplet is diluted in an inert environment whose main effect is to inhibit polymerization. Additionally, there is a concentration effect on the reaction because both alkene and iodine are brought together by interaction with the micellar surface, which accelerates formation of the cationic intermediate that rapidly generates the product. Thus intermolecular iodination is favored over polymerization. Moreover, the reaction is regioselective and only one of the two possible iodohydrins, 2-iodo-1-phenylethan-1-ol, is formed, because the forming positive charge is stabilized by the phenyl group in a heterolytic reaction. However, 1-octene reacted in the presence of either anionic surfactant to give a mixture of the two regioisomeric iodohydrins. Because of the difference between phenyl and alkyl groups in stabilizing carbenium-ion-like intermediates, regioselectivities differ for reactions in anionic micelles and water. In water there is poor iodohydrin conversion, but a net prevalence, 9:1, of the Markovnikov product, 1-iodooctan-2-ol, while the anionic surfactants shifted the product ratio to 2:1 and 3:1, in SDS and SANa, respectively. Considering halohydrin formation, the prevalent product still accords with the Markovnikov rule, but micelles clearly increase the anti-Markovnikov iodohydrin. One difference between the two surfactants is that with SANa a greater ratio of iodinating agent with respect to the surfactant was required, due to concomitant partial iodination of this amphiphile.

With styrene the phenyl group favors the formation of a carbocationoid intermediate and the Markovnikov product, but if 1-octene gives an intermediate iodonium-like species, water could attach at either position. Previous studies showed that the linear chain of this hydrophobic alkene is deeply located in the micellar aggregate.[8c] If octene is located in the micelle, as shown in Figure 3), carbon atom C-1 will be the more exposed to water, which partially offsets the Markovnikov-predicted attack of water at C-2. In this description we have assumed that the lifetime of a cationic intermediate is too short to allow escape into water, which increases preference for the Markovnikov product.

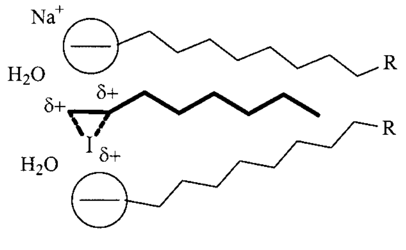

Figure 3. Tentative orientations of anionic surfactants (head groups and tails) and iodonium ion of octene in a micelle; conformations are arbitrary and are drawn for purposes of illustration

An alternative explanation could involve radical species, as frequently invoked for anti-Markovnikov regiochemistry, but we excluded it by carrying out all the experiments in the absence of light, which could have generated iodine atoms.

Optimization of Iodohydrin Syntheses

A rigorous statistical approach was used to optimize the syntheses. First, the yield (y) was assumed to be a function of four reaction parameters: temperature (T), buffer concentration [B], iodine concentration [I_2] and surfactant concentration [SDS]. The temperature could not be increased above 65 °C, owing to the volatility and low solubility in water of iodine present. Phosphate buffer (0.06 M, pH 7.0) was added to examine the effect on the products of neutralization of the hydriodic acid formed during reaction. Finally, two different concentrations of surfactant and iodine were examined, with concentrations above the cmc, which will also be significantly lowered by the very hydrophobic solutes. Higher [surfactant] forms more aggregates in solution, increasing the water−micellar interfacial reaction region.

The independent variable, y_k can be expressed as in Equation (1). The first term represents the sum of the individual effects while the second term represents potential interaction among the original variables.

$$y_k = \Sigma c_i \boldsymbol{x}_i + \Sigma_i \Sigma_j c_i \boldsymbol{x}_i \boldsymbol{x}_j \qquad (1)$$

In order to calculate estimates of the coefficient c in Equation (1), the experimental design method,[32] was adopted to perform a series of multivariate experiments. The outstanding feature of such an array of experiments is that all variables in Equation (1) are mutually orthogonal. Thus, they allow computation of the single, unbiased "effect" of every variable on the responses y_k. The obtained model function can then be used to determine specific values for each synthesis parameter (or interaction) that leads to maximum yield and minimum reaction time. By using SPECTRE software the following design matrix was obtained as a result of a two-level full factorial design (Table 4). For each variable two levels were tested: 45 °C and 65 °C; presence or absence of buffer to control pH; 0.03 mol/L and 0.06 mol/L for [I_2]; 0.01 mol/L and 0.1 mol/L for [SDS].

Table 4. Optimization of iodohydrin synthesis: experimental conditions yields and times

Entry	T (°C)	Buffer (M)	I_2 (M)	[SDS] (M)	Yield[a] (mol %)	Time[a] (h)
1	45	0	0.03	0.01	46	4
2	65	0	0.03	0.01	58	0.5
3	45	0.06	0.03	0.01	57	12
4	65	0.06	0.03	0.01	58	1
5	45	0	0.03	0.1	73	2
6	65	0	0.03	0.1	78	0.3
7	45	0.06	0.03	0.1	65	12
8	65	0.06	0.03	0.1	72	0.8
9	45	0	0.06	0.01	46	18
10	65	0	0.06	0.01	45	5
11	45	0.06	0.06	0.01	39	20
12	65	0.06	0.06	0.01	15	22
13	45	0	0.06	0.1	79	8
14	65	0	0.06	0.1	60	20
15	45	0.06	0.06	0.1	59	21
16	65	0.06	0.06	0.1	32	20

[a] Yields and times were the y_k responses used to estimate sensitivities (see text).

After running all 16 experiments the obtained yields and reaction times (Table 4) were introduced into the modeling function of SPECTRE and a refined mathematical model was obtained showing the effects of the four system variables and of two important interactions. These effects are given as "sensitivity" in Table 5. The sensitivity value is a direct measure of how much yield and time change when the related variable changes by half of the difference in the two levels of the design matrix. For example, in the design matrix [SDS] varies from 0.01 to 0.1 mol/L and half of this change will cause a change in yield ($y1$) of 9.94 units in the yield scale. The importance of the reaction parameters can thus be immediately read off the sensitivities. Therefore from Table 5 [SDS] appears to be the most important factor in increasing the yield, whereas it leaves reaction time unaffected. In contrast, the presence of buffer and the concentration of I_2 showed the strongest effect on lowering the reaction time.

Table 5. Effects of reaction parameters on iodohydrin formation shown as sensitivity

Variable	Sensitivity y1: yield	y2: time
Temperature	−2.9693	−1.7687
Buffer	−5.6802	3.2920
$[I_2]$	−8.5203	6.5452
[SDS]	9.9405	0.10334
Temperature × $[I_2]$	−6.1916	1.7686
Buffer × $[I_2]$	−5.2930	0.83910

The obtained function was then further processed by the software system to calculate the specific values for each parameter that will deliver maximum yield in the shortest reaction time. Such optimized conditions are shown in Table 6, and yields are almost quantitative for cyclohexene and 1-octene, but not for styrene.

Conclusion

Improvements in yields and shorter reaction times, relative to results in water, were obtained for all of the substrates when reactions were carried out in the presence of anionic surfactants and this was further improved when optimized conditions were used (Table 2 and 6; Figure 4). Cyclohexene gave very high yields under the optimized conditions: *trans*-2-iodocyclohexanol was obtained almost quantitatively but with no improvement in the reaction time.

An interesting result was obtained for the only aromatic system tested. After reacting for 24 hours in water, styrene gave no iodinated product with only side products recovered, the result of a polymerization reaction that is significantly faster than the productive reactions. This is probably due to the hydrophobicity of this aromatic alkene, which is insoluble in water so that, when iodine is added, ionic polymerization occurs in the styrene phase. In contrast, addition of a surfactant allows compartmentalization of styrene into micelles,[25] resulting in formation of a single halogenated product, 2-iodo-1-phenylethan-1-ol, in good yield (67%). The polymerization was not completely suppressed and some polymers were still recovered at the end of the reaction

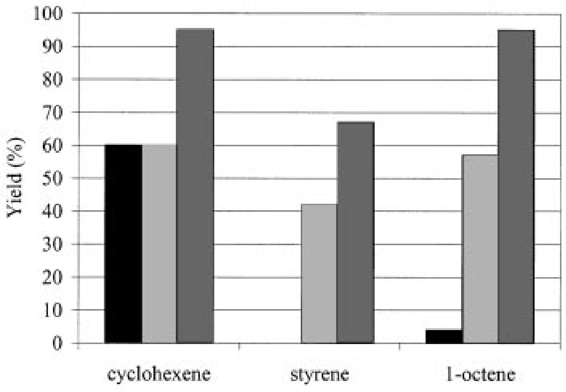

Figure 4. Iodination reaction yields for various alkenes; three different alkenes were reacted with iodine either aqueous conditions (black); in 0.05 M SDS (light gray); or by using the optimized conditions derived from the systematic approach described in the text (dark gray); the respective yields, determined as total product after extraction with Et_2O with respect to the iodine concentration, are shown

Finally a large increase in yield was obtained in micellar and optimized conditions for the linear 1-octene, which is almost completely unreactive in water, but was almost completely converted into a mixture of the two regioisomeric iodohydrins in the presence of anionic surfactants (Figure 4) but with a decrease in the relative amount of the Markovnikov product. The presence of micellar aggregates clearly influences the regioselectivity of the reaction. Only one of the possible iodohydrins is formed from styrene, with regioselectivity predicted by the Markovnikov rule, with polymerization partially suppressed by the anionic micelles. However, the anti-Markovnikov product of octene increases in anionic micelles owing to orientation of 1-octene in micelles. This is an interesting effect of micellar aggregates on

Table 6. Iodination in aqueous solution of SDS after optimization

Alkene[a]	Time (h)	Products	Regioisomers ratio ([a]/[b])	Yield (mol %)[b]
Cyclohexene	0.5	*trans*-2-iodocyclohexanol		95
Styrene[c]	8[d]	2-iodo-1-phenylethan-1-ol		67
1-Octene	7	1-iodooctan-2-ol (a) 2-iodooctan-1-ol (b)	2	95

[a] Temperature 60 °C, 0.15 M SDS, 0.03 M I_2 0.03 M phosphate buffer and 0.06 M alkene. [b] With respect to $[I_2]$. [c] 0.03 M styrene. [d] Styrene was added in small amounts over 8 hours.

the regiochemistry of the reaction, but it does not seem to change the overall reaction mechanism. Different solvation powers of micellar pseudophase and bulk water favor formation of a reaction intermediate that is more iodonium-ion like in micelles, while water stabilizes the more carbocation-like intermediate. In the micellar pseudophase, attack of water is favored on one of the two reactive carbon sites in the intermediate, resulting in a mixture of products.

Even if the system is not homogeneous it behaves like a "normal" micellar system; in fact we were able to qualitatively rationalize results in general terms of pseudophase models.

We report a new, easy and environmentally friendly method of synthesizing iodohydrins, important building blocks for organic synthesis, from alkenes and iodine in aqueous micellized anionic surfactants. We demonstrated that in the described conditions and in the presence of anionic micellar aggregates the equilibrium reaction with iodine is shifted towards the desired products, avoiding the use of scavengers or harsh oxidant. Cationic micelles are not useful in formation of iodohydrins as they probably induce the undesired back reaction with iodide ion.

Experimental Section

General Remarks: Reactions were carried out in aqueous solution with deionized, doubly distilled water. Commercial alkenes (Aldrich, Fluka) of the highest purity were used without further purification. CTABr was purified according to the method of Duynstee and Grunwald.[33] SDS and SANa (Fluka) were used without further purification. ^{1}H NMR (200.132 MHz) and ^{13}C NMR (50.323 MHz) spectroscopy was performed with an FT Bruker AC 200E NMR spectrometer. Peaks are reported relative to internal $CDCl_3$ at $\delta = 7.26$ ppm for proton and $\delta = 77.36$ ppm for carbon.

Product distribution and yields were determined by gas chromatographic analyses, using a calibrated internal standard on an HP 5890 gas chromatography system equipped with a flame-ionization detector (FID), with a fused-silica wide-bore column (30 × 0.53 mm), and poly(5%diphenyl-95% dimethylsiloxane) (CP = 8) or poly(dimethylsiloxane) (CP = 5) as the stationary phase. Yields were determined on the total recovered product with respect to total iodine and expressed as mol%.

Standard iodohydrins were prepared from the corresponding alkenes using periodic acid and sodium bisulfite.[14]

All reactions involved non-homogeneous mixtures, owing to the very low solubility of both reactants in water and their higher concentrations with respect to surfactants. Reactions were protected from light and followed visually, monitoring the disappearance of the intense iodine red color by removing the aluminum foil shield for a few seconds.

In the presence of I_2, a higher surfactant concentration was chosen (0.05 M) than that used in the presence of I_3^- (0.025 M). This is mainly due to the different solubility of these halogenating agents, the trihalide being much more soluble in water than the molecular iodine.

General Iodination Reactions without Surfactant: Molecular iodine (1.2 mmol), or I_3^-, formed in situ by adding potassium iodide (1.2 mmol), and the alkenes (2.4 mmol) were stirred, with a magnetic stirrer, in water (10 mL) at 60 °C until the red color of the iodine disappeared, but not longer than 100 h. Products were recovered by simple extraction with diethyl ether (5 times), drying the combined organic layers with $MgSO_4$, and removing the solvent in vacuo.

General Iodination Reactions with Surfactant: Reactions were performed as described above except that the iodine source and the alkene were added to the aqueous surfactant at concentrations above the cmc.

$CTAI_3$ and $CTAIBr_2$ were formed by adding I_2 and Br_2 (0.03 mmol) respectively, to aqueous CTAI (0.05 mmol); $CTABrI_2$ was prepared by adding I_2 (0.03 mmol) to CTABr (0.05 mmol) in water. These intense orange solutions were stirred at 60 °C before adding the substrates.

The products were isolated by continuous liquid−liquid extraction.

Surfactant Recovery: At the end of the reaction we stripped the product from the water−surfactant system for 6 h with a liquid−liquid extractor using diethyl ether as the solvent. The recovered water−surfactant system could then be reused for new reaction cycles.

Cetyltrimethylammonium Iodide (CTAI) Synthesis: Potassium iodide was added to a solution of CTABr (1 g) in water (50 mL). The precipitate was recovered by filtration and purified by recrystallization from acetone to yield CTAI as a white solid (1.1 g, 95% yield). ^{1}H NMR ($CDCl_3$): $\delta = 0.81$ (t, $J = 6.0$ Hz, 3 H, CH_3), 1.0−1.5 (m, 28 H, CH_2), 3.1−3.7 (m, 11 H, CH_2N and CH_3N) ppm. ^{13}C NMR ($CDCl_3$): $\delta = 14.0$ (CH_3), 22.5, 23.1, 25.9, 29.1, 29.19, 29.24, 29.3, 29.5, 31.7 (CH_2), 53.6 (NCH_3), 66.9 (NCH_2) ppm.

***trans*-2-Iodocyclohexanol:** NMR spectra conform to ref.[34] ^{1}H NMR ($CDCl_3$): $\delta = 3.58-3.78$ (m, 1 H, CHI); 3.85−4.15 (m, 1 H, $CHOH$) ppm. ^{13}C NMR ($CDCl_3$): $\delta = 23.6$, 27.2, 33.0, 37.8, 42.4, 75.2 ppm.

1-Iodooctan-2-ol: NMR spectra conform to ref.[34] ^{1}H NMR ($CDCl_3$): $\delta = 0.89$ (t, $J = 6.5$ Hz, 3 H, CH_3), 1.05−1.6 (m, 10 H, CH_2), 2.05 (s, 1 H), 3.07−3.55 (m, 3 H, CH_2I and $CHOH$) ppm. ^{13}C NMR ($CDCl_3$): $\delta = 14.1$, 16.6, 22.6, 25.6, 29.1, 31.7, 36.6, 71.1 ppm.

2-Iodooctan-1-ol: ^{1}H NMR ($CDCl_3$): $\delta = 0.89$ (t, $J = 6.5$ Hz, 3 H, CH_3), 1.05−1.6 (m, 10 H, CH_2), 2.17 (s, 1 H), 3.95−4.03 (q, 2 H, CH_2OH), 4.18−4.39 (m, 1 H, CHI) ppm. ^{13}C NMR ($CDCl_3$): $\delta =$ 14.1, 16.6, 22.6, 25.6, 29.1, 31.7, 33.6, 68.6 ppm.

2-Iodo-1-phenylethanol: NMR spectra conform to ref.[35] ^{1}H NMR ($CDCl_3$): $\delta = 2.39$ (s, 1 H, OH), 3.25−3.48 (m, 2 H, CH_2I), 4.70 (m, 1 H, $CHOH$), 7.30 (m, 5 H, C_{sp2} H) ppm. ^{13}C NMR ($CDCl_3$): $\delta = 15.1$, 73.9, 125.7, 128.3, 128.6, 141.2 ppm.

Acknowledgments

We wish to thank Dr. Jason C. Schense for help in editing the manuscript, and Prof. Clifford A. Bunton for his advice and helpful discussions. We also want to thank CNR Progetto Finalizzato Beni Culturali, COFIN '99 and INCA Green Chemistry Project, for financial support.

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Received February 10, 2003