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Table III. Neutral Hydrolysis of 1-3 in Dioxane-Water Mixtures at 25 °C

% dioxane (w/w)	n_{H_2O}	ε	$10^4 k_{obsd}$, s^{-1} 1	2	3
0.00	1.000	78.6	9.23	20.9	12.4
10	0.978	69.8	5.42	12.6	7.74
20	0.951	60.8	3.58	8.22	4.89
30	0.919	51.9	1.98	4.07	2.52
40	0.880	43.0	0.88	2.77	1.37
50	0.830	34.3	0.51	1.35	0.64
52.5	0.816	32.0	0.42	1.18	0.52

values obtained for **2** and **4** and for **3** and **5** lends support to the applicability of the enzyme model. The data in Table II indicate that inhibition of the hydrolysis is somewhat stronger by NaDodSO$_4$ than by CTAB. The association constants are quite high, in particular for **3**, the most hydrophobic substrate. As expected,[1a] the K values are rather similar for the anionic and cationic micelle.

Several factors can be invoked to rationalize the rate inhibition, the two most plausible being the reduced micropolarity and the decreased water concentration at the reaction sites in NaDodSO$_4$ and CTAB micelles.[12] Considering the first factor, it has been estimated that the effective dielectric constant is ca. 32 near the binding site of several fluorescent pH indicators at the surface of both NaDodSO$_4$ and CTAB micelles.[13] This smaller value with respect to that of water ($\epsilon = 78$) most likely reflects the proximity of the hydrocarbon chain and/or stems from a dielectric saturation effect.[14] Since the rates of neutral hydrolysis of 1-acyl-1,2,4-triazoles clearly respond to changes in solvent polarity,[9] k_{obsd} values were determined in the typically nonaqueous solvent[15] 1,4-dioxane–water as a function of the dielectric constant (ε). The results, summarized in Table III, show that at $\epsilon = 32$ the k_{obsd} values are close to the k_m values listed in Table II, the best correspondence being observed for hydrolysis of **1**–**3** in micellar NaDodSO$_4$. These findings suggest that the micellar rate effects can be accounted for without implying that the hydrolysis occurs in a relatively dry region of the micelle. Recently, in an independent study, Menger came to essentially the same conclusion based on kinetic data for the neutral hydrolysis of bis(4-nitrophenyl) carbonate in the presence of micelles of two cationic detergents.[16]

Of course, it is questionable how far any solvent system may faithfully mimic the average of the many reaction sites available at a micellar surface. But our results make it clear that the kinetic data as expressed in k_w/k_m for **1**–**3** are fully reconcilable with the reduced micropolarity at the micellar reaction sites. It is worth noting that this conclusion applies equally well for substrates of widely different hydrophobicities (**1** vs. **3**) and binding constants K. Thus, binding sites within the micelle which possess the specific structural features necessary for strong hydrophobic interactions are immersed in highly aqueous environments. This indicates that the micelles have a rugged surface, consistent with the micellar models proposed recently.[4-6,17]

Experimental Section

Materials. The 1-benzoyl-1,2,4-triazoles **2**–**5** were kindly supplied by Dr. W. Karzijn.[7,9b] NaDodSO$_4$ and CTAB were purified by standard methods.[1a] 1,4-Dioxane was purified by the method of Eigenberger[18] and finally passed through a column of alumina. The water used in the kinetic measurements was deionized and distilled twice. All solutions were acidified with dilute HCl to a pH value of ~4.0 in order to prevent catalysis by OH$^-$ ions.

1-Benzoyl-3-methyl-1,2,4-triazole (1) was prepared from 3-methyl-1,2,4-triazole[19] according to a general method:[20] mp 56.8–57.1 °C (from ether–hexane); ^{1}H NMR (Varian A-60, CDCl$_3$) δ 2.40 (s, 3 H), 8.73 (s, 1 H), 7.27–8.33 (m, 5 H); IR (Nujol) 1726 cm^{-1} (CO); UV (MeCN) λ_{max} 250.5 nm. Anal. Calcd for $C_{10}H_9N_3O$: C, 64.23; H, 4.55; N, 22.47. Found: C, 63.88; H, 4.79; N, 22.34.

Kinetic Measurements. The reactions were followed in 1-cm quartz cuvettes which were placed in a thermostated cell holder of a Cary 210 spectrophotometer. Under vigorous stirring, ca. 5 μL of a solution of **1**–**3** in acetonitrile was added to ca. 2.5 mL of the aqueous surfactant solution. The reactions were followed at the wavelength of maximum absorption of the substrates for about 3 half-lives. Good first-order kinetics were observed, and k_{obsd} values were reproducible to within 1.5%.

Binding Constants. The binding constants of **4** and **5** with CTAB were obtained with a Thomapore millipore filter. The circulation rate was 300 mL h^{-1} and the filtrate was collected at a rate of 9 mL h^{-1}. The analysis of the data was essentially similar to that used in the procedure with an artificial kidney.[21] The solute concentrations were determined by UV spectroscopy and the CTAB concentrations by titration with sodium tetraphenylborate.[22]

Registry No. **1**, 79745-99-6; **2**, 60718-51-6; **3**, 79746-00-2; **4**, 58905-26-3; **5**, 79746-01-3; SDS, 151-21-3; CTAB, 57-09-0.

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(12) One of the referees has pointed out that reduced water nucleophilicity could also be invoked as one of the factors determining the rate reduction. Although our results provide no evidence against this possibility, we note that previous studies have shown that water activity and probably also water nucleophilicity at the micellar surface do not deviate significantly from that in bulk water. See, for example: (a) Bunton, C. A.; Huang, S. K. *J. Org. Chem.* **1972**, *37*, 1790. (b) De Albrizzio, J. P.; Cordes, E. H. *J. Coll. Interface Sci.* **1979**, *68*, 292.

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Acid Hydrolysis of Carboxylic Esters in a Two-Phase System in the Presence of Catalytic Amounts of Quaternary Onium Salts. Mild and Selective Cleavage of *tert*-Butyl Esters

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Received April 13, 1981

Carboxylic acids are often protected by conversion into the corresponding *tert*-butyl esters,[1] which are highly stable under neutral and basic conditions and are indeed hydrolyzed under acidic conditions. The latter reaction is usually carried on at reflux in toluene in the presence of *p*-toluenesulfonic acid,[2] at room temperature in di-

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0022-3263/82/1947-0154$01.25/0

Table I. Hydrolysis of *tert*-Butyl Esters (1 mol) in a Two-Phase System in the Presence of Aqueous Mineral Acids (5 mol) at Room Temperature

substrate	aqueous acid (molarity)	moles of I	time, min	% yield conv[a]	% yield isol[b]
tert-butyl octanoate	H_2SO_4 (10)	0.1	1	94	93
	H_2SO_4 (10)	0.02	10	90	
	H_2SO_4 (10)	0.01	25	90	
	H_2SO_4 (10)	0	60	96	
	HBr (9)	0.1	45	96	94
	HBr (9)	0	1350	90	
	HCl (12)	0.1	100	95	93
	HCl (12)	0	1500	90	
tert-butyl dodecanoate	H_2SO_4 (10)	0.1	20	90	87
	H_2SO_4 (10)	0	1440	10	
tert-butyl benzoate[c]	H_2SO_4 (10)	0.1	40	92	91
	H_2SO_4 (10)	0	1800	92	

[a] Conversion yields as determined by GC analysis. [b] Only carboxylic acids were isolated. [c] A chloroform solution (1.5 mL/g of substrate) was used to avoid separation of benzoic acid.

chloromethane with hydrogen chloride,[3] at room temperature with an excess of trifluoroacetic acid,[4] or, in poor yields, at reflux in a 1:1 dioxane–sulfuric acid mixture.[5]

We now report that *tert*-butyl esters can be much more advantageously converted into carboxylic acids in a two-phase system by working at room temperature with aqueous mineral acids, i.e., 10 M H_2SO_4, 9 M HBr, or 12 M HCl,[6] in the presence of catalytic amounts of lipophilic quaternary onium salts such as hexadecyltributylphosphonium bromide (I, Table I) according to eq 1.

$$RCOOC_4H_9\text{-}t \xrightarrow[\text{room temperature}]{\text{HX(aq), I (catalyst)}} RCOOH \qquad (1)$$

$$X = HSO_4, Br, Cl; R = \text{alkyl, aryl}$$

tert-Butyl octanoate was used as a standard substrate for the screening of reaction conditions. The reaction times strongly depend on the amount of the catalyst (Table I), in the presence of I (0.1 mol) the reaction being 15–60 times faster than in its absence. Moreover, the rate decreases according to sequence: 10 M H_2SO_4 > 9 M HBr > 12 M HCl, this likely reflecting the different acidic strength of the aqueous medium.[7] By working at room temperature with 10 M H_2SO_4 (5 mol) in the presence of I (0.1 mol), in the case of *tert*-butyl octanoate and dodecanoate (1 mol) a nearly quantitative yield of carboxylic acid was obtained in 1 and 20 min, respectively (Table I).

Though the reactions were usually performed in the absence of organic solvents, the hydrolysis can be carried on in the presence of chloroform in comparable times (Table I). The selectivity of reaction 1 is high: alcohols,[8] ethers,[9] alkenes,[10] nitriles,[11] carboxylic amides,[11] and carboxylic esters of primary alcohols not being affected under the reaction conditions.

These last substrates, however, can be advantageously hydrolyzed with a similar procedure under more drastic reaction conditions (Table II).

Table II. Hydrolysis of Carboxylic Ester of Primary Alcohols and Phenols (1 mol) with 9 M HBr (5 mol) at 110 °C

substrate	reaction conditions time, h	reaction conditions moles of I	% yield conv[a]	% yield isolated[b] alkyl bromide or PhOH	% yield isolated[b] acid
methyl octanoate	0.25	0.1	94		91
methyl octanoate	1.5	0	90		
butyl octanoate	3.5	0.1	94	84	91
octyl octanoate[c,d]	3.5	0.1	94	86	92
octyl octanoate	10	0.05	93		
octyl octanoate	70	0	91		
phenyl octanoate[e]	0.1	0.1	94	91	92
methyl dodecanoate	0.33	0.1	97		94
octyl benzoate	12	0.1	94	86	92
dodecyl acetate	2.5	0.1	96	94	

[a] Conversion yields as determined by GC analysis. [b] All of the isolated products were identified by comparing their spectroscopic, chromatographic, and physical data with those of authentic samples. [c] 94% GC yield in 22 and 7 h with 1.5 and 3.5 mol of 9 M HBr, respectively. [d] 90% GC yield in 22 h at 100 °C. [e] Same results with 0.5–5 mol of 9 M HBr.

The classic saponification of esters[12] carried on in a two-phase system in the presence of quaternary onium salts is of limited applicability.[13] On the contrary, acid hydrolysis under two-phase conditions (eq 2) is general,

$$RCOOR' \xrightarrow[110\ ^\circ C]{\text{HBr(aq), } Q^+X^- \text{ (catalyst)}} RCOOH \qquad (2)$$

$$R' = \text{alkyl, aryl}; Q = \text{alkyl}_4N, \text{alkyl}_4P$$

is very simple, and favorably compares with the best reported method[14] which requires large amounts of CH_3COOH or HCOOH as solvents and methanesulfonic acid as a hydrolyzing agent at reflux temperatures. Reaction 2 is carried on at 110 °C with aqueous 9 M HBr and catalytic amounts of quaternary onium salts.

Alkyl and phenolic esters are hydrolyzed in nearly quantitative yields (Table II) to give the corresponding carboxylic acids and alkyl bromides or phenols, respectively. As expected,[8-10] the reaction time decreases with increasing amounts of quaternary onium salts. The reaction rates are 6–20 times faster in the presence of cat-

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alysts[15] (0.1 mol) than in their absence, the highest differences being met with in the case of substrates insoluble in the aqueous phase. In the case of esters of primary alcohols, attempts to perform the hydrolysis with 10 M H_2SO_4 failed. This is likely due to the fact that, also under two-phase conditions, acid hydrolysis of *tert*-butyl esters proceeds via unimolecular alkyl-oxygen fission ($A_{AL}1$), whereas in the case of esters of primary alcohols the reactions involve cleavage of the acyl-oxygen bond ($A_{AC}2$), nucleophilic assistance by ions such as Br^- apparently playing an important role.[17]

In the case of alkyl esters the rate strongly depends on the amount of the acid, while in the case of phenolic esters the rate is not affected by the quantity of the acid in the range 0.5–5 mol. This is likely related to the fact that with alkyl esters HBr is consumed during the reaction.

Experimental Section

GC Data were obtained on a Hewlett-Packard Model 5840 A gas chromatograph using a 2-m 3% SE-30 on Chromosorb column acting in the presence of internal standards; conversions were corrected for detector response.

Materials. Mineral acids were reagent grade products. Quaternary onium salts were commercial products. Esters, prepared by standard procedures, assayed by GC showed $\geq$98% purity: methyl,[18] *n*-butyl,[18] *n*-octyl,[19] and phenyl octanoates,[20] methyl dodecanoate,[21] *n*-octyl benzoate,[22] *n*-dodecyl acetate.[23] *tert*-Butyl esters were prepared from the corresponding acid chlorides and *tert*-butyl alcohol in the presence of *N,N*-dimethyl aniline in anhydrous ethyl ether or benzene according to a described procedure:[24] *tert*-butyl octanoate,[25] *tert*-butyl dodecanoate,[25] *tert*-butyl benzoate.[26]

Typical Procedure for the Hydrolysis of Esters of Primary Alcohols. A mixture of ester (0.1 mol), 55.5 mL of 48% hydrobromic acid (0.5 mol), and the quaternary onium salt (0.01 mol) was heated at 110 °C under magnetic stirring, the process being monitored by GC analysis. At the end of the reaction the layers were separated by adding ethyl ether. The organic phase was washed with water, 5% sodium hydrogen carbonate solution, and water again and then dried. Elimination of the solvent and distillation of the residue afforded the alkyl bromide. By treating the distillation residue with petroleum ether, pure catalyst was recovered in $\geq$90% yield. Acidification and extraction of the aqueous alkaline phase afforded the carboxylic acid.

In the case of phenolic esters, the carboxylic acid and the phenol were recovered from the organic phase by extraction with 5% sodium hydrogen carbonate and 10% sodium hydroxide, respectively.

Typical Procedure for the Hydrolysis of *tert*-Butyl Esters. A mixture of *tert*-butyl ester (0.1 mol), aqueous acid (0.5 mol; see Table I), and the quaternary onium salt (0.01 mol) was stirred at room temperature, the process being monitored by GC analysis. At the end of the reaction the mixture was worked up as described above to yield the carboxylic acid and the catalyst.

Registry No. *tert*-Butyl octanoate, 5457-66-9; *tert*-butyl dodecanoate, 7143-18-2; *tert*-butyl benzoate, 774-65-2; methyl octanoate, 111-11-5; *n*-butyl octanoate, 589-75-3; *n*-octyl octanoate, 2306-88-9; phenyl octanoate, 5457-78-3; methyl dodecanoate, 111-82-0; octyl benzoate, 94-50-8; dodecyl acetate, 112-66-3; octanoic acid, 124-07-2; dodecanoic acid, 143-07-7; benzoic acid, 65-85-0; *n*-butyl bromide, 109-65-9; *n*-octyl bromide, 111-83-1; phenol, 108-95-2; *n*-dodecyl bromide, 143-15-7.

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Communications

Oxidation of Thiols by Nitric Oxide and Nitrogen Dioxide: Synthetic Utility and Toxicological Implications

Summary: Thiols are readily oxidized to disulfides by either nitric oxide or nitrogen dioxide. Reaction conditions are mild, and quantitative yields can be obtained. The reactions are useful for preparative purposes and may have toxicological significance.

Sir: The vital role of thiols and disulfides in living systems has focused attention on their interconversion reactions.[1,2] Although the literature contains reports of many reagents that oxidize thiols to disulfides,[3] it is surprising that the oxides of nitrogen (NO_x) have been virtually ignored in this respect. There are, however, two brief reports. In 1928, Reihlen et al.[4] reported that ethanethiol reacts with NO in the presence of KOH to give a 95% yield of ethyl disulfide and a gas consisting of 90% N_2O and 10% N_2, plus unreacted NO. In 1962, Longhi et al.[5] reported that several thiols are oxidized to disulfides in excellent yields by NO in the presence of sodium methoxide; the nitrogen-containing products were not identified, and the mechanism was not discussed.

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