isooctane/ether, 1/1, to give 5.8 g (47%) of 2,3-diethylmaleimide: mp 69–70 °C (lit.[47] mp 68 °C, lit.[48] mp 68–70 °C); $R_t$ (GC) 3.30 min.

***cis*-3,4-Diethylpyrrolidine-2,5-dione (*cis*-2,3-Diethylsuccinimide).** To 180 mg (0.85 mmol) of the above 3,4-diethyl-1*H*-pyrrole-2,5-dione in 10 mL of ethyl acetate was added 18 mg of $PtO_2$. Hydrogen at 50 psi was applied for 6 h,[31] the solution was filtered through Celite, and the filtrate was evaporated to give 132 mg (100%) of residue. GC analysis showed a 95/5 mixture of cis/trans isomers which may be due to epimerization during analysis, as the cis compound was never found completely free of the trans by GC analysis.[50] The product was recrystallized from MeOH/$H_2O$ and sublimed at 70 °C/1 torr to give a 98/2 ratio of cis/trans 2,3-diethylsuccinimide as white crystals: mp 87–89 °C; $R_t$ (GC) cis 5.16 min, trans 4.17 min; UV $\lambda_{max}$ (log $\epsilon$) 246 (1.93), 221 nm (2.28); IR (KBr) 3130, 1670, 1340 $cm^{-1}$; NMR ($CDCl_3$, 90 MHz) $\delta$ 1.02 (t, 6 H, 2 × $CH_2CH_3$, $J$ = 7.5 Hz), 1.54–1.77 (m, 4 H, 2 × $CH_2CH_3$), 2.70–2.83 (m, 2 H, 2 × CH), 8.32 (br, s, 1 H, NH). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.9; H, 8.4; N, 9.0. Found: C, 61.9; H, 8.4; N, 8.8.

***trans*-3,4-Diethylpyrrolidine-2,5-dione (*trans*-2,3-Diethylsuccinimide).** To the above *cis*-3,4-diethylpyrrolidine-2,5-dione (153 mg, 1.00 mmol) was added a solution of 2.24 g (2.00 mmol) of potassium *tert*-butoxide in 60 mL of *tert*-butyl alcohol. After refluxed for 2 h, the solution was cooled and the *tert*-butyl alcohol was evaporated. Aqueous 1 M $H_3PO_4$ (20 mL) was added and the aqueous phase was extracted with $CH_2Cl_2$ (5 × 10 mL) which was dried and evaporated to give 143 mg (93%) of *trans*-2,3-diethylsuccinimide, mp 59–60 °C after recrystallization from $H_2O$ and sublimation at 70 °C/1 torr: $R_t$ (GC) 4.17 min; UV $\lambda_{max}$ (log $\epsilon$) 244 (1.64), 220 nm (2.22); IR (KBr) 3140, 1670, 1175 $cm^{-1}$; NMR ($CDCl_3$, 90 MHz) $\delta$ 1.00 (t, 6 H, 2 × $CH_2CH_3$, $J$ = 7.5 Hz), 1.60–1.90 (m, 4 H, 2 × $CH_2CH_3$), 2.42–2.53 (m, 2 H, 2 × CH), 8.80 (br, s, 1 H, NH). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.9; H, 8.4; N, 9.0. Found: C, 62.2; H, 8.4; N, 8.9.

**3-Ethyl-4-methyl-1*H*-pyrrole-2,5-dione (2-Ethyl-3-methylmaleimide).**[15,47,51] This compound was prepared from 3-ethyl-4-methylpyrrole[20,21,52] as described for the 3,4-diethyl-1*H*-pyrrole-2,5-dione above in 45% yield: mp 66–68 °C (lit.[15] mp 66–67 °C; lit.[47] mp 67–68 °C; lit.[51] mp 68 °C); $R_f$ (TLC) 0.89.

***cis*-3-Ethyl-4-methylpyrrolidine-2,5-dione (*cis*-2-Ethyl-3-methylsuccinimide).**[15,31] This compound was prepared as described[15] in quantitative yield: mp 48–50 °C (lit.[31] mp 50 °C); $R_f$ (TLC) cis 0.20, trans 0.30; $R_t$ (GC) cis 1.9 min, trans 1.3 min.[50]

***trans*-3-Ethyl-4-methylpyrrolidine-2,5-dione (*trans*-2-Ethyl-3-methylsuccinimide).**[31] This compound was prepared in an analogous manner to the *trans*-3,4-diethylpyrrolidine-2,5-dione above in 64% yield: mp 57–59 °C (lit.[31] mp 60–61 °C); $R_f$ (TLC) 0.30; $R_t$ (GC) 1.3 min.

**Bile Pigment Oxidative Degradations.**[32] To a solution of 250 mg of $Na_2Cr_2O_7$ in 6 mL of $H_2O$ was added 10 mg of the bile pigment in 2 mL of THF. The oxidation was allowed to proceed at room temperature for 2 h, then 10 mL of $H_2O$ was added, and the mixture was extracted with $CH_2Cl_2$ (5 × 10 mL). The combined organic phase was dried and evaporated. The residue of oxidation products from the octaethyldioxotetrapyrrole was analyzed by GC. In addition to the succinimide and maleimide products, an incomplete degradation product appears with a $R_t$ 8.30 min. The oxidation products from the bile pigments **20a**, **20b**, **21a**, and **21b** were analyzed by TLC.[33,34,37] In addition to the succinimide and 2-ethyl-3-methylmaleimide, 3-(2-(methoxycarbonyl)ethyl)-4-methyl-1*H*-pyrrole-2,5-dione (hematinic acid methyl ester) was seen at $R_f$ 0.50.

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**Registry No. 7**, 77469-08-0; **8**, 89279-27-6; **9**, 89279-28-7; **10**, 89279-29-8; **11**, 89361-42-2; **12**, 89361-43-3; **13a**, 766-45-0; **13b**, 766-36-9; **14**, 53751-01-2; **15a**, 89279-30-1; **15b**, 77611-80-4; **16a**, 31402-15-0; **16b**, 77611-79-1; **17a**, 13129-05-0; **17b**, 13129-09-4; **18a**, 89361-44-4; **18b**, 89361-45-5; **19a**, 89361-46-6; **19b**, 89361-47-7; **20a**, 89361-48-8; **20b**, 89361-49-9; **21a**, 89361-50-2; **21b**, 89361-51-3; 3,4-diethylpyrrole, 16200-52-5; 3,4-diethyl-3-pyrrolinone, 60651-43-6; 3,4-diethyl-1*H*-pyrrole-2,5-dione, 34085-07-9; *cis*-2,3-diethylsuccinimide, 89279-31-2; *trans*-2,3-diethylsuccinimide, 89279-32-3.

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# Catalytic Cleavage of Active Phosphate and Ester Substrates by Iodoso- and Iodoxybenzoates

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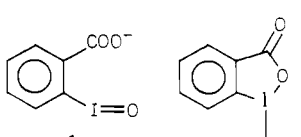
**Abstract:** *p*-Nitrophenyl acetate, *p*-nitrophenyl hexanoate, and *p*-nitrophenyl diphenyl phosphate (PNPDPP) were cleaved by *o*-iodosobenzoate, *o*-iodoxybenzoate, and 5-(*n*-octyloxy)-2-iodosobenzoate (**3**) in aqueous micellar cetyltrimethylammonium chloride solutions at pH 8. The system **3**/CTACl was the best catalyst and PNPDPP was the most reactive substrate. In a remarkably rapid hydrolytic reaction at 25 °C, $1.0 \times 10^{-5}$ M PNPDPP was cleaved by $7.14 \times 10^{-5}$ M **3** in $2.0 \times 10^{-4}$ M CTACl with $k_\psi$ = 1.04 $s^{-1}$. Experiments in which [PNPDPP] > [**3**] demonstrated that the catalyst "turned over"; i.e., degradation of an intermediate phosphate was not rate limiting.

When solubilized in pH 8 micellar cetyltrimethylammonium chloride (CTACl), *o*-iodosobenzoate (**1**) is an efficient catalyst




1




2

for the cleavage of *p*-nitrophenyl acetate (PNPA) and *p*-nitrophenyl diphenyl phosphate (PNPDPP).[1] The actual source of catalytic power is 1-hydroxy-1,2-benziodoxolin-3-one (1,3-dihydro-1-hydroxy-3-oxo-1,2-benziodoxole) (**2**) the valence tautomeric form in which **1** prefers to exist[2] and which appears to be a powerful O nucleophile. In this full report, these results are

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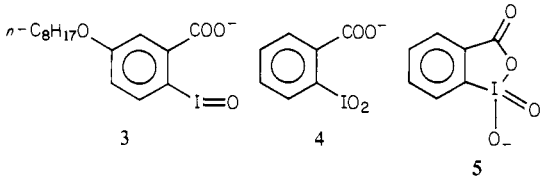
Table I. Iodosobenzoate and Iodoxybenzoate Cleavages in Micellar CTACl[a]

| case | catalyst | substrate | $10^2 k_\psi^{max}$, $s^{-1}$ [b] | $10^4 k_o$, $s^{-1}$ [c] | $k_\psi^{max}/k_o$ |
|---|---|---|---|---|---|
| 1 | *o*-iodoxybenzoate | PNPA | 1.27 (10.0) | 2.47 | 51.4 |
| 2 | *o*-iodoxybenzoate | PNPH | 1.20 (1.50) | 1.66 | 72.3 |
| 3 | *o*-iodoxybenzoate | PNPDPP | 1.78 (0.80) | 5.96 | 29.9 |
| 4 | *o*-iodosobenzoate | PNPA[d] | 1.80 (10.0) | 4.05 | 44.4 |
| 5 | *o*-iodosobenzoate | PNPH | 5.63 (1.00) | 1.64 | 343 |
| 6 | *o*-iodosobenzoate | PNPDPP | 6.45 (1.00) | 6.62 | 97.4 |
| 7 | (octyloxy)iodosobenzoate | PNPA | 3.39 (1.25) | 0.86 | 394 |
| 8 | (octyloxy)iodosobenzoate | PNPH | 54.0 (0.30) | 1.57 | 3440 |
| 9 | (octyloxy)iodosobenzoate | PNPDPP | 103 (0.20) | 5.72 | 1800 |

[a] Kinetic data are taken from Tables I-V of the supplementary material. Conditions: 0.02 M phosphate buffer, pH 8.0, $\mu$ = 0.08 (NaCl), 0.645 vol % DMF, 0.645 vol % $CH_3CN$, 25 ± 0.5 °C, [substrate] = $1.0 \times 10^{-5}$ M, [catalyst] = $1.0 \times 10^{-4}$ M (cases 1-6) or $7.14 \times 10^{-5}$ M (cases 7-9). [b] $k_\psi^{max}$ values are from Tables I-V of the supplementary material. Reproducibilities are <±3%. Values in parentheses are concentrations of CTACl × $10^3$ M at which $k_\psi^{max}$ is observed. [c] Rate constant in CTACl solution in *absence* of catalyst, but under otherwise identical conditions, including [CTACl] used to determine $k_\psi^{max}$; reproducibility <±3%. [d] Data from ref 1. Conditions: 0.02 M phosphate buffer, pH 8.0, $\mu$ = 0.08 (NaCl), 1.1 vol % DMF, 25 ± 0.5 °C, [PNPA] = $1.0 \times 10^{-5}$ M, [*o*-iodosobenzoate] = $1.0 \times 10^{-4}$ M.

significantly broadened. The newly synthesized (octyloxy)-iodosobenzoate **3** is found to be a far more potent catalyst than




3 4 5

**1**, particularly in the cleavage of PNPDPP. Additionally, we describe the catalytic properties of *o*-iodoxybenzoate (**4**), which is known to exist as the valence tautomer **5**.[3]

The results, which follow, contain [surfactant]–rate constant profiles for the cleavages of substrates PNPA, PHPH (*p*-nitrophenyl hexanoate), and PNPDPP by CTACl-solubilized catalysts **1**, **3**, and **4**.

## Results

**Synthesis.** The preparation of **3** involved the modification of older procedures[4] and is outlined in Scheme I. Coupling benzenediazonium ion to *o*-hydroxybenzoic acid (**6**) afforded the 4-phenylazo derivative, **7**, which was reduced to the corresponding aniline, **8**, with sodium dithionite. Conversion of **8** to the precursor iodobenzene **9** was accomplished by diazotization followed by dediazoniation with KI. The phenolic oxygen of **9** was then alkylated with *n*-octyl iodide/NaOEt affording ether **10**. The synthesis was then completed using the standard, two-step, chlorination/hydrolysis method for conversion of an iodobenzene to an iodosobenzene.[5]

**Kinetic Studies.** The catalytic properties of *o*-iodoxybenzoate (**4**), *o*-iodosobenzoate (**1**), and 5-(*n*-octyloxy)-2-iodosobenzoate (**3**) were assessed by determining full rate constant–[surfactant] profiles for the cleavages of PNPA, PNPH, and PNPDPP in micellar CTACl. These studies were all carried out under identical conditions: 0.02 M phosphate buffer, pH 8.0, $\mu$ = 0.08 (NaCl), 0.645 vol % DMF, 0.645 vol % $CH_3CN$, 25 ± 0.5 °C, [substrate] = $1.0 \times 10^{-5}$ M, [catalyst] = $1.0 \times 10^{-4}$ M (or $7.14 \times 10^{-5}$ M for catalyst **3**).

***o*-Iodoxybenzoate.** Tables I and II of the supplementary material present rate constants for cleavages of PNPA, PNPH, and PNPDPP by **4** as a function of [CTACl]; $1.0 \times 10^{-4}$ M ≤ [CTACl] ≤ $2.0 \times 10^{-2}$ M. The data are graphically presented in Figure 1. The associated values of $k_\psi^{max}$ and the CTACl concentrations necessary to obtain these rate constants appear in Table I, cases 1–3.

***o*-Iodosobenzoate.** Rate constant–[surfactant] data for the reaction of micelle-solubilized **1** with PNPA have been published.[1]

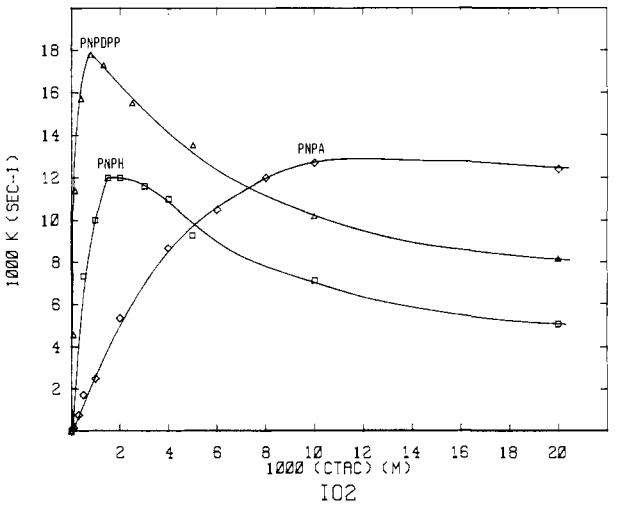
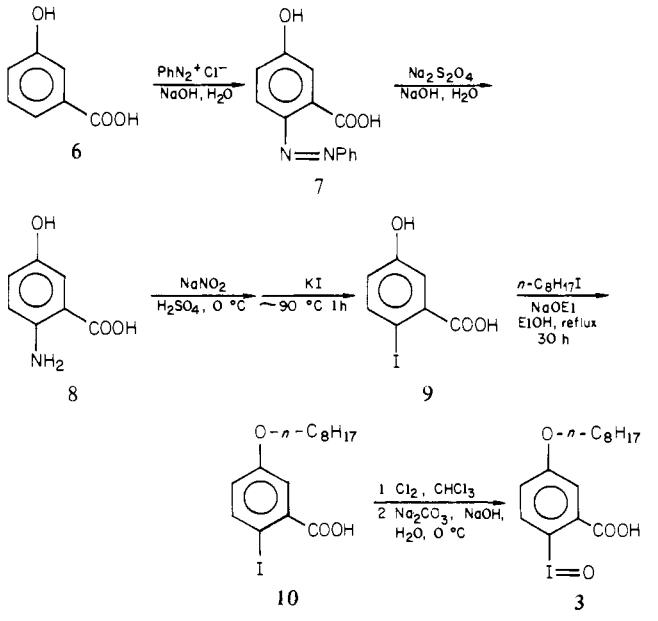



**Figure 1.** Pseudo-first-order rate constants ($k_\psi$, $s^{-1}$) for the cleavage of PNPA, PNPH, and PNPDPP by $1.0 \times 10^{-4}$ M *o*-iodoxybenzoate as a function of [CTACl] at pH 8.0. See text for reaction conditions and Table I for $k_\psi^{max}$ values.

Scheme I




Data for the analogous reactions of **1** with PNPH and PNPDPP appear in Table III of the supplementary material. The three profiles are reproduced in Figure 2, with $k_\psi^{max}$ values collected in Table I, cases 4–6.

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Table II. Cleavage of Excess Substrate by (Octyloxy)iodosobenzoate[a]

| substrate | [substrate], M | [CTACl], M | [substrate]/[catalyst][b] | $k$ $s^{-1}$ [c] |
|---|---|---|---|---|
| PNPA | $1.00 \times 10^{-5}$ | $1.25 \times 10^{-3}$ | 1:7.1 | 0.034 |
| PNPA | $7.14 \times 10^{-5}$ | $1.25 \times 10^{-3}$ | 1:1 | 0.030 |
| PNPA | $2.50 \times 10^{-4}$ | $1.25 \times 10^{-3}$ | 3.5:1 | 0.029[d] |
| PNPDPP | $1.00 \times 10^{-5}$ | $2.00 \times 10^{-4}$ | 1:7.1 | 0.98 |
| PNPDPP | $7.14 \times 10^{-5}$ | $2.00 \times 10^{-4}$ | 1:1 | 0.96 |
| PNPDPP | $2.50 \times 10^{-4}$ | $2.00 \times 10^{-4}$ | 3.5:1 | 0.90[d] |

[a] Conditions: 0.02 M phosphate buffer, pH 8.0, $\mu = 0.08$ (NaCl), 0.645 vol % DMF, 0.645 vol % $CH_3CN$, 25 ± 0.5 °C. [b] [Catalyst] = $7.14 \times 10^{-5}$ M. [c] Reproducibility is <±3%. [d] Reproducibility is <±5%.

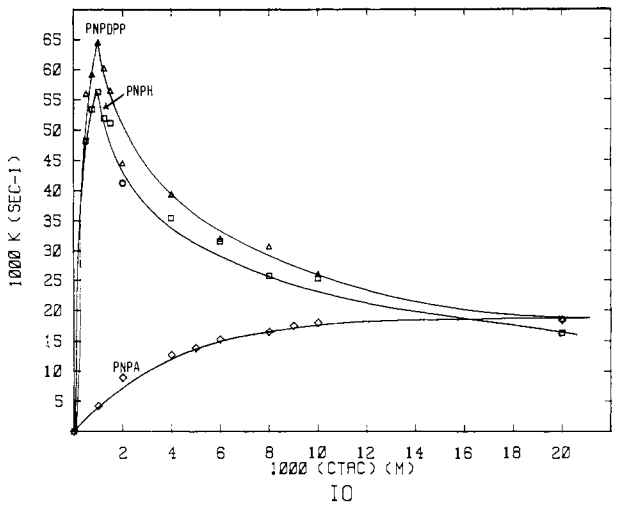



**Figure 2.** Pseudo-first-order rate constants ($k_\psi$, $s^{-1}$) for the cleavage of PNPA, PNPH, and PNPDPP by $1.0 \times 10^{-4}$ M *o*-iodosobenzoate as a function of [CTACl] at pH 8.0. See text for reaction conditions and Table I for $k_\psi^{max}$ values.

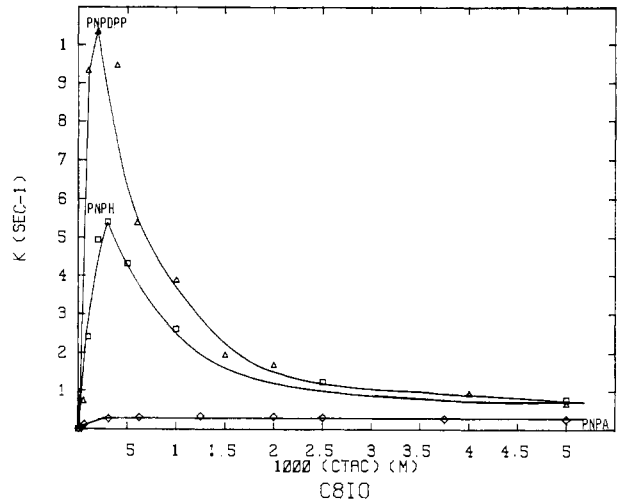



**Figure 3.** Psuedo-first-order rate constants ($k_\psi$, $s^{-1}$) for the cleavage of PNPA, PNPH, and PNPDPP by $7.14 \times 10^{-5}$ M 5-(*n*-octyloxy)-2-iodosobenzoate as a function of [CTACl] at pH 8.0. See text for reaction conditions and Table I for $k_\psi^{max}$ values.

**5-*n*-Octyloxy-2-iodosobenzoate.** Kinetic data for the reactions of CTACl-solubilized **3** with PNPA, PNPH, and PNPDPP are collected in Tables IV and V of the supplementary material. The profiles appear in Figure 3, with $k_\psi^{max}$ values listed in Table I, cases 7–9.

**Turnover Experiments.** Previously, we observed that the apparent value of $k_\psi$ for the liberation of *p*-nitrophenoxide ion from PNPA or PNPDPP by (CTACl micellar) **1** decreased only moderately in the presence of excess substrate.[1] This was taken as evidence favoring efficient turnover of intermediate O-acetylated or O-phosphorylated intermediates derived from **2** (cf. Table II in ref 1). A similar study has now been carried out for cleavages of PNPA and PNPDPP by CTACl-solubilized micellar **3**. The results, which appear in Table II, are supportive of true catalysis (i.e., turnover) by (octyloxy)iodosobenzoate.

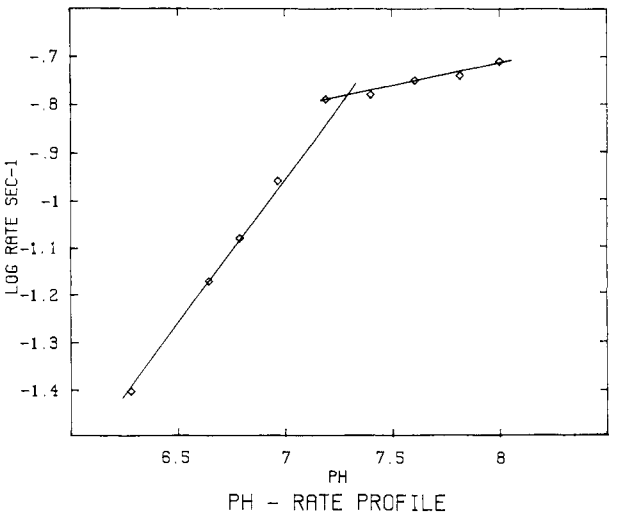
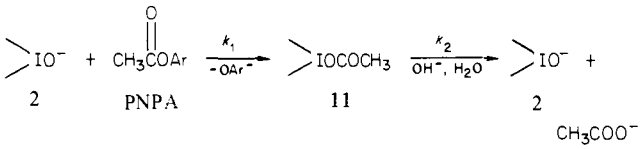



**Figure 4.** pH–rate profile for the cleavage of PNPDPP by $1.0 \times 10^{-4}$ M **3** in $1.5 \times 10^{-3}$ M CTACl; log $k_\psi$ ($s^{-1}$) vs. pH. The discontinuity at pH 7.2 is taken as the systemic $pK_a$ of **3**. See text for reaction conditions.

Scheme II

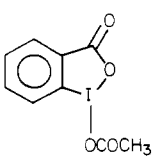



**$pK_a$ Determinations.** pH–rate constant profiles were determined for reactions of $1.0 \times 10^{-5}$ M PNPA with $1.0 \times 10^{-4}$ M **1** in $1.0 \times 10^{-2}$ M CTACl and for $1.0 \times 10^{-5}$ M PNPDPP with $1.0 \times 10^{-4}$ M **3** in $1.5 \times 10^{-3}$ M CTACl (0.02 M phosphate or acetate buffers, $\mu = 0.08$, 25 °C). For reactions of **1** and PNPA, a plot of log $k_\psi$ vs. pH gave a sharp break at pH 7.25, which was taken as the systemic $pk_a$ of **1** under the micellar reaction conditions.[1] The new data for reactions of micellar **3** and PNPDPP are depicted in Figure 4. From the graph, the systemic $pK_a$ appears to be ~7.2. These data indicated that catalysts **3** and **1** are present to ~80–85% in their ionized (heterocyclic) catalytically active forms in micellar solutions at pH 8.

We similarly determined systemic $pK_a$ values for cleavages of PNPA and PNPDPP by CTACl-solubilized *o*-iodoxybenzoate (**4**) under conditions identical with those employed with *o*-iodosobenzoate (see above). The apparent $pK_a$ values for catalyst **4** were 7.8 (PNPA substrate) or 7.4 (PNPDPP) substrate, corresponding to 61% or 80% ionization, respectively, under our reaction conditions.

## Discussion

Our previous observations[1] of rapid PNPA cleavage in the presence of CTACl-solubilized *o*-iodosobenzoate (**1**) (with $pK_a$ ~7.2), contrasted with *no* catalysis in the presence of *m*-iodosobenzoate, were consistent with substrate cleavage by *o*-iodosobenzoate acting as an O nucleophile in its preferred[2] heterocyclic form, **2**. Additionally, the observation that **11** the

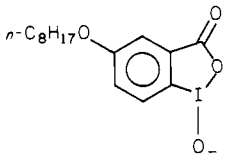



11

*O*-acetyl derivative of **2**,[2b] was hydrolyzed ~20 times more rapidly ($k_\psi$ ~0.4 ± 0.1 $s^{-1}$ at pH 8 in 0.01 M CTACl) than PNPA was cleaved by **2** under these conditions suggested Scheme II as an appropriate representation of the overall reaction mechanism.

Here, $k_2 > k_1$ so that cleavage of the substrate rather than turnover of intermediate **11** is the rate-determining step. Two further observations were consistent with this mechanism.[1] (1) Micellar **1** was capable of cleaving 5-fold excess PNPA or PNPDPP with only 30% or 6% decreases, respectively, in the apparent values of $k_1$ (relative to $k_{obsd}$ with [substrate] = [**1**]). (2) Solvent isotope effects ($k_{H_2O}/k_{D_2O}$) were near unity for PNPA and PNPDPP cleavages by **1**/CTACl. The first observation is further evidence for efficient catalyst turnover, whereas the second supports a nucleophilic cleavage mechanism involving anionic **2**, but is inconsistent with mechanisms in which **2** would function as a general base catalyst.

We questioned whether the substitution of an electron-donor substituent para to the iodoso group of **1** (**2**) would buttress the available electron density at the iodosyl oxygen atom and thus enhance its nucleophilicity. Accordingly, an oxygen atom was introduced at the 5-position of **1**, and a hydrophobic chain was added to ensure strong bonding of the new catalyst to the CTACl carrier micelle. The resulting molecule, **3** (**3′**), is significantly more potent than **1** (**2**).

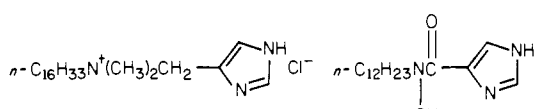



**3′**

Table I collects values of $k_\psi^{max}$ for cleavages of PNPA, PNPH, and PNPDPP by the three CTACl-micellized catalysts **2**, **3′**, and **5**. It is clear from this table, and from Figures 1–3, that **3′** is the most effective catalyst toward any of the substrates. Its kinetic advantage increases with increasing substrate hydrophobicity (i.e., binding), and in the important test of phosphate cleavage (PNPDPP), catalyst **3′** is in a class by itself (see below).

On the other hand, *o*-iodoxybenzoate (**4** or **5**) is an inferior catalyst in micellar CTACl. It is particularly, deficient, relative to the iodosobenzoates, when tested with the hydrophobic substrates PNPH or PNPDPP. Conversion of catalyst **2** to **5** involves further oxidation of the iodine atom, a change that increases its electronegativity and should decrease the nucleophilicity of its directly bonded anionic oxygen atom.[6] *o*-Iodoxybenzoic acid is also less ionized than *o*-iodosobenzoic acid under our pH 8 micellar conditions, as judged by pH–rate constant profiles for the cleavage of PNPDPP ($pK_a$ ~7.4 vs. ~7.2, see above). This difference accounts for a factor of ~1.6, about half of the 3.6-fold kinetic advantage of iodoso- over iodoxybenzoate in micellar cleavage of PNPDPP (Table I, cases 6 vs. 3).

We have indicated[1] that *o*-iodosobenzoate–CTACl is apparently the only monofunctional O functionalized micellar catalyst capable of *both* efficient cleavage *and* turnover with active ester and phosphate substrates.[7] Detailed kinetic comparisons of the reactivities toward PNPA of **2**/CTACl with those of (e.g.) micellar **12**[8] and **13**/CTABr[9] have been presented and will not be repeated here.[10] The *o*-iodosobenzoate system proved to be comparable in cleavage rate constant and superior in turnover properties.[10]




**12**




**13**

(Octyloxy)iodoso catalyst **3′** is only modestly superior to **2**/CTACl in the cleavage of PNPA (Table I, cases 7 and 4), although, toward the more hydrophobic ester, PNPH, the kinetic superiority of **3′**/CTACl reaches an order of magnitude (cases 8 and 5). Nevertheless, the esterolytic behavior of **3′**/CTACl toward PNPH is not remarkable; in terms of $k_\psi^{max}$, it is comparable to that of **12**.[11]

It is when we consider the behavior of **3′**/CTACl toward phosphate substrate PNPDPP that its properties turn out to be truly striking. It cleaves this substrate with $k_\psi^{max}$ ~1.0 $s^{-1}$ at pH 8 at a catalyst concentration of 7.14 × $10^{-5}$ M in the presence of only 2.0 × $10^{-4}$ M CTACl (Table I, case 9).[12] The pseudo-first-order rate constant corresponds to a second-order rate constant of ~14 400 L/mol s. Relative to CTACl alone, under comparable conditions, **3′**/CTACl provides a kinetic advantage of ~1800 in PNPDPP cleavage.

Table II demonstrates that the efficiency of PNPDPP cleavage decreases only ~10% when the ratio of [substrate]/[**3′**] is changed from 1:7 to 3.5:1. This suggests that turnover of a putative O-phosphorylated **3′** intermediate is *not* rate limiting.

How do these properties compare with those of other micellar reagents for the cleavage of PNPDPP?[14] The new reagent is clearly superior to $10^{-4}$ M phenoxide ion[15] or benzimidazole[16] in micellar CTABr. These reagents cleave PNPDPP with $k_\psi$ ~ 0.02–0.03 $s^{-1}$ at higher pH (10–10.7) and are thus 30–50 times less reactive than **3′**/CTACl at >100 times greater [$OH^-$]. The new reagent also surpasses the performance of 2 × $10^{-3}$ M micellar **12**, which cleaves PNPDPP with $k_\psi$ = 0.20 $s^{-1}$ at pH 10.[8b] The (octyloxy)iodosobenzoate catalyst also appears to be superior to typical oximate catalysts. For example, 2-pyridinecarboxaldoximate in $10^{-3}$ M CTABr at pH 10 cleaves PNPDPP with $k_2$ = 410 $M^{-1}$ $s^{-1}$,[17] whereas in 2 × $10^{-4}$ M CTACl at pH 8, the comparable $k_2$ for **3′** is ~14 400 $M^{-1}$ $s^{-1}$.

Its high kinetic activity at low concentrations and nearly neutral pH, coupled with efficient turnover, make micellar **3′**/CTACl unique among micellar catalysts for the cleavage of active phosphates. We are continuing our development of these iodoso reagents and have now successfully attached the phenolic residue of **3′** to a Merrifiedl resin.[18] The properties of this and other polymeric catalysts will be described in future publications.

## Experimental Section

**General Methods.** Melting points are uncorrected. NMR spectra were measured with a Varian T-60 spectrometer and chemical shifts are reported relative to internal $Me_4Si$. Microanalyses were performed by Robertson Laboratory, Florham Park, NJ.

**Materials.** PNPA, PNPH, and *o*-iodosobenzoic acid were obtained from Sigma Chemical Co. and used as received. PNPDPP was prepared and purified by literature methods.[19] CTACl was obtained from

(6) The two oxygen atoms of **5** are structurally distinct. The bond from I to the second oxygen atom in **5** is approximately perpendicular to the "molecular plane" of the essentially planar iodoso framework (e.g., as in **2**).[3]

(7) Review: 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"; Patai, S., Ed.; Wiley: New York, 1979; Part 2, pp 945ff.

(8) (a) 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. (b) Brown, J. M.; Bunton, C. A.; Diaz, S.; Ihara, Y. *J. Org. Chem.* **1980**, *45*, 4169; *J. Chem. Soc., Chem. Commun.* **1974**, 971.

(9) Kunitake, T.; Okahata, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1976**, *98*, 7799.

(10) See particularly ref 11, 12, 15, and 16 in ref 1.

(11) Moss, R. A.; Nahas, R. C.; Ramaswami, S.; Sanders, W. J. *Tetrahedron Lett.* **1975**, 3379. In 0.01 M $PO_4$ buffer, pH 8, $k_\psi^{max}$ for PNPH cleavage by 2.5 × $10^{-3}$ M **12** was 0.43 $s^{-1}$. Case 8 of Table I lists almost identical kinetic parameters for **3′**/CTACl (although these were determined at higher ionic strength).

(12) $k_\psi$ declines sharply at higher [CTACl], cf. Figure 3. We might be dealing here with **3′**/CTACl premicelles (or small hydrophobic ionic aggregates), but the overall $k_\psi$/[CTACl] reaction profile displays the typical shape associated with a micelle-catalyzed reaction.[13]

(13) Fendler, J. H.; Fendler, E. J. "Catalysis in Micellar and Macromolecular Systems"; Academic Press: New York, 1975; Chapter 4.

(14) For a recent summary of micellar and vesicular reagents for PNPDPP cleavage, see: Moss, R. A.; Ihara, Y. *J. Org. Chem.* **1983**, *48*, 588.

(15) Bunton, C. A.; Cerichelli, G.; Ihara, Y.; Sepulveda, L. *J. Am. Chem. Soc.* **1979**, *101*, 2429.

(16) Bunton, C. A.; Hong, Y. S.; Romsted, L. S.; Quan, C. *J. Am. Chem. Soc.*, **1981**, *103*, 5785, 5788.

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

(18) Moss, R. A.; Shin, J.-S., unpublished work.

Eastman and recrystallized 5 times from methanol/ether. *o*-Iodoxybenzoic acid[3] was prepared from *o*-iodobenzoic acid (Aldrich) by chlorination/hydrolysis.[3,5,20] Our material was recrystallized 3 times from hot water, had a decomposition point of 232 °C, and was 99 ± 1% pure by iodometric titration with KI/0.1 N $Na_2S_2O_3$.[5]

**5-(*n*-Octyloxy)-2-iodosobenzoic Acid (3-OH).** Aniline (17.3 g, 0.186 mol) in 500 mL of water was diazotized at 5 °C to benzenediazonium chloride by using 27 mL of concentrated HCl and a solution of 12.8 g (0.186 mol) of sodium nitrite in 100 mL of water, added with stirring over 30 min. After an additional 30 min of stirring, the diazonium ion solution was added to a solution of 25.6 g (0.186 mol) of *m*-hydroxybenzoic acid (**6**, Aldrich) and 22.5 g of NaOH in 250 mL of water. The addition was done slowly and with vigorous stirring. After completion of the addition, the mixture was heated to 65–70 °C until completion of solution.

The resulting red azo compound, **7**, was then reduced without isolation. To the hot reaction mixture was added slowly and with stirring a solution of 68 g of NaOH in 100 mL of water. This was followed by the addition of 97.5 g (0.56 mol) of sodium dithionite in small portions.[21] The reaction mixture was then cooled to room temperature, 200 g of crushed ice was added, and the pH was adjusted to 5.5 with dilute aqueous HCl. The temperature was kept <5 °C during the acidification.

The resulting precipitate of **8** was immediately filtered and diazotized. It was dissolved in 500 mL of water and 33 mL of concentrated $H_2SO_4$. The reaction temperature was held <5 °C by an ice–salt bath, and a solution of 12.8 g (0.186 mol) of sodium nitrite in 100 mL of water was slowly added over 30 min. After diazotization, a solution of 42 g (0.25 mol) of KI in 100 mL of water was added, and the solution was heated to 80–90 °C for 1 h.

Cooling to 0 °C then gave dark red crystals of **9**, which were decolorized by treatment with 10 g of activated charcoal in 350 mL of hot water. The resulting slurry was filtered while hot, and the filtrate was cooled to 0 °C affording yellow-red crystals. The decolorization procedure was repeated with 5 g of activated charcoal in 200 mL of hot water. There was finally obtained 12.8 g (0.048 mol) of 5-hydroxy-2-iodobenzoic acid (**9**) (26% yield based on **6**), as light yellow crystals, mp 201–203 °C (lit.[4] mp 196 or 198 °C). The NMR spectrum ($Me_2SO$-$d_6$) featured ring protons $H_3$, $H_4$, and $H_6$ at $\delta$ 7.73 (d, $J_{3,4}$ = 9 Hz), 6.70 (d of d, $J_{4,6}$ = 4, $J_{3,4}$ = 9 Hz), and 7.23 (d, $J_{4,6}$ = 4 Hz), respectively. The IR spectrum (KBr) showed broad OH absorptions at 3500–2600 $cm^{-1}$ and a C=O absorption at ~1690 $cm^{-1}$, in addition to typical aromatic bands.

Alkylation of **9** was accomplished with *n*-octyl iodide. A solution of sodium ethoxide was prepared from 1.09 g (47.4 mmol) of sodium and 50 mL of absolute ethanol. To this solution were added 6.2 g (23.5 mmol) of **9** and 5.64 g (23.5 mmol) of *n*-octyl iodide. The mixture was refluxed for 30 h. The ethanol was then removed under reduced pressure, the residual yellow solid was mixed with 200 mL of water, and the whole was extracted twice with 25-mL portions of pentane. The *aqueous* phase was then acidified with 2 N $H_2SO_4$ and extracted twice with 150-mL portions of $CH_2Cl_2$. The $CH_2Cl_2$ extract was backwashed twice with 50-mL portions of water, dried, and stripped to afford crude octyl ether **10**.

Crude **10** was dissolved in the minimum amount of absolute alcohol and chromatographed on silica gel using $CHCl_3$/EtOH (2:1) as the eluent. The chromatography was followed by silica gel TLC; the required fraction showed **10** as a spot with $R_f$ ~0.7–0.8. Eluent containing **10** was treated with a small quantity of activated charcoal, filtered, and stripped. The resulting **10** was recrystallized from hot water to give 3.0 g (8.0 mmol, 34%) of pure **10**: mp 66–68 °C; IR (KBr) 3300–2500, 1700 $cm^{-1}$ (COOH); NMR ($CDCl_3$) $\delta$ 11.0 (s, 1 H, COOH), 7.88, 6.80, 7.58 ($H_3$, $H_4$, $H_6$, 1 H each, multiplicities and $J$ values are identical with those of **9**), 3.98 (t, 2 H, $J$ = 6 Hz, $OCH_2$), 2.1–1.1 (m, 15 H, $C_6H_{12}$), ~0.88 (m, 3 H, $CH_3$).

Anal. Calcd for $C_{15}H_{21}IO_3$: C, 47.9; H, 5.59, I. 33.8. Found: C, 48.6; H, 5.68; I, 33.5.

The conversion of **10** to iodoso compound **3** generally followed the procedure of ref 5 for the conversion of iodobenzene to iodosobenzene, except that the yellow iodo dichloride derived from chlorination of **10** was dried in vacuo, not in air. In the hydrolysis procedure, 2.2 g of **10**·$Cl_2$ (4.9 mmol) was mixed with 8 g of crushed ice and 2.3 g of $Na_2CO_3$ to obtain a paste, to which was added 5.7 mL of 3 N NaOH in 15 mL of ice water. After 30 min at 15 °C, the resulting solution was neutralized with 3 N $H_2SO_4$. The precipitate was filtered, washed with 50 mL of water, and dried in vacuo to give white crystals, which were triturated with $CHCl_3$. The final white crystals, 1.33 g (3.9 mmol, 69%) of **3** (acid form), had mp 171–173 °C and showed 100 ± 5% of activity by KI/$Na_2S_2O_3$ iodometric titration.[5]

*Anal.* Calcd for $C_{15}H_{21}IO_4$: C, 45.9, H, 5.36. Found: C, 45.8; H, 5.37.

**Kinetic Studies.** Slower reactions were followed on a Gilford Model 250 spectrophotometer coupled to a Gilford Model 6051 recorder. Faster reactions were followed on a Durrum Model D-130 stopped-flow spectrophotometer coupled either to a Tektronix Model 5103N/D15 storage oscilloscope or, via a custom-built interface, to a Commodore Model 8032 computer. Constant-temperature circulating baths maintained reaction temperatures at 25 ± 0.5 °C. All buffers were prepared from Steam-Distilled water (distilled, U.S.P., Electrified Water Co., East Orange, NJ) and were purged with nitrogen. Rate constants were obtained from computer-generated correlations of log ($A_\infty - A_t$) with time for the appearance of *p*-nitrophenoxide ion at 400 nm. Conditions for all of the kinetic runs are described under Results. Rate constants are tabulated in Tables I–V of the supplementary material and presented graphically in Figures 1–3. Micellar reactions were generally followed to >90% completion and showed good first-order kinetics ($r$ > 0.999). Reproducibilities of the rate constants were <±3%. Values of $k_\psi^{max}$ appear in Table I.

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**Supplementary Material Available:** Tables I–V containing (respectively) rate constants for cleavage of PNPA and PNPH by **4**/CTACl, rate constants for cleavage of PNPDPP by **4**/CTACl, rate constants for cleavage of PNPH and PNPDPP by **1**/CTACl, rate constants for cleavage of PNPA by **3**/CTACl, and rate constants for cleavage of PNPH and PNPDPP by **3**/CTACl (5 pages). Ordering information is given on any current masthead.

(19) Gulick, W. M., Jr.; Geske, D. H. *J. Am. Chem. Soc.* **1966**, *88*, 2928.
(20) Formo, M. W.; Johnson, J. R. In "Organic Syntheses"; Horning, E. C., Ed.; Wiley: New York, 1955; Collect. Vol. 3, 486.
(21) Addition was carried out until the red color of **7** was discharged.