Base-catalysed hydrolysis of γ-lactones: reactivity–structure correlations for 3-(substituted phenoxy- and thiophenoxymethylene)-(Z)-1(3H)-isobenzofuranones

Keith Bowden,[1]* Richard J. Ranson,[1] Alexander Perjéssy,[2] Margita Lácová,[2] Oĺga Hritzová[3] and Walter M. F. Fabian[4]

[1]Department of Biological and Chemical Sciences, Central Campus, University of Essex, Wivenhoe Park, Colchester, Essex CO4 3SQ, UK
[2]Department of Organic Chemistry, Faculty of Natural Sciences, Comenius University, Mlynská dolina CH-2, 842 15 Bratislava, Slovak Republic
[3]Department of Organic Chemistry, Faculty of Natural Sciences, P. J. Safárik University, Moyzesova 11, 041 67 Kosice, Slovak Republic
[4]Institute of Organic Chemistry, Karl-Franzens University Graz, Heinrichstr. 28, A-8010 Graz, Austria

ABSTRACT: Rate coefficients were measured for the base-catalysed hydrolysis of a series of substituted 3-(phenoxy- or thiophenoxymethylene)-*(Z)*-1(3*H*)-isobenzfuranones (3-phenoxy- or thiophenoxymethylenephthalides) in 70% (v/v) aqueous dioxane at 30.0 °C, in addition to the carbonyl stretching frequencies in chloroform and tetrachloromethane following deconvolution and band separation, when required. The Hammett reaction constants for the alkaline hydrolysis of the 3-/4-substituted phenoxy and thiophenoxy series are *ca* 0.75 and 1.10, respectively. These results are related to electrostatic field and resonance effects. Successful correlations between the carbonyl stretching frequencies and substituent constants and the rates of alkaline hydrolysis were found. Computational studies using the semi-empirical AM1 method correctly model both the details of the mechanistic pathway and the substituent effects. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: γ-lactones; base-catalysed hydrolysis; reactivity–structure correlations; isobenzofuranones

INTRODUCTION

The alkaline hydrolysis of relatively small-ring unsaturated lactones has been investigated.[1] The lactones are much more reactive than comparable acyclic esters or relatively large-ring lactones. The former have their ester group in a *cis (E)* conformation and the latter in a *trans (Z)* conformation.[2] The mechanistic pathway for the alkaline hydrolysis is shown in Scheme 1 and the rate-determining step is considered to be the addition of hydroxide anion to the lactone carbonyl group, *i.e. k'_1*.[1] The reactivity–structure correlations for 3-(aryl- and alkylmethylene)-*(Z)*-1(3*H*)-isobenzofuranones have been studied recently.[3] A good correlation was found for the alkaline hydrolysis of the 3- or 4-substituted phenyl series with σ to give a ρ value of *ca* 1.5 for 70% aqueous dioxane at 30.0 °C. The rates for *all* 37 phthalides give a very successful correlation with the carbonyl stretching frequencies in chloroform.

The infrared spectra of some 3-(phenoxy- and thiophenoxymethylene)-*(Z)*-1(3*H*)-isobenzofuranones have

been investigated previously.[4] However, the Fermi resonance effect has not been analysed previously for these compounds. The Fermi resonance interaction on the carbonyl stretching frequencies has been investigated for a series of 3-(arylmethylene)-*(Z)*-1(3*H*)-isobenzofuranones after deconvolution and band separation.[5] It has been shown[5,6] that the unperturbed frequencies of car-
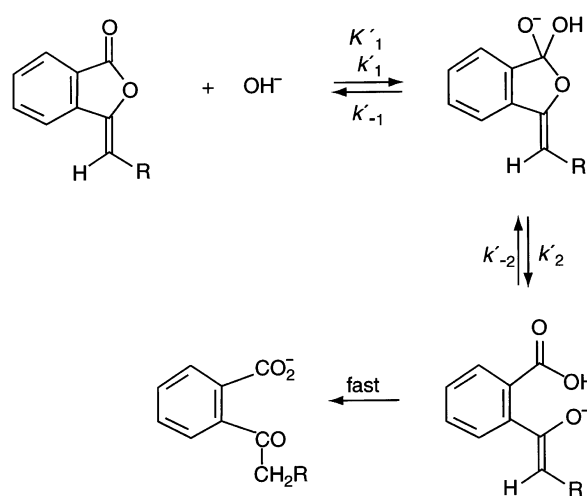

Scheme 1

bonyl stretching vibrations exhibit excellent linear correlations with Hammett σ constants.

The additivity of substituent effects on reactivity has been investigated in several systems.[7] Additivity has been observed to be followed in many cases, except when significant steric interactions occur between the multi-substitution.

The present investigation consisted of a study of the rates of alkaline hydrolysis of a series of substituted 3-(phenoxy- and thiophenoxymethylene)-*(Z)*-1(3*H*)-isobenzofuranones, **1a** and **1b**, in 70% (v/v) dioxane water at 30.0 °C, and for the parent phthalides at several other

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1a R = O—⟨phenyl⟩—X

1b R = S—⟨phenyl⟩—X

1c R = ⟨phenyl⟩—X
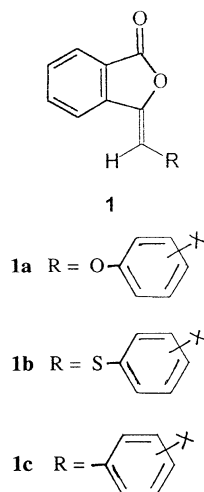
temperatures. The infrared spectra of these phthalides were studied in both chloroform and tetrachloromethane in the 1700–1850 cm^{-1} region under the conditions required for the investigation of Fermi resonance effects. The results for the alkaline hydrolysis are related to the substituent effects, in terms of σ values, and the carbonyl stretching frequencies of the phthalides. The inclusion of 2- with 3-/4-substituents in reaction series was investigated, in addition to additivity of substituent effects.

EXPERIMENTAL AND RESULTS

Materials

The synthesis of the substituted 3-(phenoxy- and thiophenoxymethylene)-(Z)-1(3*H*)-isobenzofuranones   was

completed by the reaction of phthalic anhydride with the corresponding substituted phenoxy or thiophenoxy-acetic acids by the Gabriel modification of the Perkin synthesis.[8] Previously unreported compounds are listed in Table 1. The purity and structures of the lactones were monitored by IR and ^{1}H and ^{13}C NMR spectroscopy and elemental analyses. Their melting points, after repeated recrystallization and drying under reduced pressure (P_2O_5), were either in good agreement with literature[8] values or are given in Table 1.

The solvents were purified using established procedures.[9]

Measurements

Rate coefficients for the alkaline hydrolysis of the lactones were determined spectrophotometrically by use of a Perkin-Elmer Lambda 5 or 16 spectrophotometer. The reactions were followed at the wavelengths shown in Table 2. The detailed procedure used was that described previously.[10] The products of the reaction were found to be anions of the corresponding carboxylic acids in quantitative yield and were further confirmed spectrophotometrically by comparison of the spectrum of the acid in base with that of the reaction product.[1,3] The rate coefficients for the alkaline hydrolysis of the lactones **1a** and **1b** in 70% (v/v) aqueous dioxane at 30.0 °C, and for the parent compounds at several temperatures, are given in Table 2. The reaction is first order in both substrate and hydroxide anion. The activation parameters for the parent lactones are given in Table 3.

The IR measurements were made in chloroform and tetrachloromethane solutions using a Zeiss Specord M-80 spectrometer and recorded at room temperature using NaCl cells of 0.1, 0.5 or 1.0 cm thickness. The concentrations of the solutions were 8×10^{-3}, 2×10^{-3} or 8×10^{-4} mol dm^{-3}. Peak positions were determined with an accuracy of ± 0.2 cm^{-1} against polystyrene standard spectra. The absorption intensities of the Fermi doublet components were determined after mathematical deconvolution and separation of overlapping bands. Curve analysis was performed by a digital curve-fitting routine. The carbonyl stretching frequencies for the lactones are shown in Table 2 as either unperturbed or directly measured values.

Table 1. Physical properties of previously unreported compounds **1a** and **1b**

Compound	M.p. (°C)	Recryst. solvent	Formula	Anal.	Yield (%)
1a (X = 4-OCH$_3$)	159–161	Acetic acid	C$_{16}$H$_{12}$O$_4$	C, H	35
1a (X = 4-Br)	205–207	Acetic acid	C$_{15}$H$_9$BrO$_3$	C, H, Br	30
1a (X = 2-CH$_3$,4,6-(Cl)$_2$)	157–158	Acetic acid	C$_{16}$H$_{10}$Cl$_2$O$_3$	C, H, Cl	25
1a (X = 2-Br)	124–126	Ethanol	C$_{15}$H$_9$BrO$_3$	C, H, Br	27
1a (X = 3-Br)	147–149	Ethanol	C$_{15}$H$_9$BrO$_3$	C, H, Br	30
1b (X = 2,5-(CH$_3$)$_2$)	132–134	Acetic acid	C$_{17}$H$_{14}$O$_2$S	C, H, S	52
1b (X = 3-CH$_3$)	96–97	Acetic acid	C$_{16}$H$_{12}$O$_2$S	C, H, S	58

Table 2. Rate coefficients (k_2) for the alkaline hydrolysis of 3-(substituted phenoxy- or thiophenoxymethylene)-(Z)-1(3H)-isobenzofuranones in 70% (v/v) aqueous dioxane at 30.0°C, together with their carbonyl stretching frequencies (ν_{CO}) in chloroform and tetrachloromethane[a]

| | | | | ν_{CO} (cm^{-1}) | |
No.	Phenoxy substituent	k_2 (dm^3 mol^{-1} s^{-1})	λ (nm)[b]	In chloroform	In tetrachloromethane
1	H	0.652 (1.37, 2.45, 4.94)[c]	325	1776.0	1791.2
2	2-CH$_3$	0.431	330	1775.6 (1755.6)[d]	1790.8
3	2-Br	0.685	277	1778.2	1792.0
4	2-Cl	0.691	275	1775.6	1796.6
5	3-CH$_3$	0.572	330	1777.1 (1760.3)[d]	1791.2
6	3-Br	1.28	279	1784.0	1796.8
7	3-Cl	1.08	280	1785.2	1793.0
8	3-F	1.18	278	1783.6	1797.2
9	3-NO$_2$	2.85	320	1788.8	1798.8
10	4-CH$_3$	0.525	330	1776.6	1791.2
11	4-OCH$_3$	0.525	285	1775.2	1790.8
12	4-Br	0.973	277	1782.5	1792.8
13	4-Cl	1.04	278	1779.0	1795.2
14	4-F	0.730	278	1780.0	1794.2
15	2-CH$_3$, 4-Cl	0.676	325	1778.8 (1761.0)[d]	1793.6
16	2,4-(Cl)$_2$	1.12	325	1783.4	1794.8
17	2-CH(CH$_3$)$_2$, 5-CH$_3$	0.277	280	1773.8	1789.6
18	3,4-(CH$_3$)$_2$	0.458	330	1776.0	1792.8
19	3,5-(CH$_3$)$_2$	0.500	330	1770.0 (1761.3)[d]	1792.4
20	3-CH$_3$,4-Cl	0.964	330	1779.5 (1770.9)[d]	1791.4
21	2,4,5-(Cl)$_3$	1.81$_5$	280	1782.4	1796.4
22	2,4-(Cl)$_2$, 6-CH$_3$	5.16	276	1780.1	1794.4
23	2,4,6-(Cl)$_3$	15.5$_5$	277	1780.1	1793.1
Thiophenoxy substituent					
24	H	2.13 (3.90, 7.45, 12.55)[c]	350	1781.6	1792.8
25	3-CH$_3$	1.91	350	1778.8	1792.0
26	3-Cl	3.94	345	1784.0	1795.6
27	4-CH$_3$	1.42	355	1780.4	1792.0
28	4-Br	4.14	350	1783.6	1795.2
29	3-NO$_2$	12.6	325	1789.6	1797.8
30	4-NO$_2$	17.6	360	1789.2	1798.8
31	2,5-(CH$_3$)$_2$	0.870	345	1778.4	1791.2
32	2,5-(Cl)$_2$	7.07	345	1787.6	1798.8
Phenylsulfinyl					
33	H	3.39$_5$	365	1782.4	1793.6
Phenyl					
34	H[e]	1.02 (2.22, 3.81, 7.70)[c]	340	1776.8	1796.8

[a] Rate coefficients were reproducible to $\pm$3%.
[b] Wavelength used to monitor alkaline hydrolysis.
[c] At 40.0, 50.0 and 60.0°C, respectively.
[d] Unperturbed values for the first overtone of the out-of-phase carbon-hydrogen deformation vibration involved in Fermi resonance.
[e] Literature values. [1]

Table 3. Activation parameters for the alkaline hydrolysis of 3-(substituted methylene)-(Z)-1(3H)-isobenzofuranones in 70% (v/v) aqueous dioxane at 30.0°C[a]

Substituent	$\Delta H^{\ddagger}$ (kcal mol^{-1})[b]	$\Delta S^{\ddagger}$ (cal mol^{-1} K^{-1})[b]
OPh	12.8	−17
SPh	11.4	−20
Ph[c]	12.7	−17

[a] Values of $\Delta H\ddagger$ and $\Delta S\ddagger$ are considered to be accurate to $\pm$500 cal mol^{-1} and $\pm$2 cal mol^{-1} K^{-1}, respectively.
[b] 1 cal = 4.184 J.
[c] Literature values. [1]

Calculations

All the calculations were performed by AM1[11] using the VAMP program package.[12] Geometries were completely optimized without any restrictions using the keyword PRECISE. Transition states were approximately located by reaction path calculations, refined by gradient norm minimization and characterized as true transition states by force constant calculations. Downhill optimizations [intrinsic reaction coordinate (IRC) calculations] along both directions of the normal mode corresponding to the

Table 4. Observed log k_2 for the alkaline hydrolysis and heat of formation (ΔH_f), bond orders [p(C=O)] and dipole moments (μ) of the phthalides

| Compound[a]	Log k_2	ΔH_f (kcal mol^{-1})[b]	p (C=O)	μ (D)
1	−0.186	−15.9 (−16.4, 44.5)[d]	1.8579	6.01
2[c]	−0.336	−22.8 (−23.2, 44.5)[d], −22.0 (−22.5, 44.7)[d]	1.8565, 1.8540	5.78, 6.33
5[c]	−0.243	−23.55, −23.5	1.8570, 1.8571	5.90, 6.27
7[c]	0.033	−22.3, −22.6	1.8620, 1.8617	6.50, 5.16
8[c]	0.072	−60.4, −60.7	1.8630, 1.8628	6.71, 4.91
9[c]	0.455	−10.4 (−11.3, 44.0)[d], −11.2 (−12.0, 43.8)[d]	1.8712, 1.8703	9.52, 4.48
10	−0.280	−23.5	1.8569	6.12
11	−0.280	−53.3	1.8559	6.88
13	0.017	−22.7	1.8619	5.71
14	−0.137	−60.6	1.8612	5.68
19	−0.301	−31.1	1.8563	6.10
24	0.328	13.0	1.8601	5.63
25[c]	0.281	5.3, 5.3	1.8595, 1.8595$_5$	5.61, 5.92
26[c]	0.595	6.4, 6.2	1.8636, 1.8633	5.95, 4.49
27	0.152	5.2	1.8592	5.85
29[c]	1.100	18.0, 17.3	1.8710, 1.8699	8.67, 2.59
30[c]	1.246	17.0	1.8743	6.33

[a] Numbering of compounds refers to Table 2.
[b] 1 cal ≡ 4.184 J.
[c] Conformations **2a** and **2b**, respectively.
[d] SCRF values for reactant phthalide and TS1, respectively.

imaginary frequency established the two minima connected by the transition structure in question. Solvent effects (H$_2$O) were approximated by the SCRF[13] method. In Table 4 are given the heats of formation (ΔH_f in kcal mol^{-1}) and dipole moments (μ in debye), together with the bond orders [p(C=O)] for the carbonyl group. For 2- and 3-substituted derivatives, two conformations (**2a** and **2b**) are considered. For electron-withdrawing
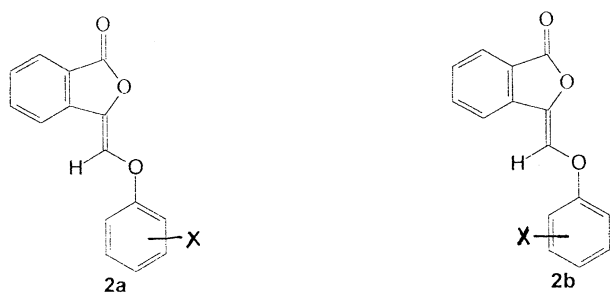

substituents (*e.g.* F, Cl and NO$_2$), conformation **2b** is more stable, whereas for electron-releasing substituents (*e.g.* CH$_3$), conformation **2a** is more stable. In the latter case, the energy difference is too small to be significant. Furthermore, the dipole moments of conformation **2a** are higher in the case of the F, Cl and NO$_2$ substituents, whereas the reverse is true for CH$_3$. For the SCRF results in Table 4, the heats of formation (ΔH_f in kcal mol^{-1}) of the lactones 1, 2 and 9 (Table 2) and the first transition state, TS1, are given. The reaction pathway considered is shown in Scheme 2. The addition of the nucleophile was found to be rate determining, as in our previous study.[3] The computed structures for the more stable conforma-

tions of the substrate, TS1 and TS2 for the lactone 9 (Table 2) are shown as Figs 1–3.
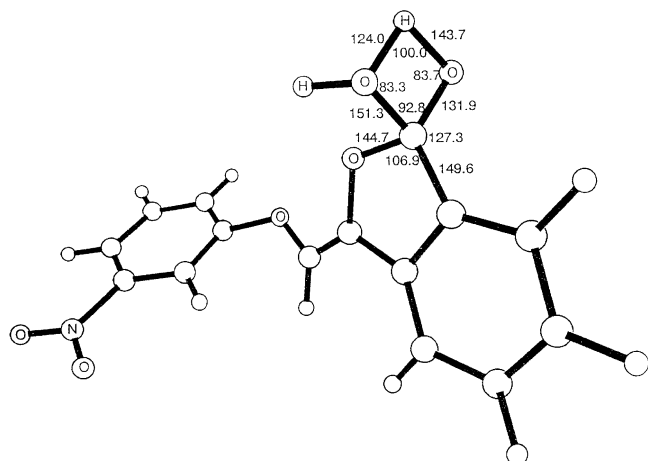
DISCUSSION

Carbonyl stretching vibrations

The 3-(substituted phenylmethylene)-(*Z*)-1(3*H*)-isobenzofuranones **1c** and their tricarbonylchromium complexes exhibit significant splitting of their absorption
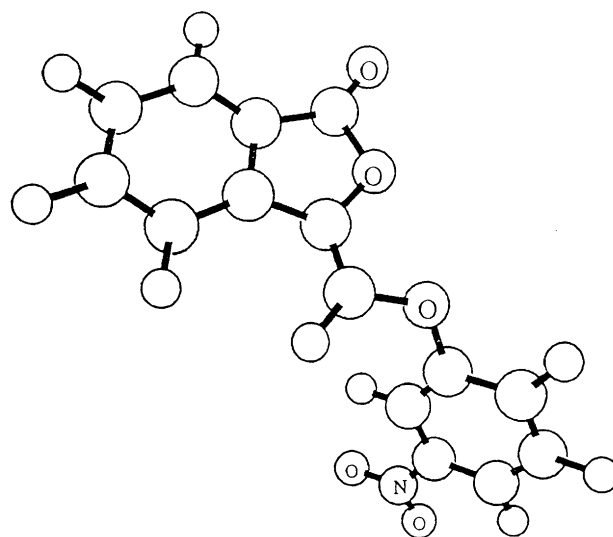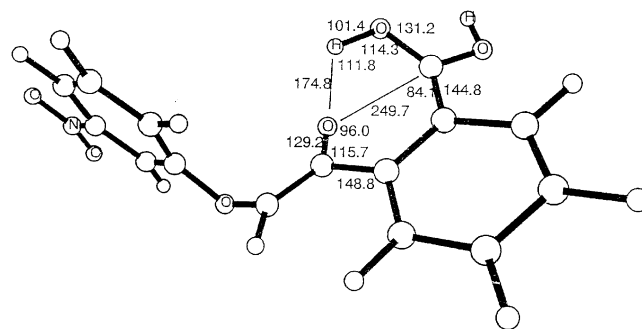

Figure 1. Computed conformation of compound 9, Table 2

Figure 2. Computed conformation for TS1 of lactone 9, Table 2

Figure 3. Computed conformation for TS2 of lactone 9, Table 2

bands in the carbonyl stretching vibration region resulting from Fermi resonance of the fundamental carbonyl stretching vibration with the first overtone of the out-of-plane carbon–hydrogen deformation vibration in the arylmethylene moiety.[5,6] For the corresponding phenoxy systems, **1a**, only the compounds numbered 2, 5, 15, 19

and 20 in Table 2 exhibit a Fermi resonance doublet in the ν_{CO} absorption bands. The infrared spectra of the above five compounds were corrected for Fermi resonance after deconvolution and band separation.[5] The carbonyl stretching vibrations of the phenythio system, **1b**, are all unsplit.

The carbonyl stretching frequencies of the 3-/4-substituted phenoxy lactone system **1a** measured in both chloroform and tetrachloromethane were correlated with Hammett σ constants,[14] as shown in Table 5. The former give a satisfactory correlation, but that for the latter is

Table 5. Correlations of the carbonyl frequencies, ν_{CO}, and alkaline hydrolysis, log k_2, of the phenoxy and thiophenoxy lactones **1a** and **1b**.[a]

System	Parameter	ρ	s	ν_0 or log k_0	r	n
ν_{CO}(3-/4-subst. phenoxy) in CHCl$_3$	σ	14.6	1.5	1778.8	0.954	11
ν_{CO}(3-/4-subst. phenoxy) in CCl$_4$	σ	8.5	1.8	1792.0	0.874	11
ν_{CO} (all phenoxy)[b] in CHCl$_3$	σ	13.6	1.5	1777.8	0.932	20
ν_{CO} (all phenoxy)[b] in CCl$_4$	σ	7.2	2.4	1792.4	0.812	20
ν_{CO} (3-/4-subst. thiophenoxy) in CHCl$_3$	σ	10.8	1.2	1781.0	0.971	7
ν_{CO} (3-/4-subst. thiophenoxy) in CCl$_4$	σ	7.6	0.4	1793.0	0.992	7
ν_{CO} (all thiophenoxy) in CHCl$_3$	σ	10.8	0.9	1781.0	0.980	9
ν_{CO} (all thiophenoxy) in CCl$_4$	σ	7.7	0.6	1793.0	0.983	9
Log k_2(3-/4-subst. phenoxy)	σ	0.740	0.057	−0.164	0.974	11
Log k_2(3-/4-subst. thiophenoxy)	σ	1.096	0.079	0.327	0.987	7
Log k_2(3-/4-subst. phenyl)[d]	σ	1.485	0.085	−0.013	0.980	15
Log k_2 (all phenoxy)[c]	ν_{CO}(CHCl$_3$)	0.0486	0.0058	—[e]	0.855	21
	ν_{CO}(CCl$_4$)	0.0855	0.0126	—[e]	0.842	21
Log k_2 (all thiophenoxy)	ν_{CO}(CHCl$_3$)	0.0986	0.0099	—[e]	0.966	9
	ν_{CO}(CCl$_4$)	0.137	0.016	—[e]	0.954	9
Log k_2 (all aryl)[d]	ν_{CO}(CHCl$_3$)	0.0975	0.0052	—[e]	0.959	33
	ν_{CO}(CCl$_4$)	0.101	0.014	—[e]	0.774	36
Log k_2 (both phenoxy and thiophenoxy)	p(C=O)[f]	79.9	10.1	—[e]	0.898	17
Log k_2 (all phenoxy)	p(C=O)[f]	54.3	3.4	—[e]	0.983	11
Log k_2 (all thiophenoxy)	p(C=O)[f]	71.4	5.8	—[e]	0.987	6
Log k_2 (all aryl)[d]	p(C=O)[f]	89.2	5.1	—[e]	0.962	26
ν_{CO} (all phenoxy) in CHCl$_3$	p(C=O)[f]	1097	3	—[e]	0.895	11
ν_{CO} (all phenoxy) in CCl$_4$	p(C=O)[f]	594	1	—[e]	0.929	11
ν_{CO} (all thiophenoxy) in CHCl$_3$	p(C=O)[f]	687	2	—[e]	0.950	6
ν_{CO} (all thiophenoxy) in CCl$_4$	p(C=O)[f]	463	1	—[e]	0.970	6

[a] s is the standard deviation, r the correlation coefficient and n the number of substituents.
[b] Except compounds 4, 21 and 23 (Table 2).
[c] Except compounds 4 and 23 (Table 2).
[d] Literature values.[3]
[e] Computed as $\Delta\nu$ or Δp(C=O) from that of parent compound for series.
[f] Bond order of reacting carbonyl group (see Table 4), using the most stable conformation when required.

poor. For the 3-/4-substituted thiophenoxy lactone system **1b**, both correlations are very good. As a first approximation, for 2- and 6-substituents, *para*-σ values were used and simple additivity of σ values was assumed for di- and tri-substituted compounds (see below). The correlations including the unperturbed carbonyl stretching frequencies for chloroform solutions are greatly improved when compared with previous studies.[4] However, the correlations for *all* the phenoxy lactones are poorer than those for the 3-/4-substituted system alone. It might have been expected that the frequencies, and also the reactivity studies, would be better correlated using σ° values,[14] which are designed to apply to systems having an insulating link for resonance effects between the phenyl and reactive groups. Correlations using σ° values were, in the main, significantly poorer than those using σ values. It appears that the oxygen or sulfur links do *not* act as an insulating link here.

Alkaline hydrolysis

The rates of alkaline hydrolysis of the parent 3-phenoxy and 3-thiophenoxy compounds relative to those of the 3-phenyl lactone are *ca* 0.64 and 2.1, respectively, whereas that of the 3-phenylsulfinyl lactone is *ca* 3.3. These are in the order expected from the polar effects of the groups, *i.e.* the *para*-σ values are -0.03 (OPh), 0.07(SPh), -0.01(Ph) and 0.44 (SOPh).[14]

The activation parameters for the alkaline hydrolysis of the 3-phenoxy and 3-thiophenoxy lactones are shown in Table 3. They clearly indicate the bimolecular nature of the reaction. Comparison with each other and the 3-phenyl lactone indicates a significant decrease in the enthalpy of activation for the 3-thiophenoxy lactone, which arises from the greater electron-withdrawing capacity of the thiophenoxy group.

Transmission of polar effects

The Hammett equation [Eqn (1)] correlations of the rates of alkaline hydrolysis of the phenoxy and thiophenoxy systems, **1a** and **1b**, are shown in Table 5.

$$\log(k/k_0) = \rho\sigma \tag{1}$$

Both correlations are good and the ρ values found are less than that those for the corresponding phenyl system, **1c**, as would be expected. The values of ρ/ρ_0 are *ca* 0.51 and 0.74 for the phenoxy and thiophenoxy compared with the phenyl system. These values are greater than might be expected and could arise from a conformation of the phenoxy and thiophenoxy groups that is favourable for electrostatic field transmission. The latter would place the substituents closer to the reaction site than in an 'extended' conformation. The transmissive capacity of the sulfur link is significantly greater than that of the oxygen

link. It would be expected that the electrostatic field and/or σ-inductive transmission would be comparable for both systems. The phenoxy and thiophenoxy groups are both in direct conjugation with the lactone carbonyl group through the π-electron system. Thus, the π-electron transmission must be more effective for the sulfur link, possibly arising from the greater polarizability of sulfur.

The relative effects of the 2- and 4-substituents on the alkaline hydrolysis can be assessed for the phenoxy lactones by lactones 2, 10 (CH$_3$); 3, 12 (Br); and 4, 13 (Cl) in Table 2. The ratio k_2(2-X)/k_2(4-X) = 0.73 ($\pm$0.05). This indicates a reduction in transmission of the substituent effect for the 2- compared with the 4-position. Previously, it had been found that the transmission in *ortho*-substituted benzoic and 3-substituted acrylic acids was between 1.5 and 2.5 times that in *para*-substituted benzoic acids.[15] For an electrostatic field effect this ratio was considered to reduce to about unity as the reaction site and the substituted phenyl group are separated, as is observed.[16]

Correlation of rates and carbonyl stretching frequencies

In our previous study of 37 diverse aryl and alkyl lactones of the type **1c**, a very successful correlation was obtained between the rates of alkaline hydrolysis and the carbonyl stretching frequencies in chloroform, using equation (2);

$$\log k_2 = a\,\nu_{CO} + \text{constant} \tag{2}$$

whereas the measurements in tetrachloromethane gave a poor correlation.[3] The latter appeared to be due to the carbonyl stretching vibration remaining perturbed in this solvent. For the thiophenoxy lactones, **1b**, studied here, a very successful correlation of this type is shown in Table 5 for measurements made in *both* chloroform and tetrachloromethane. The correlations for the more extensive series of phenoxy lactones, **1b**, shown in Table 5 are satisfactory, but not as good as those found previously[3] for the aryl and alkyl lactones or the thiophenoxy lactones studied here.

The conclusion must be that the factors controlling reactivity and carbonyl stretching frequencies must be the same. The stabilization of the initial state, relative to the transition state, for alkaline hydrolysis by, in the main, electrostatic field effects must be duplicated in governing the ease of the stretching vibration as represented by the canonical structures **3a** and **3b**.

Additivity of substituent effects in alkaline hydrolysis

The additivity of substituent effects can be investigated for the lactones 15, 16 and 18–23 in Table 2. Additivity is shown for the reactivity of lactones 15, 16 and 18–21

$$\text{C=O} \longleftrightarrow \overset{+}{\text{C}}-\text{O}^-$$

3a   3b
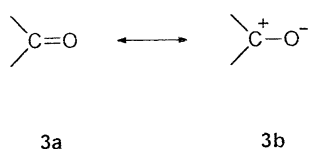
within 95–100% of that expected. However, lactones 22 and 23 are very much more reactive than expected from additivity. These two lactones are both 2,6-disubstituted systems and the only such lactones studied. It seems possible that a conformational switch occurs for these particular di-*ortho*-substituted lactones in which the electrostatic field effect is much more efficiently transmitted from the dipolar substituents to the reaction site.

Calculations

Semi-empirical calculations on the mechanism of the addition of anionic nucleophiles to carbonyl groups face several problems: (i) small anions such as OH^- are poorly described by these procedures (the same also holds for lower level *ab initio* calculations).[11] (ii) For isolated molecules, e.g. gas-phase calculations, addition occurs without any barrier.[17–19] Therefore, the activation energies of reactions measured in solution have been attributed to desolvation of the anionic nucleophile rather than to its addition.[20] Hence it cannot be expected that reasonable agreement between experimental solution-phase activation energies and those calculated for the addition of anionic nucleophiles will be obtained without explicit consideration of solvation shells. (iii) Instead of the experimentally observed OH^- addition, frequently deprotonation is found by semi-empirical calculations.[18b] Similarly, an AM1 transition state for the alkaline hydrolysis of carbamates corresponds to a switch between $E1cB$ and $B_{Ac}2$ mechanisms rather than one for addition of OH^- to the carbonyl group.[18a]

However, the size of the molecules considered in this study precludes a treatment by reasonably high-level *ab initio* methods. Therefore, we used semi-empirical (AM1[11]) molecular orbital calculations. Given the above-mentioned limitations, the reactions in question were modelled using H_2O rather than OH^- as a nucleophile. Such an approach has proved to give reliable results in related reactions.[3,21] Using H_2O as a reagent implies that, besides addition to the carbonyl carbon, proton transfer to the oxygen atom is also necessary. Hence the activation energy for such a process will be considerably higher than that for a simple addition. Furthermore, the stability of tetrahedral intermediates appears to be overestimated by the AM1 method. For instance, the *ab initio* MP2/6–31G*//HF/6–31G* reaction energy[22] for addition of H_2O to the formyl group of glyoxylic acid is $-11.4\,\text{kcal mol}^{-1}$ (1 cal = 4.184 J), whereas AM1 calculations yield a value of -22.1 kcal

mol^{-1}. As a consequence, the activation energy of the ring-opening reaction of the tetrahedral intermediates will be overestimated. However, apart from these drawbacks, a reasonable description of mechanistic aspects and also substituent effects on the kinetics, can be expected. To model the experimental conditions, H_2O was used as a solvent in the calculations (SCRF approximation[13]).

The barriers to the hydrolysis reaction calculated in Table 4 follow the trends found for the hydrolysis of the lactones 1, 2 and 9 (Table 2). Furthermore, in Table 5 are shown the correlations between $\log k_2$ for the alkaline hydrolysis and the respective bond order $p(C=O)$. While the correlation of the phenoxy and thiophenoxy lactones taken together is only moderately satisfactory, the correlations of the two series taken separately are very good. The unperturbed carbonyl stretching frequencies for both series in both solvents give linear correlations with $p(C=O)$ of the same order of significance as those with σ. These demonstrate clearly the success of the computational approach in correctly predicting reactivity and physical properties quantitatively.

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