alternative open zwitterions **7** and **8** cannot give directly the acyl-shifted and ene products, respectively, and in our view are therefore less likely candidates. When an appropriate allylic hydrogen is available, the intermediate follows a path to the ene product regardless of solvent. Lacking an appropriate hydrogen, cyclization to the dioxetane predominates in methanol, where intermolecular hydrogen bonding satisfies part of the negative charge of the intermediate. In acetone, where external hydrogen bonds are unavailable, stronger interaction with the carbonyl group leads exclusively to the acyl-shifted product.

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o-Iodosobenzoate: Catalyst for the Micellar Cleavage of Activated Esters and Phosphates

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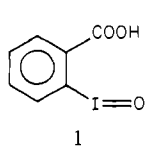
Long ago, *o*-iodosobenzoic acid (**1**) was suggested to exist in



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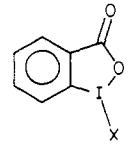

2, X = OH
3, X = O⁻
4, X = $OCOCH_3$

its 1-hydroxy-1,2-benziodoxolin-3-one valence tautomeric form (**2**).[1] Cogent support for this proposal appeared in 1965.[2] From the anomalously high pK_a of **1** or **2** (variously given as 6.22[2] or 7.4[3]), we infer that its conjugate base, anion **3**, could be a potent O nucleophile near neutral pH. However, despite its well-established biochemical role as an oxidant of protein thiol groups,[4] the nucleophilic properties of *o*-iodosobenzoic acid (*o*-IBA) have not been defined.

We now report that, when solubilized in aqueous micellar solutions of cetyltrimethylammonium chloride (CTACl) at pH 8, *o*-IBA is an efficient cleavage reagent for *p*-nitrophenyl acetate (PNPA) and *p*-nitrophenyl diphenyl phosphate (PNPDPP). More importantly, in the presence of excess substrate, *o*-IBA rapidly "turns over"; i.e., it is a true catalyst. Finally, the kinetic inactivity (under comparable conditions) of *m*-iodosobenzoic acid leaves little doubt that the functional group cooperativity expressed in structures **2** or **3** is essential to the catalytic activity of *o*-IBA.

Pseudo-first-order rate constants for cleavages of PNPA under various reaction conditions appear in Table I. In the absence of CTACl (run 1), nonmicellar catalysis by *o*-IBA is minimal, and the reaction is slow. Micellar cleavages are also sluggish when *o*-IBA is omitted (run 2) or when such bogus catalysts as benzoic acid (run 3) or *m*-iodosobenzoic acid[5] are added.[6] However, when 10^{-4} M *o*-IBA and 10^{-5} M PNPA are reacted in the presence of increasing concentrations of CTACl, we observe a [surfactant]/rate constant profile typical[7] of micelle-catalyzed reactions (*cf.* Figure 1).

Table I. Rate Constants for Cleavages of PNPA by *o*-Iodosobenzoate[a]

run	[CTACl], M	10^4[2], M	$10^4 k_\psi$, s^{-1}
1	1.0×10^{-2} [b]	1.0	2.64 ± 0.03
2	1.0×10^{-2}	0.0	4.05 ± 0.05
3	1.0×10^{-2}	1.0[c]	4.45 ± 0.16
4	1.0×10^{-2}	1.0[d]	6.20 ± 0.02
5	1.0×10^{-4}	1.0	2.66 ± 0.06
6	1.0×10^{-2}	1.0	180 ± 2.5
7	2.0×10^{-2}	1.0	185 ± 1.0
8[e]	1.0×10^{-2}	1.0	238 ± 9.0

[a] Conditions: 0.02 M phosphate buffer, 1.1 vol % DMF, pH 8.0, μ = 0.08 (NaCl), 26 ± 0.5 °C. The substrate concentration was 1×10^{-5} M, and the reactions were followed by the release of *p*-nitrophenoxide ion at 400 nm. Reproducibilities are average deviations of at least two determinations. [b] $Me_4N^+Cl^-$ instead of CTACl. [c] Benzoic acid instead of 2. [d] *m*-iodosobenzoic acid instead of 2. [e] pH 7.88 and PNPDPP instead of PNPA.

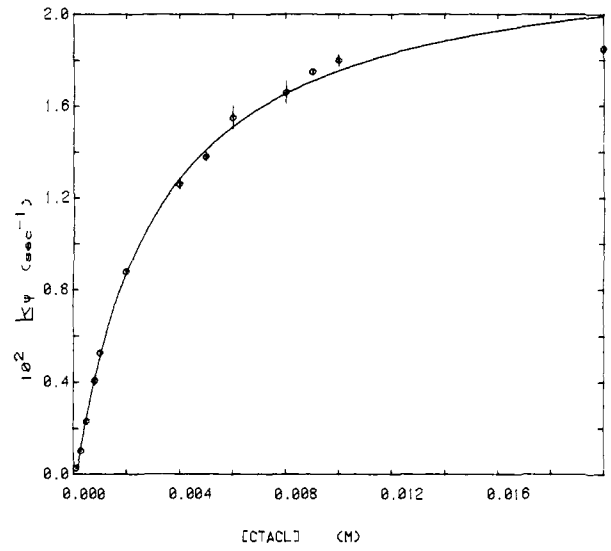

Figure 1. Pseudo-first-order rate constants, k_ψ (s^{-1}) vs. [CTACl] (M) for the micellar cleavage of 1×10^{-5} M PNPA by 1×10^{-4} M *o*-iodobenzoic acid. For other reaction conditions, see Table I and text. The solid line is generated from Lineweaver–Burke parameters described in the text.

Rate constants determined at 13 CTACl concentrations, ranging from 1.0×10^{-4} M (submicellar, run 5, Table I) to 2.0×10^{-2} M (run 7), appear in the figure; k_ψ reaches a maximum value ($\sim 1.8 \times 10^{-2}$ s^{-1}) at $\sim 1.0 \times 10^{-2}$ M CTACl (run 6) and then enters a plateau region. Lineweaver–Burke analysis[7] of these data gives $k_{micellar} = 2.18 \times 10^{-2}$ s^{-1} and $K/N = 362$ M^{-1}, where K/N is the ratio of the binding constant (for PNPA and/or **2**) to the micellar aggregation number. The solid line in Figure 1, which is generated from these parameters and a best-fit critical micelle concentration of 3×10^{-4} M, agrees very well with the experimental data up to the beginning of the plateau. From $k_{micellar}$ and $k_{buffer} = 1.8 \times 10^{-5}$ s^{-1} (for uncatalyzed cleavage of PNPA under closely comparable buffer conditions[6]), we obtain a factor of

(1) Meyer, V.; Wachter, W. *Chem. Ber.* **1892**, *25*, 2632. Willgerodt, C. "Die Organischen Verbindungen mit Mehrwertigen Jod"; Enke: Stuttgart, 1914; p 134. Banks, D. E. *Chem. Rev.* **1966**, *66*, 243 (see especially p 255).

(2) Baker, G. P.; Mann, F. G.; Sheppard, N.; Tetlow, A. J. *J. Chem. Soc.* **1965**, 3721. See, also, the X-ray crystal structure: Shefter, E.; Wolf, W. *J. Pharm. Sci.* **1965**, *54*, 104; *Nature (London)* **1964**, *203*, 512.

(3) Caraway, W. T.; Hellerman, L. *J. Am. Chem. Soc.* **1953**, *75*, 5334. A similar value (7.35 ± 0.13) is given by Wolf et al.: Wolf, W.; Chen. J. C. J.; Hsu, L. L. J. *J. Pharm. Sci.* **1966**, *55*, 68.

(4) Means, G. E.; Feeney, R. E. "Chemical Modification of Proteins"; Holden-Day: San Francisco, 1971; pp 167 ff. See also: Mahoney, W. L.; Hermodson, M. A. *Biochemistry* **1979**, *18*, 3810.

(5) Willgerodt, C. *Chem. Ber.* **1894**, *27*, 2326.

(6) Micellar CTACl alone (run 2) accelerates the pH 8 hydrolysis of PNPA by ~9 times: Moss, R. A.; Nahas, R. C.; Ramaswami, S.; Sanders, W. J. *Tetrahedron Lett.* **1975**, 3379. We therefore estimate that *nonmicellar* *o*-IBA (run 1) provides a catalytic factor of ~6 in PNPA cleavage, relative to buffer alone.

(7) Fendler, J. H.; Fendler, E. J. "Catalysis in Micellar and Macromolecular Systems" Academic Press: New York, 1975; especially chapters 4 and 5.

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Table II. Cleavage of Excess Substrate by *o*-Iodosobenzoate[a]

run	substrate	[substrate], M	[substrate]/[2]	$10^4 k_\psi$, s^{-1}
1	PNPA	1.0×10^{-5}	1:10	152 ± 1[b]
2	PNPA	1.0×10^{-4}	1:1	130 ± 2
3	PNPA	5.0×10^{-4}	5:1	100 ± 1
4	PNPA	1.0×10^{-3}	10:1	90 ± 2
5	PNPDPP	1.0×10^{-5}	1:10	260 ± 4
6	PNPDPP	1.0×10^{-4}	1:1	249 ± 8
7	PNPDPP	5.0×10^{-4}	5:1[c]	235 ± 5

[a] Conditions: 0.02 M phosphate buffer, 3.3 vol % DMF, pH 8.0, μ = 0.08 (NaCl), 26 ± 0.5 °C; [CTACl] = 0.01 M; [2] = 1.0×10^{-4} M. Release of *p*-nitrophenoxide ion was followed at successively longer λ (lower ϵ) as [substrate] increased. [b] The lower rate constant, relative to run 6 in Table I, is due to the higher concentration of DMF (3.3 vs. 1.1 vol %). [c] Solubility problems with PNPDPP prevented us from obtaining data at 10:1 substrate/2.

~1200 for the catalysis of PNPA cleavage by micellar *o*-IBA/CTACl.

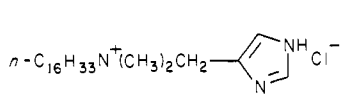
The cleavage of the active phosphate substrate, PNPDPP, is also strongly catalyzed by *o*-IBA/CTACl. At 0.01 M surfactant and 1×10^{-4} M *o*-IBA, $k_\psi = 2.38 \times 10^{-2}$ s^{-1} (run 8). Comparison with an uncatalyzed reaction in 0.02 M Tris buffer at pH 9, which gives $k_\psi = 2.9 \times 10^{-5}$ s^{-1},[8] leads to a catalytic factor of >820.

A pH-rate constant profile (not shown) was determined for reactions of 10^{-5} M PNPA with 10^{-4} M *o*-IBA in 10^{-2} M CTACl (0.02 M phosphate or acetate buffers, μ = 0.08). Ten rate constants were determined over the pH range 4.5-9.55. A sharp discontinuity (abrupt decrease in slope) in log k_ψ vs. pH was found at pH 7.25, with excellent linearity on either side of the break point. Taking 7.25 as the systematic pK_a of *o*-IBA under our reaction conditions implies that **2** is ~85% converted to **3**, its catalytically active form, at pH 8.0.

We prepared[2] **4**, the acetyl derivative of **2** and the putative intermediate in nucleophilic cleavage of PNPA by anion **3**.[9] Ester **4** decayed rapidly at pH 8 in 0.01 M micellar CTACl, with k_ψ ~0.4 ± 0.1 s^{-1}. The reaction was followed spectrophotometrically at 276 nm, λ_{max} for **4** (in DMF, ϵ 2520). Although the hydrolytic instability of **4** makes for poor precision in this determination, the rate constant for deacetylation of **4** is ~20 times larger than k_ψ for PNPA cleavage by *o*-IBA under comparable conditions (Table I, run 6). Thus **4** should not accumulate during the reaction of PNPA with *o*-IBA/CTACl. Indeed, no increase in absorbance at 276 nm could be detected during such reactions.

The behavior of *o*-IBA/CTACl in the presence of *excess* substrate was consistent with these indications of efficient turnover. The data in Table II (runs 1-4) show that the apparent value of k_ψ for liberation of *p*-nitrophenoxide ion from PNPA decreased by only ~40% as the substrate/catalyst ratio increased from 1:10 to 10:1. The kinetics remained pseudo first order, and "burst kinetics"[10] were not observed. A similar pattern held for the cleavage of PNPDPP (runs 5-7); there was no evidence for the accumulation of a phosphoryl derative of *o*-IBA.

Micellar reagents such as the imidazolyl surfactant **5** catalyze



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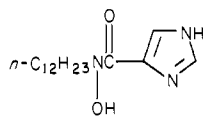

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cleavages of PNPA[11] and PNPDPP[12] at moderate pH with kinetic parameters similar to those of *o*-IBA/CTACl.[12] However, to our knowledge, *o*-IBA/CTACl is the only "monofunctional" O-functionalized micellar catalyst capable of both efficient cleavage *and* turnover with active ester and phosphate substrates.[13] For example, oximate ions in micellar CTABr rapidly cleave *p*-nitrophenyl esters at pH 8 and PNPDPP at pH 10, but hydrolytic regeneration of the acylated or phosphorylated oximates is very slow at pH 8.[14] Certain bifunctional O,N catalysts such as lauryl(4-imidazolecarbo)hydroxamic acid, **6**, in micellar CTABr are capable of true catalytic cleavage of activated esters[15] but lack the "off the shelf" simplicity of *o*-IBA/CTACl. Moreover, in the cleavage of PNPA, *o*-IBA in CTACl is more efficient than either **5** or **6** (in CTABr) because the deacetylation of **4** is more rapid than the acetylation of **2** and doesn't become rate-limiting when the substrate is in moderate excess.[16]

Acknowledgment. We are grateful to the U.S. Army Research Office, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation for financial support.

(8) Moss, R. A.; Ihara, Y. *J. Org. Chem.*, in press.

(9) Solvent isotope effects (k_{H_2O}/k_{D_2O}) were determined for cleavages of PNPA and PNPDPP in 0.2 M phosphate buffer at pH (pD) 8.0 (μ = 0.54). With [CTACl] = 0.01 M, [**2**] = 1×10^{-4} M, and [substrate] = 1×10^{-5} M, the solvent isotope effects were 1.03 and 1.12 for PNPA and PNPDPP, respectively. These values are consistent with nucleophilic cleavage mechanisms involving anion **3** but inconsistent with mechanisms in which **3** functions as a general base.

(10) Bender, M. L.; Kézdy, F. J.; Wedler, F. C. *J. Chem. Educ.* **1967**, *44*, 85.

(11) Tagaki, W.; Chigira, J.; Ameda, T.; Yano, Y. *J. Chem. Soc., Chem. Commun.* **1972**, 219. Tonellato, U. *J. Chem. Soc., Perkin Trans. 2* **1976**, 771. Moss, R. A.; Nahas, R. C.; Ramaswami, S. *J. Am. Chem. Soc.* **1977**, *99*, 627. With 5×10^{-3} M **5** in 0.4 M, pH 8 phosphate buffer, PNPA is cleaved with k_ψ ($=k_{acylation}$ of **5**) = 0.051 s^{-1}, followed by $k_{decylation}$ (of *N*-acetyl-**5**) = 0.015 s^{-1}. Note that deacylation is slower than acylation; the opposite is true for *o*-IBA/CTACl.

(12) Brown, J. M.; Bunton, C. A.; Diaz, S.; Ihara, Y. *J. Org. Chem.* **1980**, *45*, 4169. Brown, J. M.; Bunton, C. A.; Diaz, S. *J. Chem. Soc., Chem. Commun.* **1974**, 971. For micellar **5** and PNPDPP, k_ψ = 0.0031 s^{-1} at pH 8; the imidazole here functions as a general base catalyst.

(13) Reviews: O'Connor, C. J.; Ramage, R. E.; Porter, A. J. *Adv. Colloid Interface Sci.* **1981**, *15*, 25. Kunitake, T.; Shinkai, S. *Adv. Phys. Org. Chem.* **1980**, *17*, 435. Bunton, C. A.; Romsted, L. S. In "The Chemistry of Functional Groups, Suppl. B: The Chemistry of Acid Derivatives", Part 2; Patai, S., Ed.; Wiley: New York, 1979; pp 945 ff.

(14) Bunton, C. A.; Ihara, Y. *J. Org. Chem.* **1977**, *42*, 2865.

(15) Kunitake, T.; Okahata, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1976**, *98*, 7799. At pH 8 (30 °C, 0.01 M borate, μ = 0.01), **6**/CTABr cleaves PNPA ~5 times faster than *o*-IBA/CTACl. However, deacetylation of *O*-acetyl-**6** is ~7 times *slower* than deacetylation of **4**.

(16) Under micellar conditions at pH 8, $k_{deacetylation}$ is ~0.4, 0.015, and 0.065 s^{-1} for acetylated **2**, **5**,[11] and **6**,[15] respectively.

Rearrangement of an Alkyl-Substituted Anthraquinone. A Model for the Biosynthetic Rearrangement of the Averufin Side Chain

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Various mechanisms have been proposed for the biosynthesis of aflatoxin B_1 (**1**, Chart I) a potent carcinogenic mycotoxin produced by the fungi *Aspergillus flavus* and *Aspergillus parasiticus*.[1-3] In all these biosynthetic schemes, versicolorin A (**2**), has been proposed as an intermediate, which in turn is derived from averufin (**3**). Averufin (**3**) bears an unbranched C_6 side chain on a polyhydroxyanthraquinone, and its conversion to the branched-chain aldehyde versiconal acetate (**4**) has been speculated to involve loss of the terminal acetyl unit by a Baeyer-Villiger process,[1] as well as a side-chain skeletal rearrangement proceeding

(1) Steyn, P. S.; Vleggaar, R.; Wessels, R. L. In "The Biosynthesis of Mycotoxins"; Steyn, P. S., Ed.; Academic Press: New York, 1980; pp 105-155, and references therein.

(2) Simpson, T. J.; De Jesus, A. E.; Steyn, P. S.; Vleggaar, R. *J. Chem. Soc., Chem. Commun.* **1982**, 631.

(3) Simpson, T. J.; De Jesus, A. E.; Steyn, P. S.; Vleggaar, R. *J. Chem. Soc., Chem. Commun.* **1982**, 632.

0002-7863/83/1505-0682$01.50/0