The Hydrolysis of Phthalide, Thiophthalide, and Methyl *o*-Methoxybenzoate in Highly Alkaline Media. Curvature in the k_{hyd} vs [OH⁻] Profile

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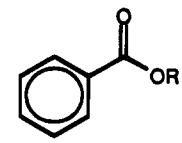
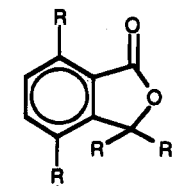
Received April 5, 1994®

The hydrolyses of phthalide (**2a**) and thiophthalide (**3**) have been studied in highly alkaline media, $T = 25$ °C, $\mu = 3$ (KCl). For both esters, an upward curvature in the plot of k_{hyd} vs [OH⁻] is observed, suggestive of the onset of a second order in [OH⁻] process in the hydrolysis. Carbonyl ^{18}O-exchange studies indicated that no ^{18}O is lost from the ester recovered from the hydrolysis media at times up to $3t_{1/2}$ hydrolysis. Solvent kinetic isotope (skie) studies indicate that for **3**, $(k_{hyd})_{H_2O/D_2O}$ is inverse throughout the entire range of [OL⁻]. The lack of ^{18}O-exchange and the inverse nature of the skie on k_{hyd} suggest that the curvature in the k_{hyd} vs [OH⁻] plots is not due to the involvement of two hydroxides in the hydrolytic process. A correlation of the k_{hyd} data with the acidity function H_- appropriate for highly alkaline media is linear and suggests the involvement of a single hydroxide throughout the entire [OH⁻] range. A reinvestigation of the alkaline hydrolysis of methyl *o*-methoxybenzoate (**4**) accompanied by ^{18}O-exchange studies failed to detect unambiguous evidence for a *bona fide* second order in [OH⁻] process.

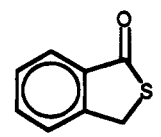
Alkaline hydrolysis of carboxylic acid esters is a well-studied reaction that adheres to the mechanism depicted in Scheme 1.[1] Seminal ^{18}O-exchange studies of Bender and co-workers[2] and Shain and Kirsch[3] have established that alkyl benzoates **1a–c**, when hydrolyzed in OH^-/H_2O, undergo reversal from the anionic tetrahedral intermediate (To^-) which is competitive with breakdown to product. Thus, methyl benzoate exhibits a k_{hyd}/k_{ex} ratio (defined as $k_{hyd} = k_1k_2[OH^-]/(k_{-1} + k_2)$; $k_{ex} = k_1k_{-1}[OH^-]/2(k_{-1} + k_2)$; $k_{hyd}/k_{ex} = 2k_2/k_{-1}$)[4] of 27.7,[3] while that for ethyl and isopropyl benzoate is 12.6[3] and 2.7,[2a] respectively.[5] Alkaline hydrolysis of benzoate esters with leaving groups such as phenoxides or benzyloxy anions apparently proceeds with no observable concomitant ^{18}O-exchange, nor is it observed in the hydrolysis of lactones such as phthalide **2a** or γ-butyrolactone.[2c] Recent results with more heavily substituted phthalides such as the tetramethyl derivative **2b** indicate that carbonyl ^{18}O-exchange is observable, but this is probably a consequence of an equilibrium reformation of the phthalide from hydrolyzed product,[6] the equilibrium lying dominantly to the side of **2b**.



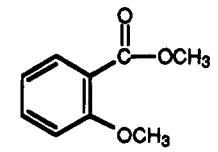
1a R=CH_3
b R=CH_2CH_3
c R=$CH(CH_3)_2$
d OR=SCH_2CH_3



2a R=H
b R=CH_3



3



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Alkaline hydrolysis of thiol esters has also been extensively studied,[7] and current evidence indicates that the mechanism is similar to that for the oxygen ester analogues. In fact, where comparisons can be made, the rate constants for hydrolysis of thiol esters and their corresponding oxygen esters are similar. Very few ^{18}O-exchange studies with thiol esters have been reported, the most notable being with ethyl trifluorothiolacetate[8] which exhibits ^{18}O-exchange below pH 2, but none at

® Abstract published in *Advance ACS Abstracts,* July 1, 1994.

(1) For leading references see: (a) Kirby, A. J. In *Comprehensive Chemical Kinetics*; Bamford C. H., Tipper, C. F. H., Eds.; Elsevier: Amsterdam, **1972**; Vol. 10, Chapter 2. (b) Kaiser, E. T.; Kézdy, F. J. *Prog. Bioorg. Chem.* **1976**, *4*, 239. (c) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; pp 54–100 and references cited therein.

(2) (a) Bender, M. L. *J. Am. Chem. Soc.* **1951**, *73*, 1626. (b) Bender, M. L.; Thomas, R. J. *Ibid.* **1961**, *83*, 4189. (c) Bender, M. L.; Matsui, H.; Thomas, R. J.; Toberg, S. W. *Ibid.* **1961**, *83*, 4193.

(3) Shain, S. F.; Kirsch, J. F. *J. Am. Chem. Soc.* **1968**, *90*, 5848.

(4) The factor of 2 in k_{ex} comes from the necessary assumption that the anionic tetrahedral intermediates are in rapid protonic equilibrium so that half the reversal leads to ^{18}O-exchange in recovered starting material. There is, however, some evidence to suggest that the anionic tetrahedral intermediates may be sufficiently short-lived that protonic equilibration is incomplete; see refs 2b and 5.

(5) There is some discrepancy between the k_{hyd}/k_{ex} values reported by Bender[2a] and Shain and Kirsch[3] for ethyl benzoate, with the latters' value more probably being correct. The value given by Bender[2a] for isopropyl benzoate in H_2O is, as far as we know, unconfirmed.

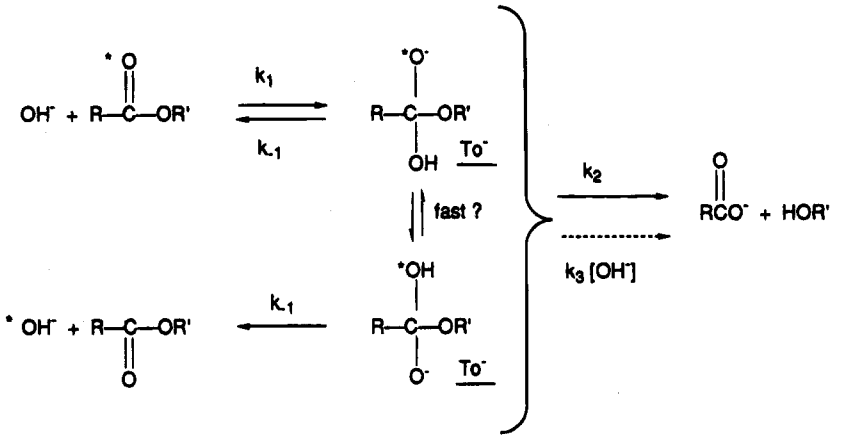
(6) Hillery, P. S.; Cohen, L. A. *Bioorg. Chem.* **1992**, *20*, 313.

(7) (a) Tarbell, D. S.; Harnish, D. P. *Chem. Rev.* **1951**, *49*, 47. (b) Noda, L. H.; Kuby, S. A.; Lardy, H. A. *J. Am. Chem. Soc.* **1953**, *75*, 913. (c) Hawkins, P. J.; Tarbell, D. S. *Ibid.* **1953**, *75*, 2982. (d) Morse, B. K.; Tarbell, D. S. *Ibid.* **1952**, *74*, 416. (e) Fife, T. H.; DeMark, B. R. *Ibid.* **1979**, *101*, 7379.

(8) Bender, M. L.; Heck, H. d'A. *J. Am. Chem. Soc.* **1967**, *89*, 1211.

0022-3263/94/1959-4652$04.50/0

Scheme 1



[a] *O = ^{18}O.

higher values. This is fully in accord with the expectation that expulsion of thiolate anion from the anionic tetrahedral intermediate is favored over expulsion of OH^-, by any mechanism, at all pH values above 2.[9] Indeed, for a variety of anionic intermediates, expulsion of thiolate anions is favored over alkoxides, the exact preference being determined by the relative anion basicity and what is left behind after its departure.[10]

Our interest in potential reversibility of the anionic intermediates formed from alkaline hydrolysis was aroused by the observations of one of us[11] that the pH/rate profile for thiophthalide **3** exhibited a small but clear upward curvature at high $[OH^-]$.[11] This, and the fact that **3** hydrolyzes ~10-fold slower than the oxygen analogue **2a** under identical conditions, might be taken as preliminary evidence that the anionic tetrahedral intermediate produced from **3** suffers significant reversal concurrent with breakdown to product. The upward curvature in plots of hydrolysis rate vs $[OH^-]$ has been taken as evidence for a bimolecular process wherein a second OH^- is required to promote the passage of anionic tetrahedral intermediates into hydrolysis products. This is amply demonstrated for the base-promoted hydrolysis of certain amides where expulsion of the leaving group is (partially) rate-limiting.[12] However, such a process is considered rare for simple carboxylic acid esters, the only literature example apparently being that of Khan and Olagbemiro[13] who report kinetic evidence for the occurrence of oxydianionic intermediates in the hydrolysis of methyl salicylate and methyl *o*-methoxybenzoate **4** in highly alkaline media (e.g., the k_3 $[OH^-]$ term in Scheme 1).

The *bona fide* presence of second order in $[OH^-]$ terms for the hydrolysis of esters has important mechanistic implications for the behavior of unstable intermediates produced along the reaction pathway. In view of the above, we have undertaken a detailed investigation of the base-promoted hydrolysis and ^{18}O-exchange kinetics of **3**, **2a**, and ethyl thiobenzoate (**1d**) as well as a reinvestigation of the kinetics of hydrolysis and ^{18}O-exchange for **4**. The results of these studies indicate that none of the species exhibits ^{18}O-exchange concurrent with hydrolysis and that at present there is no unambiguous evidence for the occurrence of oxydianionic intermediates or transition states in the hydrolysis of esters or thiolesters.

Experimental Section

(a) Materials and General Methods. The following compounds were obtained from commercial suppliers: phthalide (Aldrich), *o*-anisic acid (or *o*-methoxybenzoic acid, Sigma), benzoyl chloride (Fluka), ethyl benzoate (Terrochem).

^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker WH-200 or a Bruker AM-400 spectrometer. Infrared spectra were recorded on a Nicolet 7199 or a Nicolet Magna 750 FTIR spectrometer. High-resolution mass spectra were obtained on an AEI-MS50 mass spectrometer and low-resolution spectra on an AIE-MS12 spectrometer.

All melting points were obtained on a Canlab Gallenkamp apparatus and are uncorrected.

Flash chromatography was performed using silica gel 60 (40–63-μm particle size).

(b) Syntheses. 2-[(Benzylthio)methyl]benzoic Acid (5). This compound was obtained from phthalide and benzyl mercaptan via the method described by Lumma et al.[14a] The crude orange solid was recrystallized once from MeOH/H_2O and twice from ether/petroleum ether to give a pink solid in 58% yield. This material was used without further purification: mp 106–110 °C (lit.[14b] mp 127 °C); IR ($CHCl_3$ cast film) ν 3200–2500 (OH), 1683 (C=O), 1574, 1400, 1299, 1268 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 2 H), 4.10 (s, 2 H), 7.20–7.38 (m, 7 H), 7.48 (t, 1 H), 8.07 (d, 1 H); HRMS exact mass calcd for $C_{15}H_{14}O_2S_1$ 258.0714, found 258.0718.

2-Thiophthalide (3). To 75 mL of dry benzene was added 2.5 g (0.0097 mol) of the acid **5** (mixture is cloudy). A few drops of pyridine were added, and the temperature was lowered to 0 °C (under Ar). Oxalyl chloride, 0.7 mL (0.08 mol), was then

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(10) Douglas, K. T. *Acct. Chem. Res.* **1986**, *19*, 186 and references cited therein.

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added via syringe. The mixture became a clear orange but after several hours of stirring it became cloudy again. The next day benzene and excess oxalyl chloride were removed by distillation. The brown residue was chromatographed on a silica gel flash column, 80% hexane/20% EtOAc, and then recrystallized from ether/hexane to give 0.6 g of **3** (white solid, 41% yield): mp 56–58 °C (lit.[14c] mp 56–58 °C); IR ($CHCl_3$ cast film) ν 1674 (C=O), 1604, 1585, 1486, 1241, 906 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.48 (s, 2 H), 7.48 (t, 1 H, J_{app} = 8 Hz), 7.54 (d, 1 H, J_{app} = 8 Hz), 7.63 (t, 1 H, J_{app} = 8 Hz), 7.84 (d, 1 H, J_{app} = 8 Hz).

^{18}O-Labeled 2-(Mercaptomethyl)benzoic Acid (6). To a 100-mL flask containing 60 mL of dry MeOH was added 0.97 g (0.0064 mol) of dry thiophthalide (**3**). The solution was cooled to 0 °C, under Ar, and then 0.294 g (0.0128 mol) of Na was carefully added. When H_2 evolution had ceased, 0.231 mL (0.0128 mol) of 98% $H_2{}^{18}O$ was added to the solution. The mixture was heated at reflux for 14 days. The MeOH was then removed and the solid residue dissolved in 20 mL of H_2O; concd HCl was then added dropwise until no further precipitation was observed (pH = 2). The solid was rapidly filtered and then washed with about 5 mL of cold H_2O. After drying, 0.6 g of a crude pink solid was obtained (56% yield): IR ($CHCl_3$ cast film) ν 3200–1800 (OH), 1669 (C=O), 1572, 1403, 1298, 1273 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.13 (1 H, SH), 4.12 (s, 2 H, CH_2-$SSCH_2$), 4.12 (d, 2 H, CH_2SH), 7.25–8.15 (m, 4 H); HRMS exact mass calcd for $C_8H_8{}^{16}O{}^{18}OS_1$ 170.0288, found 170.0288 (52%). (Also observed was a peak at 172.0319 (14%) due to $C_8H_8{}^{18}O_2S_1$).

From the NMR spectrum there appeared to be about 20% of disulfide present. However this mixture was used directly to make the labeled thioester without attempting to purify the thiol acid from the disulfide.

^{18}O-Labeled 2-Thiophthalide (3-^{18}O). To 60 mL of dry benzene was added 0.6 g (0.0035 mol) of the crude labeled thiol acid **6** (mixture not completely soluble), followed by 1.2 equiv of $SOCl_2$. The mixture was stirred for 0.5 h at room temperature and then heated at reflux overnight after adding an extra 2 equiv of $SOCl_2$ (residue dissolves as reaction proceeds). Benzene and excess $SOCl_2$ were removed by distillation. The crude material was purified as described for **3**. TLC and GC indicated a single component was present. Yield of **3**-^{18}O, 0.17 g (32%) of a white solid: IR ($CHCl_3$ cast film) ν 1676 (C=^{16}O), 1642 (C=^{18}O) cm^{-1}; ^1H NMR ($CDCl_3$) identical to that for compound **3**; ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.63, 123.9, 126.3, 127.9, 133.1, 135.9, 147.0, 197.71 (C=^{18}O), 197.75 (C=^{16}O); HRMS exact mass calcd for $C_8H_8{}^{16}O_1S_1$ 150.0139, found 150.0142 (81%), exact mass calcd for $C_8H_6{}^{18}O_1S_1$ 152.0183, found 152.0178 (88%).

^{18}O-Labeled 2-(Hydroxymethyl)benzoic Acid (7). This compound was synthesized from phthalide in a manner identical to the labeled thiol acid **6**, except that the reaction was over after 48 h. Compound **7** was obtained as a white solid in 82% yield (crude): mp 110–112 °C (lit.[14d] mp 127–128 °C); IR (MeOH cast film) ν 1669 (C=^{16}O), 1657 (C=^{18}O) cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 4.94 (s, 2 H), 5.38 (s, phthalide, $-CH_2-$), 7.35 (t, 1 H, J_{app} = 8 Hz), 7.55 (t, 1 H, J_{app} = 8 Hz), 7.64 (d, 1 H, J_{app} = 8 Hz), 7.97 (d, 1 H, J_{app} = 8 Hz). Small peaks due to phthalide were present in the aromatic region. Their intensity is ~10% of the peaks attributable to **7**; HRMS, exact mass calcd for $C_8H_8{}^{16}O_2{}^{18}O$ 154.0516, found 154.0516 (33%). A peak was also observed at 156.0559 (6%), corresponding to $C_8H_8{}^{16}O_1{}^{18}O_2$.

^1H NMR indicates that approximately 10% of phthalide impurity is present. It is believed that this was formed by cyclization of the labeled hydroxy acid during the acidic workup rather than being due to unreacted starting material.

^{18}O-Labeled Phthalide (2-^{18}O). To 75 mL of dry $CHCl_3$ was added 0.7 g (0.0045 mol) of the hydroxy acid **7**. $SOCl_2$ (1.5 equiv) was added, and the mixture was stirred at room temperature overnight (condenser, drying tube). Solvent and excess $SOCl_2$ were removed and the residue purified by flash chromatography (70% petroleum ether/30% EtOAc, silica), giving **2**-^{18}O in quantitative yield. One peak was observed by TLC and GC: mixture mp (authentic phthalide + **2**-^{18}O), 72–74 °C (lit.[14e] 72–74 °C); IR ($CHCl_3$ cast film) ν 1757 (C=^{16}O), 1727 (C=^{18}O), 1466, 1439, 1054, 1017 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.28 (s, 2 H), 7.48 (m, 2 H), 7.65 (t, 1 H, J_{app} = 7.5 Hz), 7.86 (d, 1 H, J_{app} = 7.5 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 71.38, 123.65, 126.17, 126.52, 130.07, 135.41, 148.74, 173.33 (C=^{18}O), 173.37 (C=^{16}O); HRMS exact mass calcd for $C_8H_6{}^{16}O_1{}^{18}O_1$ 136.0411, found 136.0410 (52%), exact mass calcd for $C_8H_6{}^{16}O_2$ 134.0368, found 134.0366 (43%).

***o*-Methoxybenzoyl Chloride (8).** The acid chloride of *o*-methoxybenzoic acid was made in the standard way using $SOCl_2$ as solvent. The crude acid chloride was purified by Kugelrohr distillation, giving **8** as a clear liquid in quantitative yield: IR (neat film) ν 1782 (C=O), 1733, 1600, 1482, 1286, 861 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 3.92 (s, 3 H), 7.0 (t, 2 H), 7.55 (t, 1 H), 8.05 (d, 1 H).

Methyl *o*-Methoxybenzoate (4). Dry pyridine (15 mL) was added to 0.5 g (0.0029 mol) of the acid chloride **8**. A white precipitate formed immediately. Then 250 μL (0.0058 mol) of dry MeOH was slowly added. After 2 h the reaction mixture was filtered and the filtrate subjected to rotary evaporation to remove excess pyridine and MeOH. The residue was dissolved in 30 mL of CH_2Cl_2 and extracted with 3 × 10 mL of 0.5 M HCl. The $CHCl_3$ layer was dried over Na_2CO_3 and filtered and the $CHCl_3$ removed. The crude yellow liquid was purified by distillation (bp 70–80 °C, 0.1 Torr (lit.[14f] bp 127–127.5 °C, 11 Torr) to give **4** in 81% yield (from the acid): IR ($CHCl_3$ cast film) ν 1729 (C=O), 1601, 1492, 1436, 1304, 1253, 1085 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.92 (s, 3 H), 3.93 (s, 3 H), 6.93–7.02 (m, 2 H), 7.43–7.52 (m, 1 H), 7.80 (dd, 1 H, J_{app} = 7.5, 2 Hz).

^{18}O-Labeled Methyl *o*-Methoxybenzoate (4-^{18}O). The labeled compound was made by the following series of steps. First the acid chloride, **8**, was hydrolyzed in 98% $H_2{}^{18}O$ to give the labeled acid. This was in turn converted via $SOCl_2$ into the 50% ^{18}O-labeled acid chloride **8**-^{18}O which was then converted to the labeled ester **4**-^{18}O by the same procedure as described above for **4**: IR (neat film) ν 1730 (C=^{16}O), 1701 (C=^{8}O) cm^{-1}; ^1H NMR identical to that for **4**; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.92, 55.94, 112.01, 120.05, 120.09, 131.59, 133.44, 159.08, 166.63 (C=^{18}O), 166.67 (C=^{16}O); HRMS exact mass calcd for $C_9H_{10}{}^{16}O_3$ 166.0630, found 166.0630 (9.3%), exact mass calcd for $C_9H_{10}{}^{16}O_2{}^{18}O_1$ 168.0673, found 168.0672.

Ethyl Thiobenzoate (1d). To a 25-mL flask under Ar was added 10.4 mL (0.140 mol) of EtSH and 2.3 mL (0.028 mol) of dried pyridine. Benzoyl chloride (1.65 mL, 0.014 mol) was then added via syringe with cooling. A white precipitate formed immediately. After 24 h, 20 mL of cold ether was added to the mixture and the pyridinium hydrochloride was removed by filtration. The ether phase was then extracted with 2 × 10 mL of 1.4 M HCl and then with 10 mL of 10% K_2CO_3, dried over $MgSO_4$, and filtered and the ether removed *in vacuo* to give a clear liquid. The thioester was purified by Kugelrohr distillation (bp 70–80 °C, 0.075 Torr (lit.[14g] bp 146 °C, 31 Torr) and then by flash chromatography on silica gel (90% hexane/10% EtOAc) to yield 2.2 g of material (95% yield): IR (neat film) ν 1662 (C=O), 1208, 912, 690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.37 (t, 3 H), 3.08 (q, 2 H), 7.40–7.50 (m, 2 H), 7.53–7.62 (m, 1 H), 7.95–8.02 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.78, 23.45, 127.18, 128.57, 133.23, 137.28, 192.08.

^{18}O-Labeled Ethyl Thiobenzoate (1d-^{18}O). The ^{18}O-labeled ester was made from benzoyl chloride in a series of steps identical to that described for compound **4**-^{18}O, with the exception that the final step (conversion of the labeled acid chloride to the thioester), was carried out as described for **1d**: IR (neat film) ν 1662 (C=^{16}O), 1632 (C=^{18}O) cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.07 (C=^{18}O), 192.11 (C=^{16}O); HRMS exact mass calcd for $C_9H_{10}{}^{16}O_1S_1$ 166.0453, found 166.04521 (15.5%), exact mass calcd for $C_9H_{10}{}^{18}O_1S_1$ 168.0496, found 168.04948 (12.82%). (Other spectral characteristics identical to those for **1d**.)

(c) Kinetics. Hydrolysis. All base solutions were made by dilution of 19 M NaOH in a drybox (CO_2 free conditions) using degassed (CO_2 free, O_2 free), deionized water (Osmonics-Aries water purifying system). KCl was used to maintain constant ionic strength. NaOH solutions were titrated with standard HCl solution (Aldrich), using bromothymol blue as indicator, or with potassium hydrogen phthalate using phenolphthalein as indicator.

(i) Thiophthalide (T = 25 °C, μ = 3.0 (KCl)). Rate

constants for the basic hydrolysis of thiophthalide were obtained under pseudo-first-order conditions by following the decrease in absorbance at 270 nm of thiophthalide, using a modified Cary 17 spectrophotometer interfaced with an IBM 486 microcomputer using OLIS software (Online Instrument Systems, Jefferson, GA, 1992). In all cases 3 mL of base solution was added to the cuvette in the drybox and then Ar was bubbled through the solution in the cell to remove O_2 (less than 1 min). The stoppered cuvette was allowed to equilibrate in the spectrophotometer cell holder for about 10 min, and then 8 μL of a 0.03 M solution of thioester in DME was injected into the cell to initiate the run ($[ester]_{UVcell} = 8 \times 10^{-5}$ M). Reactions were followed to at least 5 half-lives, and runs were performed in triplicate for each base concentration. A span of NaOH concentrations ranging from 0.01 to 3.0 M was examined.

(ii) Phthalide (T = 25 °C, μ = 3.0 (KCl)). For NaOH concentrations of 0.0108 and 0.108 M, the modified Cary 17 spectrophotometer was used to follow the kinetics, using the same procedure as for thiophthalide (except that the final concentration of phthalide in the UV cell was 4.0×10^{-4} M), and the wavelength used was 281 nm. For NaOH concentrations of 0.725–2.06 M, stopped flow kinetics were employed using a Durrum-Gibson D-110 stopped flow spectrophotometer. The oscilloscope transient recorder was interfaced with an IBM PS2, and first-order rate constants were extracted from the absorbance vs time data via the program Exponential Kinetic Fit (Version 1.2 Cantech Scientific, 1988). One drive syringe of the instrument was filled with NaOH solution (twice the desired final concentration) and the other drive syringe filled with 8.0×10^{-4} M phthalide (4% DME), with the ionic strengths of the two solutions adjusted with KCl so that the final ionic strength in the mixing cell would be 3 M. Once the drive syringes were filled with their respective solutions, they were allowed to equilibrate in the water bath for 15–20 min. About 10 runs were performed at each base concentration and the average of the k_{obs} values taken.

(iii) Hydrolysis of Phthalide and Thiophthalide in D_2O/NaOD (T = 25 °C, μ = 3.0 (KCl)). Thiophthalide. Solutions ranging in concentration from ~0.01–2.2 M NaOD were made up by adding Na to an ice-cooled solution of D_2O under Ar. The determination of the base concentrations and hydrolysis kinetics were carried out as described above.

Phthalide. Hydrolysis of phthalide in D_2O was carried out in an identical manner but only using two NaOD concentrations (0.0097 M and 0.0941 M).

(iv) Methyl *o*-Methoxybenzoate (T = 35 °C, μ = 2.0 (KCl)). The hydrolysis of methyl *o*-methoxybenzoate was followed by observing the decrease in absorbance at 310 nm using the same procedure as described for thiophthalide hydrolysis. A span of NaOH concentrations ranging from 0.005 to 1.0 M was examined.

(v) Ethyl Benzoate and Ethyl Thiobenzoate (T = 25 °C, μ = 2.0 (KCl)). The hydrolysis kinetics were followed by UV spectroscopy as described for thiophthalide except for the following changes: assay wavelength for ethyl benzoate = 245 nm, $[ester]_{UVcell} = 4.2 \times 10^{-4}$ M; assay wavelength for ethyl thiobenzoate = 275 nm, $[ester]_{UVcell} = 1.7 \times 10^{-4}$ M. The esters were hydrolyzed in NaOH solutions ranging in concentration from ~0.001–2.0 M.

^{18}O-Exchange Studies. General Procedure for ^{18}O-Exchange Experiments. One hundred mL of NaOH solution was added to a 100-mL volumetric flask in an Ar-filled drybox (CO_2 free conditions). The septum-capped flask was then equilibrated at the required temperature for ~15 min. A small aliquot of a concentrated solution of the ester in DME or EtOH was injected into the flask to give a final concentration of ester on the order of 4×10^{-4} M. The flask was inverted several times and the reaction mixture left in the water bath for the requisite amount of time (up to 3 half-lives of hydrolysis). The reaction mixture was quenched by quickly pouring it into 10 mL of 1.1 M phosphate buffer, pH 6.5. In cases where hydrolysis was very slow, the reaction solution was simply extracted quickly without quenching. The aqueous solution was extracted with 3 × 30 mL of distilled CH_2Cl_2. The combined CH_2Cl_2 extracts were then dried and filtered and the volatiles removed. The residue was dissolved in 10 drops of CH_2Cl_2 and transferred to a vial for low-resolution mass spectral analysis.

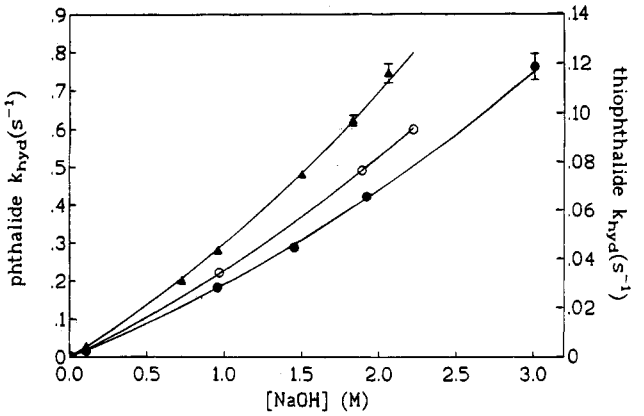


Figure 1. Plots of the k_{hyd} vs $[OL^-]$ data for hydrolysis of phthalide (**2a**) and thiophthalide (**3**) in H_2O and D_2O media, T = 25 °C, μ = 3.0 KCl. (phthalide ▲ (H_2O); thiophthalide ● (H_2O); ○ (D_2O); lines through the data computed on the basis of eq 2).

The percentage of ^{18}O in the recovered ester for each sample was then determined by taking the average over 22 scans of the parent peaks. $\%\ ^{18}O = 100I_{M+2}/(I_M + I_{M+2})$ where I_{M+2} = the intensity of the M + 2 peak corresponding to the ^{18}O-labeled ester and I_M = the intensity of the mass M peak corresponding to the unlabeled ester.

Prior to the actual exchange experiments, a control experiment was performed to show that the ^{18}O label is not lost from ester left to sit in pH 6.5 phosphate buffer (quenching buffer). The labeled ester (5 mg) was added to 100 mL of 0.1 M phosphate buffer and left for 2 h stirring. The ester was then extracted from the aqueous solution with CH_2Cl_2 as described above and submitted to mass spectral analysis. No ^{18}O label was lost from the ester.

Results

(a) Hydrolysis. Given in Figure 1 are graphical presentations of the psuedo-first-order rate constants for the hydrolysis of phthalide (**2a**) and thiophthalide (**3**) (k_{hyd}) at various base concentrations in both H_2O and D_2O (T = 25 °C, μ = 3 (KCl)): the primary data are given in Table 1S (supplementary material). The data for a given ester cannot be satisfactorily fit by a linear regression of the type

$$k_{hyd} = k_o + B[OL^-] \quad (1)$$

but can be fit by an expression that includes both first and second order in $[OL^-]$ components, e.g.

$$k_{hyd} = k_o + B[OL^-] + C[OL^-]^2 \quad (2)$$

The lines through the data in Figure 1 are those computed on the basis of fits of the k_{obsd} vs $[OL^-]$ values to eq 2, and clearly show an upward deviation from a linear regression. This deviation is also seen under conditions of μ = 1.0 (KCl) up to 1 M $[OH^-]$[11] but is more clearly defined under the conditions used here. The hydrolysis data for open analogues of the phthalides, namely ethyl benzoate (**1b**) and ethyl thiobenzoate (**1d**) (T = 25 °C, μ = 2.0 (KCl)) are given in Table 1, along with those redetermined here for methyl *o*-methoxybenzoate (**4**) under the conditions reported by Khan and Olagbemiro.[13] Each of these esters also shows some slight upward curvature in the plots of k_{hyd} vs $[OH^-]$ (not shown) and the data can be fit by eq 2. Given in Table 2 are the best fit parameters for all esters. The ratio of

Table 1. Pseudo-First-Order Hydrolysis Rate Constants for Ethyl Thiobenzoate and Ethyl Benzoate in Basic Media, T = 25 °C, μ = 2.0 (KCl), and Methyl *o*-Methoxybenzoate in Basic Media, T = 35 °C, μ = 2.0 (KCl)

ester	[NaOH] (M)	k_{hyd}[a] (s^{-1})
ethyl thiobenzoate (**1d**)	0.00099	$(2.62 \pm 0.09) \times 10^{-5}$
	0.0049	$(1.47 \pm 0.04) \times 10^{-4}$
	0.010	$(3.13 \pm 0.06) \times 10^{-4}$
	0.050	$(1.56 \pm 0.02) \times 10^{-3}$
	0.527	$(1.81 \pm 0.04) \times 10^{-2}$
	0.951	$(3.43 \pm 0.08) \times 10^{-2}$
	2.12	$(8.7 \pm 0.2) \times 10^{-2}$
ethyl benzoate (**1b**)	0.00518	$(7.7 \pm 0.2) \times 10^{-5}$
	0.00982	$(2.89 \pm 0.08) \times 10^{-4}$
	0.049	$(1.58 \pm 0.005) \times 10^{-3}$
	0.527	$(1.95 \pm 0.004) \times 10^{-2}$
	0.936	$(3.61 \pm 0.03) \times 10^{-2}$
	2.12	$(9.44 \pm 0.07) \times 10^{-2}$
methyl *o*-methoxy-benzoate (**4**)	0.00518	$(3.30 \pm 0.03) \times 10^{-4}$
	0.00982	$(6.52 \pm 0.02) \times 10^{-4}$
	0.0491	$(3.33 \pm 0.01) \times 10^{-3}$
	0.0749	$(4.9 \pm 0.1) \times 10^{-3}$
	0.0992	$(6.83 \pm 0.01) \times 10^{-3}$
	0.1963	$(1.35 \pm 0.02) \times 10^{-2}$
	0.963	0.068 ± 0.004

[a] Error in k_{hyd} is given as ±1 standard deviation in the mean calculated from three replicate kinetic runs.

B/C (M) given in column 4 is indicative of the relative ratio of the computed first and second order in [OH^-] terms.

(b) ^{18}O-Exchange. Roughly 50% ^{18}O-labeled ester (**2a**, **3**, **1d**, **4**) was subjected to the hydrolysis conditions for various times up to $1.3-2t_{1/2}$ for hydrolysis and then recovered from the reaction medium. The ^{18}O-content was determined from ~20 scans of the M^+ and $M^+ + 2$ peaks (low resolution) and compared with the ^{18}O-content of the unhydrolyzed ester. Under no circumstances did we observe any differences, outside experimental error, for the ^{18}O content relative to the time zero samples. (For original data, see Tables 2S-5S, supplementary material).

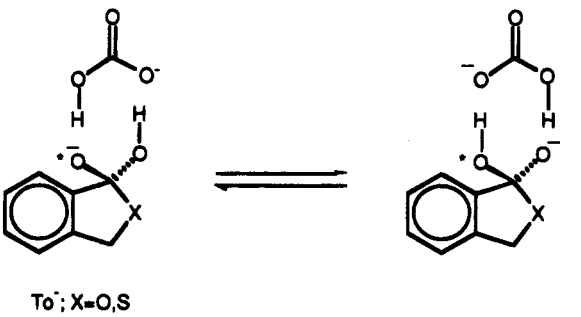
Discussion

Upward curvature in k_{hyd} vs [OH^-] plots has been generally interpreted in terms of a second-order process (as in Scheme 1) where a second OH^- promotes the forward breakdown of To$^-$ in competition with its reversion to starting material. For the hydrolysis of amides,[12] the validity of second order terms in [OH^-] can be verified by ^{18}O-exchange studies where carbonyl ^{18}O exchange in recovered starting material occurs concurrently with hydrolysis.[12a,g] The same is expected for esters such as **2a**, **3**, or **4**,[13] if second order in [OH^-] terms are important, subject to certain reservations (vide infra).

^{18}O-exchange experiments with ~50% ^{18}O-labeled **2a**, **3**, **1d**, and **4** were conducted in order to verify reversal of To$^-$: in no case was any exchange observed. The lack of exchange in this work with **2a** corroborates Bender and co-workers' earlier observations with phthalide,[2c] although the latter used a hydrolysis medium consisting of 33% dioxane.

There are least three possible explanations for the lack of observable ^{18}O-exchange in carboxylic acid derivatives that exhibit an apparent second order in [OH^-] term. First, breakdown to product could be rate limiting, but protonic equilibration of the oxygens in To$^-$ could be incomplete. In such a case, reversion to starting material could be competitive with product formation, but the same OH^- that attacks is preferentially expelled so that little or no ^{18}O-exchange is observed. This possibility of incomplete protonic equilibration of the oxygens has been suggested by Bender and Thomas[2b] for To$^-$ produced during alkaline hydrolysis of alkyl benzoates, even though some ^{18}O-exchange for these is observed. Incomplete oxygen equlibration was suggested[15] to be demonstrable for these ^{18}O-exchanging esters by determining the solvent kinetic isotope effect (skie) on k_{hyd}/k_{ex} since, if proton equilibration were somehow limiting the k_{ex} process, in D_2O the k_{hyd}/k_{ex} ratio would be greater than in H_2O. Such has been done for the hydrolysis of ethyl trifluoroacetate under acidic conditions, and for various amides[12a,g] under basic conditions, but this method is only possible for systems that exhibit some ^{18}O-exchange. As an alternative probe, we have attempted to catalyze the putative slow protonic equilibration of the oxygens in To$^-$ by conducting the hydrolysis/exchange of **2a** and **3** in HCO_3^-/CO_3^{2-} buffer at T = 25 °C, μ = 3.0 (KCl), $[buffer]_{total}$ = 0.8 M, pH = 9.56 (for **3**) and 9.81 (for **2a**). Bicarbonate was chosen because of the possibility that it might act as a bifunctional catalyst to transfer the proton between the oxygens of To$^-$, perhaps in a single concerted encounter as depicted in eq 3.

(3)



To$^-$; X=O,S

This sort of bifunctional catalysis has been observed for phosphate acting as a general acid/base in catalyzing the formation and breakdown of tetrahedral intermediates in hydrolysis reactions,[16] and for the 2-hydroxypyridine ⇌ 2-pyridone system and other catalysts in promoting the mutarotation of tetramethylglucose in benzene solution.[17a,b]

When the ^{18}O-content of the ester recovered from the hydrolytic medium at times of hydrolysis corresponding to t_0, $t_{1/2}$, $1.5t_{1/2}$, and $2t_{1/2}$ was determined (where $t_{1/2}$ = 24 h for **2a** (pH = 9.81) and 129 h for **3** (pH 9.56)), there was no observable change in the amount of ^{18}O (Tables 2S and 3S, supplementary material). This negative result is consistent either with the inability of HCO_3^-/CO_3^{2-} to promote the protonic equilibration in To$^-$ or with a situation where the To$^-$ of neither **2a** nor **3** is able to revert to starting material under any conditions employed: the latter seems most likely.

Second, it is possible that the observed upward curvature but lack of ^{18}O-exchange actually results from a kinetic sequence where there are two independent pathways for rate limiting To$^-$ formation, one in which the

(15) The possibility that the incompleteness of protonic equilibration could be tested by observing that $(k_{hyd}/k_{ex})_{H_2O} > (k_{hyd}/k_{ex})_{D_2O}$ was originally suggested by Bender and Thomas.[2b] To our knowledge, these experiments have not been reported, but are currently being undertaken in our laboratories.

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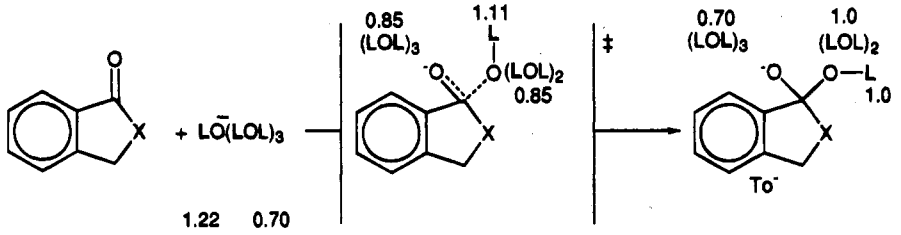
(17) (a) Swain, C. G.; Brown, J. F. *J. Am. Chem. Soc.* **1952**, *74*, 2534, 2538. (b) Rony, P. R.; Neff, R. O. *Ibid.* **1973**, *95*, 2896.

Table 2. Parameters Determined from Nonlinear Regression Fitting of k_{hyd} vs [NaOH] Data to Eq 2[a,b]

ester	B (M^{-1} s^{-1})	C (M^{-2} s^{-1})	B/C[g] (M)
thiophthalide[c] (H_2O)	0.025 ± 0.002	0.004 ± 0.001	9.0–4.6
thiophthalide[c] (D_2O)	0.030 ± 0.001	0.005 ± 0.001	6.20–4.14
phthalide[c]	0.249 ± 0.001	0.050 ± 0.004	5.52–4.52
methyl *o*-methoxybenzoate[d] (this study)	0.066 ± 0.001	0.007 ± 0.002	13.4–7.22
methyl *o*-methoxybenzoate[e]	0.031 ± 0.001	0.083 ± 0.008	0.43–0.33
ethyl thiobenzoate[f]	0.030 ± 0.001	0.006 ± 0.001	6.21–4.14
ethyl benzoate[f]	0.021 ± 0.004	0.014 ± 0.006	3.1–0.85

[a] Fitting was carried out using Inplot Version 4.0 (Graphpad Software, San Diego, 1992). Fitting was performed using "relative distance" to assess goodness of fit. [b] k_o in eq 2 (first-order rate constant for background H_2O reaction) was assigned a constant value of zero prior to fitting since the program calculated a negative value for this parameter when it was allowed to vary. [c] T = 25 °C, μ = 3 (KCl). [d] T = 35 °C, μ = 2 (KCl). [e] T = 35 °C, μ = 2 (KCl) data of Khan and Olagbemiro, ref 13. [f] T = 25 °C, μ = 2 (KCl). [g] Range computed from the standard deviations in B and C.

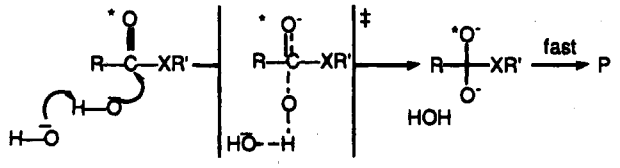
Scheme 2



[a] L = H, D; numbers refer to fractionation factors for bold L.

transition state contains a single OH^- as in Scheme 1, and a second which contains two OH^-. A plausible, albeit intuitively displeasing, process is depicted in eq 4.

(4)



For such a process there should be at least one proton in flight in the transition state, and the second order in [OH^-] term should be subject to a large, and normal, solvent kinetic isotope effect (skie).[18] A second order in [OH^-] term is actually observed for the hydrolysis of *N*-toluoyl-3,3,4,4-tetrafluoropyrolidine;[12] accordingly, the skie changes from inverse at low [OH^-] to normal at high [OH^-]. However, the data for hydrolysis of **3** in H_2O and D_2O show (Table 2) that B_{H_2O}/B_{D_2O} = 0.83 ± 0.09 and C_{H_2O}/C_{D_2O} = 0.67 ± 0.24. The fact that the skie's on both the B and C terms are inverse and experimentally indistinguishable argues against a process for C such as in eq 4 where there is a proton in flight. The observed inverse skie for C also argues against any process where there is a reversibly formed To^- with a hydroxide dependent pathway for its breakdown, since for any imaginable pathway involving a proton in flight, a large and normal skie would be observed.[12a] Rather, the lack of ^{18}O-exchange observed, and the essentially constant skie observed throughout the complete [OL^-] domain, argue strongly for a medium-based effect which leads to curvature in the k_{hyd} vs [OL^-] profile.

For phthalide (**2a**) we have determined the skie on B by comparing the second-order rate constants determined at 0.0097 M and 0.0941 M NaOD with that determined from the fits of the data in NaOH/H_2O (Table 1) to eq 1. The so-determined skie on **2a** is B_{H_2O}/B_{D_2O} = 0.77 ± 0.03, experimentally indistinguishable to what is seen with **3**.

The OL^- attack on **2a** or **3** can be analyzed as we have done previously for amides[12a,g,19] using the method of Schowen[18a,b] and Schowen,[18c] modified by the use of Gold's[20] fractionation factors for hydroxide and its solvating waters. The fractionation factor for the OL group in To^- is assumed to be 1.0 based on the value used for the To^- produced from the OL^- attack on an amide[19] and on the accepted values for a *gem*-diol.[21] Inverse skie's of 0.81 to 0.85, essentially equal to that observed for B, can be calculated if the transition state is 40% to 50% along the reaction coordinate (Scheme 2): a transition state that is 60% along the reaction coordinate gives a computed k_H/k_D value for B of 0.90. The somewhat earlier transition states for OL^- attack on these esters relative to what is observed for OL^- attack on amides[12g,19] (transition state 70% progressed; k_H/k_D = 0.97) may be due to inherent strain in the cyclic system which is relieved during OL^- attack and to less resonance stabilization of the ester relative to the amide. Those same strain factors would tend to resist reversal of To^- relative to its ring opening to form product and could account for the lack of ^{18}O-exchange exhibited by these esters.

A third, and most probable reason for the curvature of the k_{hyd} vs [OH^-] plots relates to medium and/or ion pairing effects. Recently, Pregel and Buncel[22] have investigated the KOEt-promoted elimination of methyl *p*-nitrophenyl sulfonate in ethanol solution and have found an upward curvature in the plots of k_{obsd} vs [OEt]. They have convincingly invoked significant ion pairing effects where free, and ion paired, ethoxide react independently with the substrate, the expression for k_{obsd} being given in eq 5 where $k_{ip} > k_{OEt}$.

$$k_{obsd} = k_{OEt}[OEt^-] + k_{ip}[M^+OEt^-] \quad (5)$$

While such ion-pairing effects are expected to be more

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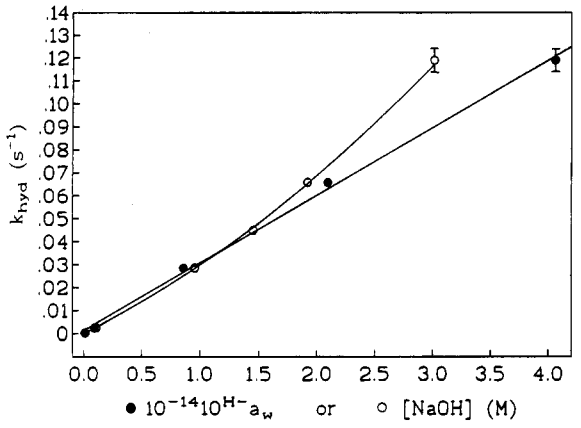

Figure 2. Plot of k_{hyd} vs [NaOH] (○) and $10^{-14}a_wH_-$ (●) for the hydrolysis of thiophthalide in H_2O, $T = 25$ °C, $\mu = 3$ (KCl).

prominent in the less polar solvent HOEt, it is known[23b] that solutions of K, Na, and Li hydroxides at concentrations in excess of 1 M contain significant concentrations of M^+OH^-. Thus, in our present case, if the ion pair is inherently more reactive than free OH^-, the upward curvature is readily explained without recourse to involvement of a second OH^-. Unfortunately, without additional detailed knowledge of the ion-pairing phenomenon in the media employed here, quantitative analysis is not possible.

Alternatively, the curvature may be a result of an inappropriate correlation of k_{hyd} with [OH^-] in strongly alkaline media at high ionic strength. The rate laws observed for a number of reactions in strongly alkaline solutions have been correlated with acidity function H_-.[23] Indeed, Kaiser and co-workers[24] have observed that hydrolysis and methanolysis of some cyclic sulfate and sulfonate esters in strongly basic media show curvature in the k_{obsd} vs [OR^-] plots at high concentration. Their analysis utilized the approximate relationship (eq 6)[25]

$$\log k_{obsd} = \log (kK_w) + (H_- + \log a_w) \qquad (6)$$

where a_w refers to the activity of H_2O in the highly alkaline medium. If the rates of hydrolysis in fact were first order in hydroxide ion, a plot of k_{obsd} vs $a_w\,10^{H_-}$ would be linear,[24] whereas a higher order dependence should be found if more than one OH^- is present in the rate-limiting transition state. Shown in Figure 2 is a plot of the k_{hyd} data for thiophthalide vs both [OH^-] and $a_w\,10^{H_-}$. We have used literature values for a_w[26] and H_-[27]: these are most valid for the conditions of ~3 M KCl and low [OH^-] and at 3 M NaOH where an exact value for both a_w and H_- is reported. For the approximated points between the extremes, we have used a weighted average of the 3 M KCl and 3 M NaOH values for a_w and reported H_- values for 1.0 and 2.0 M NaOH at 25 °C.[26] From Figure 2 the plot is indeed linear, signifying a first-order dependence of the hydrolysis rate on hydroxide.

Methyl *o*-Methoxybenzoate (4). The other reported case for the hydrolysis of a simple carboxylic acid ester being subject to a rate law containing first- and apparent second-order terms in [OH^-] is that of **4**.[13] We have therefore undertaken a reinvestigation of this hydrolysis under the reported[13] conditions, $T = 35$ °C, $\mu = 2.0$ KCl. Our results, given in Tables 1 and 2, differ considerably from those reported in that only a slight curvature is observed, e.g., $B/C = 13.4-7.22$, whereas the reported[13] B/C value was 0.43–0.33. We have also subjected ~50% carbonyl ^{18}O-labeled **4** to hydrolysis in 0.0052 M and 0.0491 M NaOH ($\mu = 2.0$ KCl) media and recovered the unreacted starting material at time zero, $t_{1/2}$, $1.5t_{1/2}$, and $2t_{1/2}$. Mass spectral analysis (Table 4S, supplementary material) shows no experimentally significant loss of ^{18}O concurrent with hydrolysis, contrasting what is expected on the basis of the published[13] kinetic results. We conclude, on the basis of our studies, that a prominent reversal of the To^- produced from **4** + OH^- does not occur nor is there significant justification to invoke a second order in [OH^-] term in the hydrolysis. The curvature observed in our study with **4** is most satisfactorily explained by medium effects.

Conclusions

The present results indicate that the hydrolysis of esters such as **2a** and **3** in highly alkaline media show significant upward curvature in the k_{hyd} vs [OH^-] plots. Yet, no ^{18}O-exchange is observed in the recovered starting material. We have attempted to facilitate, using the bifunctional buffer system HCO_3^-/CO_3^{2-}, the protonic equilibration of the oxygens in To^- only to observe that no ^{18}O-exchange is evident in the recovered starting materials. Solvent kinetic isotope effect studies also do not provide evidence that the apparent upward curvature in the k_{hyd} vs [OH^-] plots obtains from a second order in [OH^-] term since such would imply a substantial normal $(k_{hyd})_{H/D}$ effect on the latter stemming from a proton in flight. Despite the limitations imposed by our negative findings, the best current explanation for the upward curvature in the plots invokes medium and/or ion-pairing effects in the hydrolysis. Indeed, the k_{hyd} values for thiophthalide correlate nicely with H_- in a way that indicates only one OH^- is involved in the hydrolysis. A reinvestigation of the hydrolysis of **4** fails to provide evidence for the reported[13] prominent [OH^-]^2 term. It therefore seems likely that the hydrolysis of simple carboxylic acid esters proceeds through transition states involving a single OH^-, and there is, at present, no compelling evidence for second-order terms in any case.

Acknowledgment. The authors gratefully acknowledge the financial contributions of the Natural Sciences and Engineering Research Council of Canada (NSERC), the University of Alberta, and Mount St. Vincent University. In addition, they are grateful to the staff of the Mass Spectrometry Laboratory of the Department of Chemistry, University of Alberta, and to NSERC and the Alberta Heritage Foundation for Medical Research for Graduate Assistantships (B.A.K.).

Supplementary Material Available: Tables of rate constants for the hydrolysis of **3** and **2a** and mass spectrometrically determined ^{18}O-content of esters recovered from the hydrolysis media at various times (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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