Reactivity in the Para Oxo Ketene[19] Route of Ester Hydrolysis. The Effect of Internal Nucleophilicity and the Irrelevance of B Strain

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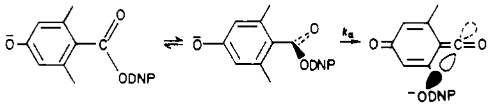
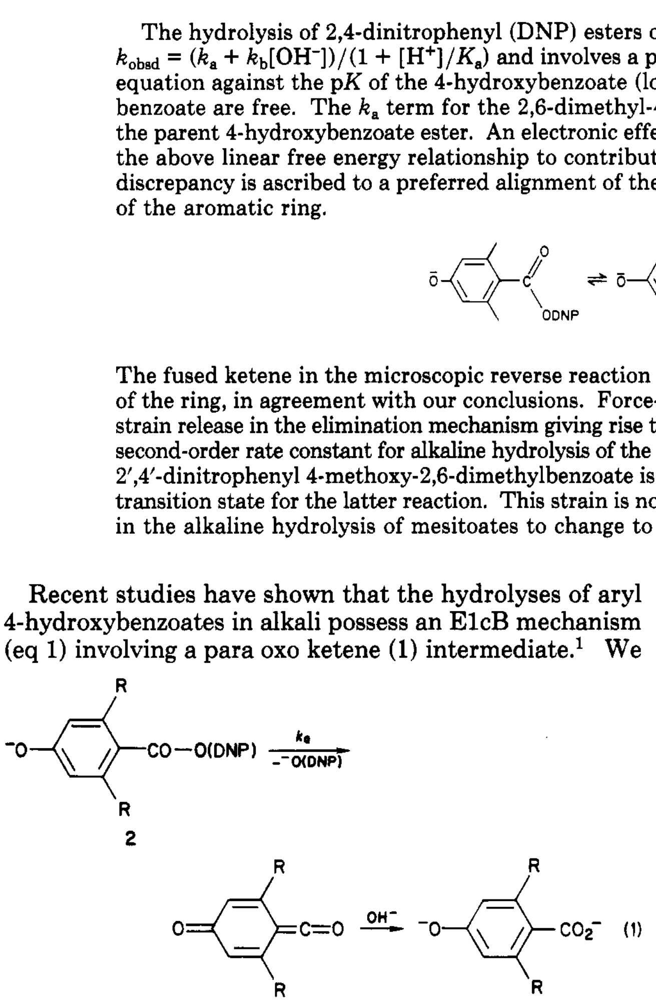
The hydrolysis of 2,4-dinitrophenyl (DNP) esters of substituted 4-hydroxybenzoic acids obeys the equation $k_{obsd} = (k_a + k_b[OH^-])/(1 + [H^+]/K_a)$ and involves a para oxo ketene intermediate. The k_a term fits a Brønsted equation against the pK of the 4-hydroxybenzoate ($\log k_a = 1.15pK_a - 11.71$) provided the 2,6-positions of the benzoate are free. The k_a term for the 2,6-dimethyl-4-hydroxybenzoate ester is 1015-fold larger than that for the parent 4-hydroxybenzoate ester. An electronic effect due to different hydroxyl pK_a's may be calculated from the above linear free energy relationship to contribute 1.6% of the discrepancy. The other component of the discrepancy is ascribed to a preferred alignment of the ester in the 2,6-dimethyl case perpendicular to the plane of the aromatic ring.



The fused ketene in the microscopic reverse reaction has a LUMO acceptor orbital perpendicular to the plane of the ring, in agreement with our conclusions. Force-field calculations of nonbonding interactions indicate *no* strain release in the elimination mechanism giving rise to k_a. The dramatic (10^7-fold) enhancement of the apparent second-order rate constant for alkaline hydrolysis of the 2,6-dimethyl ester compared with that of the corresponding 2′,4′-dinitrophenyl 4-methoxy-2,6-dimethylbenzoate is due mostly to the steric strain imposed in the tetrahedral transition state for the latter reaction. This strain is not sufficient, however, to cause the normal $B_{Ac}2$ mechanism in the alkaline hydrolysis of mesitoates to change to a "square planar" concerted process.

Recent studies have shown that the hydrolyses of aryl 4-hydroxybenzoates in alkali possess an E1cB mechanism (eq 1) involving a para oxo ketene (1) intermediate.[1] We



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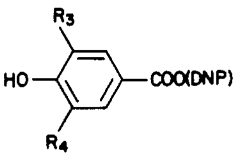
(1)

showed in a preliminary communication that the apparent alkaline hydrolysis of the neutral 2,6-dimethyl analogue (2, R = Me) was some 10^7-fold larger than that for its 4-methoxy analogue and the E1 process (k_a) some 1000-fold faster than that of the parent (2, R = H).[2] Examination of space-filling models of 1 and 2 (R = Me) indicates that there is no apparent steric interaction that could provide a B-strain effect accelerating the elimination; the ester 2, however, is constrained to take up a perpendicular conformation relative to the plane of the aromatic ring. Forcefield calculations confirm this qualitative result.

The comparison of the two esters (2, R = Me and R = H) is complicated by the difference in pK of the 4-hydroxyl groupings. The basicity of the 4-oxyanion is important in the expulsion of the 2,4-dinitrophenolate anion, and the difference in observed rate constant (k_a) could be due to the different "internal" nucleophilicity of the species.[3] To correct for this internal nucleophilicity effect we studied the effect of substituents in the 3,5-position in the 4-hydroxybenzoate 3 on k_a. In this way we can estimate how much of the enhancement in the 2,6-dimethyl ester is due to effects such as strain other than that of the change in hydroxyl pK.



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Studies on the effect of steric strain on the dissociative pathway of acyl group transfer are sparse, but Inoue and Bruice[4] have investigated the system where cyanoketene is formed as a reactive intermediate from 2-cyano esters with substituent variation at the 2-position.

Experimental Section

Materials. Substituted phenyl mesitoates were prepared by treating the phenol (1 g) in pyridine (5 mL) with an equivalent amount of mesitoyl chloride (2,4,6-trimethybenzoyl chloride),[5] which was obtained from the acid (Aldrich) and thionyl chloride; it had bp 55–58 °C (0.4 torr) [lit. bp 143–146 °C (60/torr)].[6,7a]

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(1) (a) Thea, S.; Guanti, G.; Petrillo, G.; Hopkins, A. R.; Williams, A. *J. Chem. Soc., Chem. Commun.* **1982**, 577. (b) Isaacs, N. S.; Najem, T. *ibid.* **1984**, 1361.

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(7) (a) Barnes, R. P. "Organic Syntheses"; Wiley: New York, 1941; *Collect. Vol. III*, p 557. (b) Fuson, R. C.; Corse, J.; Welldon, P. B. *J. Am. Chem. Soc.* **1941**, *63*, 2645.

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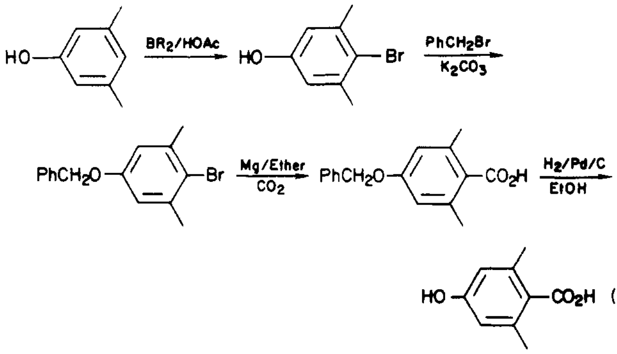
Mesitoic anhydride was prepared by treating 1 mol equiv of mesitoic acid in tetrahydrofuran with $^1/_2$ mol equiv of dicyclohexylcarbodiimide. The 2,4-dinitrophenyl esters were prepared from the corresponding benzoic acids with dicyclohexylcarbodiimide in ethyl acetate as solvent. The 4-hydroxy acids were commercial samples (Aldrich) except 2,6-dimethyl-4-hydroxybenzoic acid. This species was prepared by the following eq 2.



(2)

The 2,6-dimethyl-4-methoxybenzoic acid was prepared by methylation (Me_2SO_4) of the 2,6-dimethyl-4-hydroxybromobenzene to give 3,5-dimethyl-4-methoxybromobenzene, which was treated in a Grignard reaction with carbon dioxide according to the method of Fuson, Corse, and Welldon.[7b]

2,6-Dimethyl-4-(benzyloxy)bromobenzene was prepared by refluxing for 72 h a mixture of acetone (20 mL), 3,5-dimethyl-4-hydroxybromobenzene (0.22 mol), benzyl chloride (0.22 mol), and a slight excess of dried K_2CO_3. The product was cooled, diluted with water, and extracted with ether. The ether layer was then washed with dilute NaOH (1 M), dried (Na_2SO_4), and evaporated. The residue was washed with a little ethanol, and the white crystals (71% yield) had mp 51.5–52 °C.

2,6-Dimethyl-4-(benzyloxy)benzoic acid was prepared by the method described by Fuson, Corse, and Welldon[7b] starting from the bromobenzene. The product, recrystallized as white needles from cyclohexane in 50% yield, had mp 111–112 °C.

2,6-Dimethyl-4-hydroxybenzoic acid was prepared from the 4-benzyloxy compound by catalytic debenzylation in the presence of palladium/charcoal. The reaction was carried out with methanol as solvent in a standard hydrogenation apparatus. The product solution was filtered and evaporated, and the acid product (100% yield) was recrystallized from toluene as light colorless needles, mp 187–189 °C.

Materials were routinely checked for purity with TLC. Structures were confirmed by IR and NMR spectral analysis. Micro analyses were performed by A. J. Fassam of the Canterbury laboratory using a Carlo Erba CHN analyzer and by A. Panaro of the Institute of Pharmaceutical Chemistry at Genoa. Analyses and physical data are collected in the supplementary material.

Materials used for buffers were of analytical reagent grade or were recrystallized from bench grade products. Dioxane was purged of peroxides by the passage of the analytical reagent grade material through an activated alumina column; the absence of peroxides was checked with KI solution. Acetonitrile was purified by the method of Lewis and Smyth[8] and then distilled from a small amount of calcium hydride.

Methods. Kinetics were measured spectrophotometrically with Perkin-Elmer 554 and Unicam SP800 instruments with thermostated cell compartments and fitted with potentiometric recorders. The reaction was initiated by adding an aliquot (25 μL) of a stock solution of the ester (in either acetonitrile or dioxane) on the flattened tip of a glass rod to 2.5 mL of buffer in a silica cell (1-cm path length) in the cell compartment of the spectrometer. The absorbance was followed at 400 nm, and pseudo-first-order rate constants were obtained from plots of $A_t - A_\infty$ against time on two-cycle semilogarithmic graph paper. The pH of the buffer was measured before and after the reaction with a Radiometer PHM-62 digital pH meter calibrated to ±0.02 pH unit with either Merck or EIL standard buffers. Most of the p*K* values for the hydroxy esters were determined by spectrophotometric titration of the 4-hydroxybenzoate.

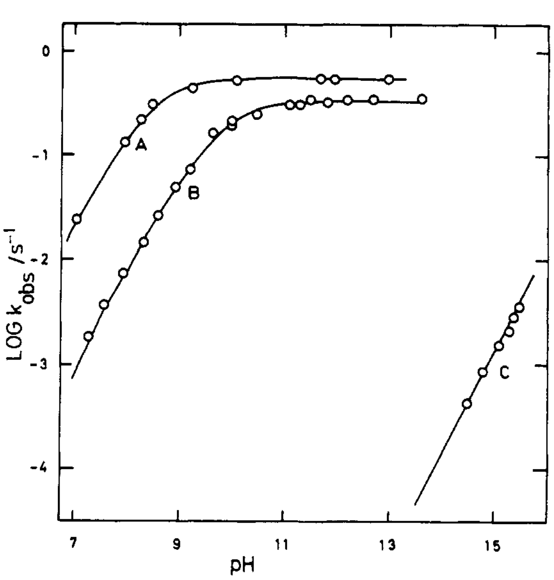


Figure 1. Dependence on pH of the hydrolysis of 2,4-dinitrophenyl 4-hydroxy-2,6-dimethylbenzoate (A) in water at 25 °C and 0.1 M ionic strength made up with KCl and (B) in 40% (v/v) dioxane/water at 25 °C and ionic strength maintained at 1 M with KCl. Lines are calculated from eq 3 ($k_b = 0$) from parameters in Table II. The hydrolysis of the 4-methoxy-2,6-dimethylbenzoate ester of 2,4-dinitrophenol (C) is shown for 40% (v/v) dioxane/water at 25 °C and 1 M ionic strength. The line for C is calculated from $k_{obsd} = k_{OH}[OH^-]$ from the parameters in Table I. The scale gives the measured pH for each solvent employed.

Temperature-dependent studies were carried out on reactions in dioxane/water medium. In order to avoid the necessity of measuring K_a and K_w at each temperature for this medium the pH was measured at 25.1 °C. The calculated hydroxide concentration was assumed to be constant throughout the temperature range, and "pH" changes were assumed to be due to changes in K_w.

Simple force-field calculations were made using the equations of Derissen and Smit[9] with average bond lengths taken from tables.[10] The tetrahedral angle and the trigonal angle were taken as 109.5° and 120°, respectively, in all cases. Calculations were performed on a Texas Instruments TI 51 III hand calculator. Space filling models (CPK) were purchased from the Ealing Corp. Interatomic distances for selected conformations were calculated by standard trigonometry, and the parameters of "set II" of Derissen and Smit[9] were employed in the calculation of energies. These authors give four sets of parameters, of which sets II and III are preferred; check calculations show that there is little difference in the results from the two preferred sets in this work. We neglect a hydrogen-bonding potential because it is expected that little interference will be felt due to C—H···O interactions; there are no O—H···O interactions in the species.[11] The Coulombic term of the force field was also neglected. This will make a small difference for the lower energy conformers, but a correction would require knowledge of the charges on the various atoms. The charge on the proton attached to neutral carbon appears, from calculations of Pople and Beveridge,[12] to vary from +0.063 in acetylene to +0.013 in methane to +0.05 in ethylene; the largest charge of +0.072 is in hydrogen cyanide. The largest charge of +0.072 is in hydrogen cyanide.

The calculations are simplified because we only need to know differences between parent and 2,6-dimethyl species. We can therefore neglect a considerable number of interactions (some of

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Table I. Rate Constants and Ionization Constants for the Alkaline Hydrolysis of 2,4-Dinitrophenyl 4-Hydroxybenzoates[a]

ester	mp/°C	pK^m	λ/nm^g	N^b	$k_{a(exptl)}/s^{-1}$	$k_{OH(calcd)}{}^e$/ $M^{-1}\ s^{-1}$	$k_b/M^{-1}\ s^{-1}$	$k_{a(calcd)}{}^e/s^{-1}$
3,5-di-*tert*-butyl	154–155	9.46^c		6	0.31 ± 0.04	1.28		3.69×10^{-5}
2,6-dimethyl	163–164	8.4^c		12	0.53 ± 0.01			
2,6-dimethyl^i		9.64^c		18	0.33			
3-methyl	164–165	7.89^d	315	7	$(1.95 \pm 0.03) \times 10^{-3}$	2.31	$(4.2 \pm 0.03) \times 10^{-2}$	1.79×10^{-6}
parent		7.68^d	308	11	$(5.22 \pm 0.2) \times 10^{-4\,f}$	3.17	$(7.38 \pm 0.04) \times 10^{-2\,f}$	1.52×10^{-6}
3-methoxy	195–196	7.57^d	330	7	$(9.25 \pm 0.31) \times 10^{-4}$	4.56	6.94 ± 0.05	1.70×10^{-6}
3-chloro	166–167	6.07^d	315	7	$(4.00 \pm 0.2) \times 10^{-5}$	17.0	0.199 ± 0.001	2.00×10^{-7}
3,5-dimethoxy^h	173–174	8.4^c		21	$(1.12 \pm 0.09) \times 10^{-2}$	6.55	$(4.6 \pm 0.03) \times 10^{-2}$	1.65 ± 10^{-5}

[a] Except where stated, water solvent at 25 °C, ionic strength maintained at 0.1 M with KCl. Range of pH employed for kinetics 7–13. Buffers were hydroxide at pH 11–13, carbonate, borate, and tris(hydroxymethyl)aminomethane and (except for hydroxide) were held at 0.01 M total buffer species. [b] Number of data points for the kinetics including duplicates. [c] Measured from the kinetics. [d] Measured spectroscopically at the stated wavelength. [e] Calculated as shoon in the text. [f] These are slightly improved over the previously reported figures.[1] [g] Wavelength for the spectroscopic determination of pK. [h] Ethanol/water 40% (v/v) ionic strength maintained at 0.1 M with NaCl, 25 °C. [i] Dioxane/water 40% (v/v) ionic strength maintained at 1 M with KCl, 25 °C. Value of pK_w for this system is 15.25. [m] The error on these values is between 0.01 and 0.03 pK unit.

which are very strong) that cancel in the two species.

Results

The 2,4-dinitrophenyl esters of substituted 4-hydroxybenzoic acids hydrolyzed in aqueous buffers and the excellent pseudo-first-order rate constants fit eq 3. The

$$k_{obsd} = (k_a + k_b[OH^-])/(1 + [H^+]/K_a) \qquad (3)$$

parameters from the data are recorded in Table I. Figure 1 illustrates the pH dependence for the 4-hydroxy-2,6-dimethyl ester hydrolysis compared with that for the 4-methoxy analogue. A ratio of about 10^7 is observed between the *apparent* bimolecular hydroxide rate constant for the hydroxyl species compared with the true bimolecular rate constant for the methoxyl species, providing further strong evidence for the difference in mechanisms between the two esters. We can calculate the value of k_{OH} for bimolecular attack of hydroxide ion on the neutral 4-hydroxy esters using a Hammett relationship (eq 4) for

$$\log k_{OH} = 1.23 + 1.97\textstyle\sum\sigma \qquad (4)$$

this mechanism for substituted 2,4-dinitrophenyl benzoates.[13] Values of the *apparent* k_a are then calculated from k_{OH} by using $k_a = k_{OH}K_w/K_a$, where K_a is experimentally determined. Both $k_{a(exptl)}$ and $k_{a(calcd)}$ obey Brønsted relationships against the pK_a of the hydroxyl function (eq 5 and 6), and these are illustrated in Figure

$$\log k_{a(exptl)} = (1.15 \pm 0.15)\text{p}K_a - (11.71 \pm 1.15) \qquad (r = 0.978) \quad (5)$$

$$\log k_{a(calcd)} = (0.71 \pm 0.10)\text{p}K_a - (11.10 \pm 0.8) \qquad (r = 0.965) \quad (6)$$

2. The crossover point for these relationships occurs at pK_a = 1.39 and log k_a = −10.1.

The parameter k_b, representing bimolecular attack of hydroxide ion on the anionic ester, follows the Hammett relationship (eq 7), where σ refers to the 3,5-substituted

$$\log k_b = (1.27 \pm 0.55)\textstyle\sum\sigma - (1.28 \pm 0.1) \quad (r = 0.801) \qquad (7)$$

positions. There is considerable scatter, but the Hammett ρ value is, within the error limits, similar to that expected for the $B_{Ac}2$ mechanism (ca. 2).[13,14a]

Table II collects rate constants measured at various temperatures and the resultant pseudo thermodynamic

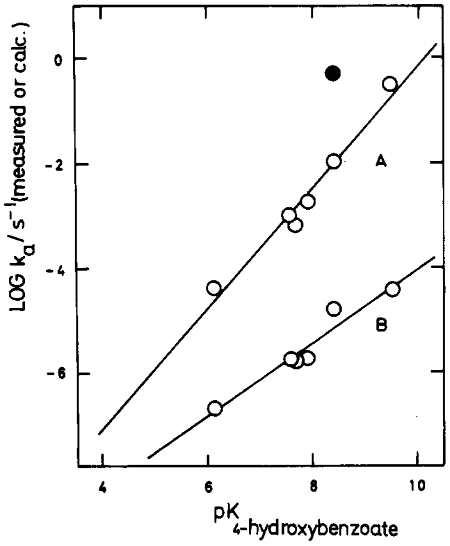

Figure 2. Brønsted plots for the hydrolysis of 2,4-dinitrophenyl esters of 4-hydroxybenzoic acids at 25 °C and 0.1 M ionic strength made up with KCl in water solvent: (A) measured values and (B) values *calculated* for bimolecular attack of hydroxide ion on the neutral ester. The lines are calculated from the Brønsted equations (eq 5 and 6), and data are from Table I (see text for details of the calculation of $k_{a(calcd)}$). Identity, in increasing order of pK for the ester: 3-chloro, 3-methoxy, parent, 3-methyl, 3,5-dimethoxy, 3,5-di-*tert*-butyl. The 2,6-dimethyl species is represented by (●).

Table II. Temperature Dependencies of Rate Constants for the Hydrolysis of 2,4-Dinitrophenyl 4-Hydroxy-2,6-dimethylbenzoate[a]

rate constant	T/°C	N^d	
k_a, s$^{-1\,b}$			
0.237	21.1	3	E_a = 20.9 ± 1.9 kcal/mol
0.317	23.3	3	$\Delta S_0{}^{\ddagger}$ = 3.2 ± 2.8 eu/mol^e
0.410	25.1	3	$\Delta H_0{}^{\ddagger}$ = 20.4 ± 1.9 kcal/mol
$10^{-5}k_aK_a/K_w$, M^{-1} s$^{-1\,c}$			
0.871	21.0	2	
1.21	23.3	2	
1.39	25.1	2	
1.65	27.3	2	E_a = 15.5 ± 0.3 kcal/mol
2.07	29.9	2	$\Delta S_0{}^{\ddagger}$ = 6.6 ± 0.4 eu/mol^e
3.13	35.2	2	$\Delta H_0{}^{\ddagger}$ = 14.9 ± 0.3 kcal/mol
4.51	39.6	2	
6.80	44.8	2	
10.1	49.8	2	

[a] Carried out with 40% dioxane/water (v/v), ionic strength maintained at 1 M with KCl. [b] pH 11.0 at 25.1 °C, K_2CO_3 buffer at 0.01 M total concentration. [c] pH 7.98 at 25.1 °C, tris(hydroxymethyl)aminomethane buffer at 0.01 M total concentration. [d] Number of data points. [e] At 25 °C.

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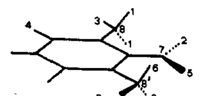
Table III. Kinetics of the Alkaline Hydrolysis of Activated Mesitoic Acid Derivatives[a]

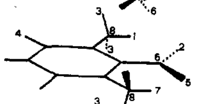
substrate	mp/°C	$pK^{LG\,g}$	$10^3k_{OH}{}^d/M^{-1}\,s^{-1}$	N^c	λ^b nm
anhydride	104.5–105[f]	3.4	124	12	260
phenyl esters					
2,4-dinitrophenyl	169–171	4.11	72	6	370
2,4-dinitro-6-methylphenyl	102–103	4.44	1.3	4	400
2,6-dinitrophenyl	109–110	3.71	5.3	5	400
2-chloro-4-nitrophenyl	145–146	5.45	12.5	5	400
4-chloro-2-nitrophenyl	121–121.5	6.46	2.9	4	400
4-nitrophenyl	100–110	7.14	2.7	6	400
3-nitrophenyl	114–115	8.35	1.2	3	350
4-chlorophenyl	88–89	9.38	0.32	2	300
2,4-dinitrophenyl 4-methoxy-2,6-dimethylbenzoate	138–139		3.9[e]	6	400

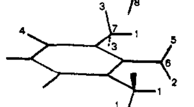
[a] Ethanol/water at 50% (v/v), 25 °C, ionic strength maintained at 0.1 M with NaCl. The hydroxide ion concentration varied from 0.02 to 0.1 M. [b] Wavelength for kinetics. [c] Number of data points. [d] Error on these values is not greater than ±5%. [e] 40% (v/v) dioxane/water at 25 °C; ionic strength made up to 1 M with KCl. [f] Lit. mp 104 °C (Bunton, C. A.; Perry, S. G. *J. Chem. Soc.* **1960**, 307). [g] Jencks, W. P.; Regenstein, J. In "Handbook of Biochemistry"; Sober, H. A., Ed.; Chemical Rubber Publishing Co.: Cleveland, OH, 1970.

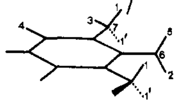
parameters for 1 M standard states at 25 °C. The value of $\Delta S_0{}^{\ddagger}$ for k_a for the 2,6-dimethyl ester in dioxane/water (40%, v/v) is positive, confirming our previous result for the parent and also providing further evidence for the E1cB process.

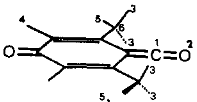
The results of the simple force-field calculations comparing nonbonding energy differences between the parent and the 2,6-dimethyl species are given in structures **4–6**.

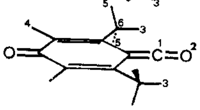
A  (4a, 16.9)

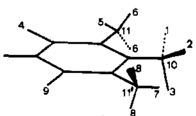
B  (4b, 66.91)

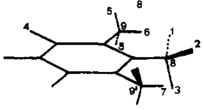
C  (4c, 2.07)

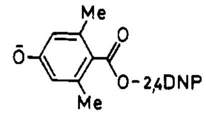
D  (4d, 0.10)

E  (5a, 0.66)

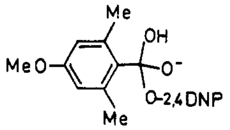
F  (5b, 2.61)

G  (6a, 28.3)

H  (6b, 94.0)



(4e)



(6c)

In order to increase clarity the full atom structures have not been given for either the ester **4** or the adduct **6**, both of which are illustrated in nonstereochemical form (**4e** and **6c**). The carbonyl oxygen is labeled 2 and ether oxygen as 5 in the structures, and the numbers are used to identify individual interactions quoted in the supplementary material. The following bond lengths (Å) were adopted: C═C (Ar), 1.39; Ar—CO, 1.47; C—H (Ar), 1.08; C—H (Me), 1.10; Ar—C, 1.51; C═O, 1.23; CO—OR, 1.36; C═O, 1.43; C═C (ketene), 1.30;[14b] C═O (ketene), 1.18.[14b] The figures quoted adjacent to the stuctures (kcal/mol) are the nonbonding energy *differences* between the 2,6-dimethyl ester and the parent (2,6-dihydrogen). The energy differences do not include interactions that cancel out when the conformations are compared; some of these interactions are not negligible and include the interactions between the ortho hydrogen or methyl and the aromatic carbon bearing the acyl function. We have omitted interactions that are negligible. Considerable saving in calculation arises from the identical interactions in the parent and 2,6-dimethyl analogue. A full description of the interaction energies employed is given in the supplementary material.

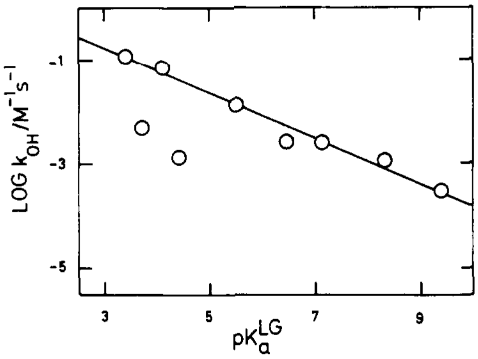


Figure 3. Brønsted dependence of the alkaline hydrolysis of aryl mesitoates on the pK of the leaving phenol (50% (v/v) ethanol/water, 25 °C, ionic strength maintained at 0.1 M with NaCl). The line is calculated from eq 8 and the data are from Table IV. Identity, in increasing order of pK of the leaving XOH function: anhydride, 2,6-dinitrophenyl, 2,4-dinitrophenyl, 2,4-dinitro-6-methylphenyl, 2-chloro-4-nitrophenyl, 4-chloro-2-nitrophenyl, 4-nitrophenyl, 3-nitrophenyl, 4-chlorophenyl.

The results reinforce qualitative conclusions drawn from a perusal of space-filling models. Interactions in the three sets of conformations (**4–6**) that are essentially constant or negligable throughout have been omitted. The "total" energy is that computed from the interaction energies quoted making use of symmetry. In particular we omit any energy due to the ester aryl group interacting with other parts of the molecule; we assume this group takes up the least interacting conformation. We chose particular conformations for the 2,6-dimethyl substituent, the ester and tetrahedral functions to include those combinations giving rise to least and most nonbonding interaction energy. It is possible, but not necessary, to interpolate energies for intermediate conformations. The *planar* conformation of the ester has high nonbonding interactions for all the possible methyl torsional angles (**4a** and **4b**). The *perpendicular* conformation, however, has relatively low energies for the methyl torsional angles (**4c** and **4d**), and these are about 0.55 kcal/mol less than those in the para oxo ketene (**5a** and **5b**, respectively).

The hydrolysis of mesitoate esters and mesitoic anhydride in alkaline solutions obeys excellent pseudo-first-order kinetics in ester. The rate constants are proportional to the hydroxide ion concentration, and the derived second-order rate constants for hydroxide attack are collected in Table III. The rate constants are somewhat scattered, but a Brønsted relationship with the pK_a of the leaving hydroxyl group (eq 8) correlates all but the 2,6-disubsti-

$$\log k_{OH} = (-0.43 \pm 0.03)pK_a{}^{LG} + (0.51 \pm 0.20) \qquad (r = 0.989) \quad (8)$$

tuted esters tolerably well; this is illustrated in Figure 3.

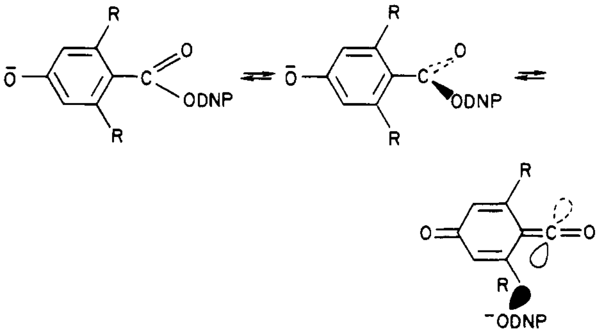
Discussion

We can calculate values of k_a ($k_{a(calcd)}$) for regular $B_{Ac}2$-type attack of hydroxide ion on the neutral 2,4-dinitrophenyl esters of 4-hydroxybenzoic acids, and the values (Figure 2) fall well below the observed k_a's for these esters, confirming our previous mechanistic conclusions concerning the k_a term for these esters.[13] We estimate that a change in mechanism occurs from E1cB to $B_{Ac}2$ as the pK_a of the hydroxyl group of the ester falls below 1.39. Below this value the "internal nucleophilicity" of the 4-oxyanion is too weak to be able to support the expulsion of the 2,4-dinitrophenolate ion through the E1cB mechanism.

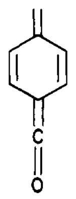
The effect of the pK_a of the 4-hydroxyl group on the reactivity in k_a can be measured (eq 5), and we can therefore correct the reactivity of the 2,6-dimethyl-4-hydroxybenzoate 1015 × k_a for the parent ester, Table I) for this simple electronic contribution. Calculations using eq 5 and the pK_a of the 2,6-dimethyl ester (for water, 8.4) yield a value for the k_a ($9.12\ 10^{-3}/s^{-1}$) accounting for only 1.6% of the ratio. The discrepancy could arise from two main sources involving (a) the ester being forced to react from its perpendicular and most favorable conformation and (b) release of steric strain from ground to transition state.

Studies of space-filling molecular models indicate that there is no steric strain release going from the 2,6-dimethyl ester in its perpendicular conformation to the para oxo ketene to enhance the k_a rate constant over that for the parent ester. Detailed calculations using force-field equations and parameters of Derissen and Smit[9] confirm this. The strain-energy change from the least hindered ester conformation (**4d**) to the least hindered ketene conformation (**5a**) is +0.56 kcal/mol compared with that of the parent. The values of their differences are probably within the "error" of the estimation method. It is interesting to note that the elimination of leaving group from the anion of 2-*tert*-butyl-2-cyanoacetate[4] is accompanied by a small B-strain effect. We should emphasize that the strain changes to the transition state will be smaller than the quoted ones which refer to ground and product states, and moreover the calculations refer to the molecules in the gas phase; no account is taken of solvent interactions.

The postulate that the perpendicular form of the ester, preferred for elimination, requires that the microscopic reverse reaction involves attack of the phenolate ion on the para oxo ketene from a direction perpendicular to the plane of the aromatic ring (eq 9). This stereochemistry has some support from molecular orbital calculations for analogous species[15] which indicate that the lowest unoccupied molecular orbital (LUMO) possesses a large contribution from a vacant p-orbital on the ketene carbon perpendicular to the aromatic plane (energies of the MOs are 2.245 and 2.027 eV for **7** and **8**, respectively).[15] The lowest in-plane vacant orbital (NLUMO) on the ketene carbon possesses a much higher energy (3.823 and 3.824 eV for **7** and **8**, respectively).[15] The addition of nucleophiles to these ketenes will thus be favored for perpendicular attack. This could be the same for the para oxo ketene in the microscopic reverse of the reaction studied here. It is not expected that the carbonyl function will alter the relative levels of LUMO and NLUMO significantly. It should be noted that regular ketenes have LUMO and NLUMO almost degenerate.[15,16] Recent work, however, of Schiess and co-workers[17] has shown that species such as **8** produced by flash photolysis of benzocyclobutenones is markedly influenced by ortho substitution (R = H → Me) in the reaction with methanol. This suggested to the authors that the reaction was in plane.[17] In-plane reaction is also found by Nguyen and Hegarty[14b] for the addition of water dimer to ketene, which yields initially the enediol. These reactions are more complicated than the simple addition of a nucleophile to a ketene and must involve a proton transfer at some stage to enable them to proceed; this could alter the stereochemistry of the addition in the way observed. Enediol formation (the analogue of this is not seen in the reverse of eq 9) would certainly lead to steric problems in **5** (R = Me).



(9)



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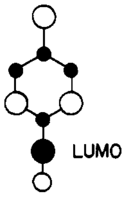

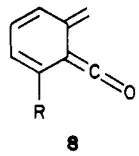

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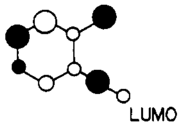
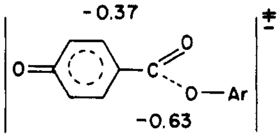


The large dependence of $k_{a(exptl)}$ on the pK_a of the hydroxyl group (eq 5) is consistent with charge being almost completely donated into the aromatic ring in the transition state. This of course does not imply that C–OAr fission is almost complete. Results from our previous work[13] indicate that this is not so and, taken in conjunction with the present data, are consistent with the greater part of the charge being spread into the conjugated system (eq 10).



(10)

The effective charge on the aryl oxygen in the transition state (−0.63) is taken from the previous study.[13] It is interesting at this stage to speculate on the location of the rest of the charge which previously resided largely on the oxygen in the ground state (**2**). If the balance of −0.37 unit is spread on the aromatic ring, there will be very little left for the oxygen of the para oxo group, in agreement with the very large charge change observed here ($\beta = 1.15$); for an exact description of the charge change we should need to know β_{eq} for the equilibrium formation of the para oxo ketene from the substituted hydroxybenzoate. It is not expected that much charge would "leak" onto the ester or ketene carbonyl during the reaction as the π-orbital system for this bond is orthogonal to that of the aromatic plane

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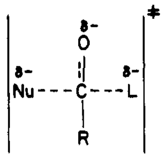
(15) Kuzuya, M.; Miyake, F.; Kamiya, K.; Okuda, T. *Tetrahedron Lett.* **1982**, 2593.

(16) Houk, K. N.; Strozier, R. W.; Hall, J. A. *Tetrahedron Lett.* **1974**, 897.

(17) Schiess, P.; Eberle, M.; Huys-Francotte, M.; Wirz, J. *Tetrahedron Lett.* **1984**, 2201.

in the "reacting" conformation of the ester oxyanion (eq 9).

Speculations on a Concerted Mechanism of Acyl Group Transfer. Concerted mechanisms of acyl group transfer almost certainly exist where the tetrahedral adduct is too unstable to exist as a discrete molecule. The transition-state geometry for these reactions will be close to that of the tetrahedral structure. "Concerted" in this case does not mean that entering and leaving bonds are equally formed or broken in the transition state but that bond-making and bond-breaking take place in unison. Such a process is called synchronous by Dewar.[18] Another geometry has been neglected for some 20 years, and this involves attack of the nucleophile in a plane with the trigonal ester to give a sort of "square-planar" transition state (**9**). The attacking nucleophile essentially donates its electrons into the antibonding orbital to the breaking C–L bond. The similarity of the central R–C–O grouping to an acylium ion configuration prompted us to enquire of the existence of such a mechanism in the present 4-hydroxybenzoate elimination reactions. The stabilization effected by the 4-oxyanion is sufficient to cause the reaction to proceed via a discrete unsaturated intermediate.[13] That is, the nucleophile and leaving group bonds in structure **9** have zero strength. Electronic factors stabilizing structure **9** will also stabilize either the transition state for the E1cB path or that for the $B_{Ac}2$ mechanism. We tried to disfavor the $B_{Ac}2$ mechanism in a reaction that could not involve the E1cB mechanism by increasing steric requirements for the tetrahedral adduct. Mesitoate hydrolysis in alkali has a β_L which, despite the scatter (Figure 3), is well accommodated by the value expected for $B_{Ac}2$ attack by the hydroxyl ion.[14a] The test for the occurrence of a mechanism involving significant leaving bond cleavage as in **6** is a much more negative β_L than in the $B_{Ac}2$ mechanism. Clearly, in this simple case the amount of steric retardation (structures **6a** and **6b**) caused by the dimethyl groups ortho to the ester is not sufficient to reduce the reactivity of the $B_{Ac}2$ mechanism to a level that allows the "square-planar" one operate. The decrease in reactivity caused by the steric requirements is only about 1000-fold comparing the alkaline hydrolysis rate constants for the 2,4-dinitrophenyl esters of 4-methoxybenzoic acid[13] and 4-methoxy-2,6-dimethylbenzoic acid (Table III).



9

$$\left[\begin{array}{c} \overset{\delta-}{O} \\ \| \\ \overset{\delta-}{Nu}---C---\overset{\delta-}{L} \\ | \\ R \end{array}\right]^{\ddagger}$$

Acknowledgment. We thank the CNR and Ministero della Pubblica Istruzione (Italy) and NATO (RG 115.80) for support of this work. Part of the work was carried out during tenure of a Ciba-Geigy Senior Fellowship (A.W.).

Registry No. 2,4-Dinitrophenyl 3,5-di-*tert*-butyl-4-hydroxybenzoate, 95741-32-5; 2,4-dinitrophenyl 2,6-dimethyl-4-hydroxybenzoate, 87513-48-2; 2,4-dinitrophenyl 3-methyl-4-hydroxybenzoate, 95741-33-6; 2,4-dinitrophenyl 4-hydroxybenzoate, 83187-56-8; 2,4-dinitrophenyl 3-methoxy-4-hydroxybenzoate, 95741-34-7; 2,4-dinitrophenyl 3-chloro-4-hydroxybenzoate, 95741-35-8; 2,4-dinitrophenyl 3,5-dimethoxy-4-hydroxybenzoate, 95741-36-9; 2,4-dinitrophenyl mesitoate, 95741-37-0; 2,4-dinitro-6-methylphenyl mesitoate, 95741-38-1; 2,6-dinitrophenyl mesitoate, 95741-39-2; 2-chloro-4-nitrophenyl mesitoate, 95741-40-5; 4-chloro-2-nitrophenyl mesitoate, 95741-41-6; 4-nitrophenyl mesitoate, 70076-07-2; 3-nitrophenyl mesitoate, 95741-42-7; 4-chlorophenyl mesitoate, 95741-43-8; 2,4-dinitrophenyl 4-methoxy-2,6-dimethylbenzoate, 87513-49-3; mesitoic acid, 480-63-7; 2,6-dimethyl-4-(benzyloxy)bromobenzene, 95741-44-9; 3,5-dimethyl-4-hydroxybromobenzene, 2374-05-2; benzyl chloride, 100-44-7; 2,6-dimethyl-4-benzyloxybenzoic acid, 95741-45-0; 2,6-dimethyl-4-hydroxybenzoic acid, 75056-97-2; mesitoic anhydride, 5745-51-7.

Supplementary Material Available: Tables of analytical data and force-field calculations (4 pages). Ordering information is given on any current masthead page.

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[18] Dewar, M. J. S. *Tetrahedron Lett.* **1984**, *106*, 209.

[19] The IUPAC name for the parent species is 6-carbonyl-1,4-cyclohexadien-3-one.

Oxidatively Assisted Nucleophilic Substitution of Iodine in Alkyl Iodides by Nucleofugic Anions

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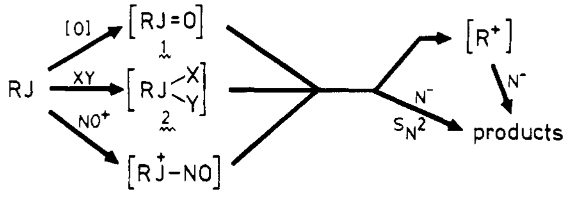
The reaction of alkyl iodides with chlorine or nitronium tetrafluoroborate in the presence of salts of perchloric or substituted sulfonic acids gave alkyl perchlorates or sulfonates as principal products. Some mechanistic aspects of this new reaction are discussed.

The oxidative nucleophilic substitution of iodine in alkyl iodides was first reported in 1905[1] and has received considerable attention in recent literature.[2-15] Effective oxidants for the reaction include Cl_2 and Br_2,[2,3] HNO_3,[4] N_2O_5,[5] $AcONO_2$,[5,6] $NOBF_4$,[7] NO_2BF_4,[8] $K_2Cr_2O_7$,[4a] $KMnO_4$,[4a]

Chart I



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