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BASE-CATALYSED HYDROLYSIS OF γ-LACTONES: REACTIVITY–STRUCTURE CORRELATIONS FOR 3-(ARYL- AND ALKYLMETHYLENE)-(*Z*)-1(3*H*)-ISOBENZOFURANONES

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Rate coefficients were measured for the base-catalysed hydrolysis of a series of γ-lactones, i.e. 39 substituted 3-(aryl- and alkylmethylene)-(*Z*)-1(3*H*)-isobenzofuranones (3-aryl- and alkylmethylenephthalides) in 70% (v/v) aqueous dioxane at 30·0 °C. A Hammett reaction constant for the 3- or 4-substituted phenyl series is *ca* 1·5, whereas those for the 2-substituted phenyl and 4-substituted 1-naphthyl series, using *para*-σ values, are *ca* 1·0 and 1·9. These results are related to an electrostatic field effect model. A very successful correlation between the rates of alkaline hydrolysis of all 39 phthalides and the carbonyl stretching frequencies in chloroform was found. Substituent effects in widely different environments give linearly related effects on both reactivity and physical properties. Computational studies using the semi-empirical AM1 method correctly modelled both the details of the mechanistic pathway and the substituent effects.

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INTRODUCTION

3-Arylmethylene-(*Z*)-1(3*H*)-isobenzofuranones (phthalides) (**1**) are an interesting series of unsaturated γ- or five-membered ring lactones. A number of studies[1–4] have been made of their methoxide-catalysed rearrangement to form 2-aryl-1,3-indandiones. However, there appears to be no reported investigation of the kinetics and mechanism of their alkaline hydrolysis.

The relatively small ring lactones are required to have their ester group in a *cis/E* conformation.[5] The alkaline hydrolysis of such lactones is much more rapid than that of acyclic esters or relatively large lactones which have their ester group in the more stable *trans/Z* form.[5–7]

The study of aryl substituent effects is comparatively straightforward when involving *meta/para*-substituted phenyl systems using the Hammett equation.[8] However, it is more difficult and complex when such substituents are proximate to the reaction site,[9] e.g. *ortho*-substituted benzoate esters. It is possible to have a template in which such *ortho*-substituents are separated from the reaction site and such proximity effects can be avoided. The (*Z*)-3-(substituted arylmethylene)phthalides provide such a system. A comparison of the effects of substituents in widely different environments on reactivity, e.g. the base-catlysed hydrolysis, and physical properties, e.g. the carbonyl stretching frequencies, should enable significant conclusions to be reached as to the source and generality of such effects.

The present investigation consisted of a study of the rates of alkaline hydrolysis of a comprehensive series of substituted 3-(aryl- and alkylmethylene)-(*Z*)-1(3*H*)-isobenzofuranones (**1**) in 70% (v/v) dioxane–water at 30·0 °C. The results are related to the substituent effects, in terms of σ values, the carbonyl stretching frequencies of the phthalides and computational studies of both substituent effects and intermediates.

RESULTS

The rate coefficients for the alkaline hydrolysis of a series of 3-(substituted aryl- and alkylmethylene)-(*Z*)-1(3*H*)-isobenzofuranones (**1**) in 70% (v/v) aqueous dioxane at 30·0 °C were measured and are given in Table 1. It appears that the kinetics of this reaction have not been studied previously. The reaction is first order both in substrate and in hydroxide anion. The products of the reactions are the 2-(aryl- or alkylacetyl)benzoate anions **4**, which were first found in 1878.[10] The pathway shown in Scheme 1 involves the addition of hydroxide anion to the lactone carbonyl group to form the tetrahedral intermediate **2**, followed by

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Table 1. Rate coefficients (k_2) for the alkaline hydrolysis of 3-(substituted aryl- and alkylmethylene)-(*Z*)-1(3*H*)-isobenzofuranones (phthalides) in 70% (v/v) aqueous dioxane at 30·0 °C, together with their carbonyl stretching frequencies (ν) in chloroform and carbon tetrachloride[a]

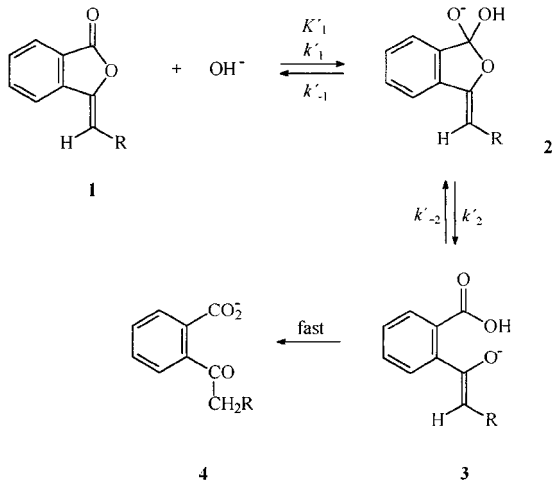
No.		Substituent Aryl/alkyl	k_2/dm^3 mol^{-1} s^{-1}	λ/nm[b]	ν/cm^{-1} [c]	
					In chloroform	In carbon tetrachloride
1	Phenyl	H	1·02	340	1776·8	1796·8
2		2-CH_3	0·919	340	1777·3	1794·8
3		2-OCH_3	0·712	355	1775·0	1794·4
4		2-F	2·23	335	1781·0	1796·8
5		2-Cl	2·75	335	1782·2	1798·8
6		2-Br	2·78	335	1782·1	1800·4
7		2-I	2·60	335	1782·5	1800·4
8		2-NO_2	7·37	340	1786·5	1802·8
9		2-NH_2	0·166	315	1770·3	1786·8
10		3-CH_3	0·639	345	1777·6	1795·2
11		3-OCH_3	1·37	344	1779·3	1796·0
12		3-F	2·08	335	1782·1	1798·8
13		3-Cl	3·51	344	1782·5	1800·4
14		3-CF_3	4·59	335	1784·0	1801·6
15		3-NO_2	11·0	340	1788·5	1803·2
16		4-CH_3	0·483	340	1775·5	1794·4
17		4-OCH_3	0·607	340	1773·9	1792·8
18		4-F	1·40	340	1779·1	1796·4
19		4-Cl	2·28	340	1780·3	1796·8
20		4-Br	$2{\cdot}11_5$	345	1781·3	1795·2
21		4-I	1·92	345	1781·0	1798·8
22		4-NO_2	18·6	360	1788·8	1802·4
23		4-NH_2	0·241	380	1769·4	1790·8
24		4-$NHCOCH_3$	0·964	355	–	1792·8
25		2,4-F_2	4·41	335	1782·3	1798·0
26		2,4-Cl_2	5·60	340	1784·4	1799·2
27		3,5-F_2	4·41	340	1787·3	1802·4
28	1-Naphthyl	H	$1{\cdot}14_5$	360	1778·4	1795·2
29		4-Cl	2·32	365	1780·4	1795·2
30		4-Br	2·83	365	1780·2	1795·2
31		4-I	2·56	365	1780·0	1793·6
32		4-NO_2	30·0	385	1787·4	1795·2
33		4-NH_2	0·282	405	1770·3	1786·8
34	2-Naphthyl	H	$1{\cdot}01_5$	350	1777·3	1795·2
35		1-NO_2	23·2	345	–	1799·6
36		1-NH_2	0·557	425	–	1791·6
37	Alkyl	H	1·92	250	1783·6	1796·4
38		CH_3	0·400	250	1774·5	1788·8
39		CH_2CH_3	0·326	255	1775·9	1790·0

[a] Rate coefficients were reproducible to ±3%.
[b] Wavelength used to monitor alkaline hydrolysis.
[c] Frequences are literature values.[16]

ring fission to give the enolate of the 2-acetylbenzoic acid **3**. The rate-determining step is considered to be k_1' in Scheme 1, as for a series of unsaturated lactones studied recently.[7] The evidence for this is based on the relative reactivity, activation parameters and substituent and solvent effects.[7]

DISCUSSION

The substituents studied here are of a very wide range of types. They have been subdivided into sensible groupings and are discussed below.



Scheme 1.

3- and 4-substituted phenyl system

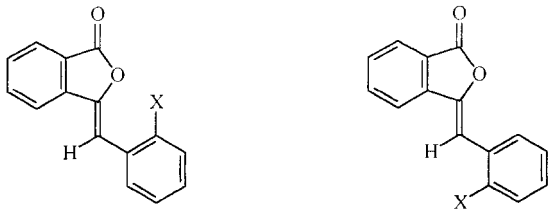
The Hammett equation (1) below[8]

$$\log (k/k_0) = \rho\sigma \qquad (1)$$

can be applied directly to the 3- and 4-substituted phenyllactones. The correlations with σ and σ^n (Ref. 8) are shown in Table 2 and relate to compounds numbered 1, 10–22 and 24 in Table 1. These exclude the 4-NH_2 substituent, which is well known to display 'exalted' resonance effects in reactions of the present type.[8] The reaction constant, ρ, is *ca* 1·5. This can be compared with the ρ value for the alkaline hydrolysis of methyl benzoates, as a reference system, ρ_0, under identical conditions, which is equal to 2·20.[11] The transmission of polar effects in **1**, with ρ/ρ_0 equal to *ca* 0·68, is significantly more than would be expected from an 'inductive' model,[12] which gives $\rho/\rho_0 = 0{\cdot}46$. A more realistic electrostatic field model is required in which the favourable position of the substituted phenyl ring, with regard to transmission of polar effects to the reaction site, can be accommodated. The *Z*-configuration of **1** provides a comparatively short substituent–reaction site direct path and low dielectric constant cavity.

2-Substituted phenyl system

A number of attempts[9,13] have been made to correlate the reactivity of 2-substituted phenyl systems. For systems in which proximity effects can be considered to be absent, it has been suggested the *para*-σ values can be used to correlate *ortho*-substituent effects.[13] Such correlations are shown in Table 2 and include the unsubstituted phenyllactone. In a previous study[13] of the ionization of 2- and 3-/4-substituted *trans*-cinnamic, 3-phenylpropionic and phenoxyacetic acids, the reaction constants for the 2-substituted series (using *para*-σ values) and those for the 3-/4-substituted series are comparable, as would be expected for transmission by a mainly electrostatic field effect. In the present study, the almost coplanar rigid system **1**, in which 2-substituents can occur in two conformations, the cisoid-**5** and transoid-**6**. The latter are very similar



5 **6**

stereochemically to those available for the 2-substituted *cis*-cinnamic acids and esters. The ρ value, shown in Table 2

Table 2. Correlations of the alkaline hydrolysis of the aryl and alkyl lactones[a]

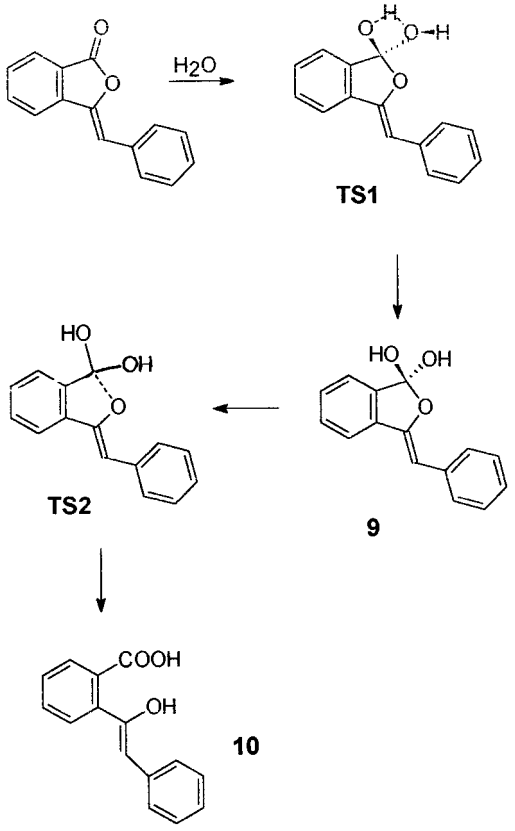
System	Parameter	ρ	s	Log k_0	r	n
3-/4-Substituted phenyl	σ	1·485	0·085	−0·013	0·980	15
	σ^n	1·617	0·059	−0·081	0·988	15
2-Substituted phenyl	σ	0·998	0·108	0·151	0·966	8
(including H)	σ^n	1·110	0·110	0·083	0·972	8
4-Substituted 1-naphthyl	σ	1·867	0·129	−0·010	0·993	5
	σ^n	1·853	0·160	−0·037	0·989	5
All lactones	(ν($CHCl_3$)	0·0986	0·0056	–[b]	0·950	36
	ν(CCl_4)	0·101	0·013	–[b]	0·797	39
All aryl lactones	ν($CHCl_3$)	0·0975	0·0052	–[b]	0·959	33
	ν(CCl_4)	0·101	0·014	–[b]	0·774	36
All lactones	p(C═O)[c]	89·2	5·1	–[c]	0·962	26

[a] s is the standard deviation in ρ, r the correlation coefficient and n the number of substituents.
[b] Computed as $\Delta\nu$ from that of compound in Table 1 (aryl = Ph).
[c] Bond order of reacting carbonyl group (see Table 3). Computed as $\Delta\rho$ (C═O) from that of compound 1 in Table 3.

and relating to compounds numbered 1–8 in Table 1 (excluding the 2-NH_2 substituent for the same reasons as for the 4-NH_2 substituent (discussed above)), for the 2-substituted derivatives in this study is *ca* 1·0, which is only two thirds of that observed for the 3-/4-substituted series. This certainly results from a partial reversed dipolar substituent effect for the former substituents arising from their stereochemical situation in which the 'distant' end of the dipole can have an enhanced role in determining the substituent effect. This type of result has been previously observed for the 2-substituted *cis*-cinnamic acids to an even greater extent.[13]

4-Substituted 1-naphthyl system

The Hammett equation (1) can also be applied to the 4-substituted 1-naphthylactones, by using the *para*-σ and σ^n values for the 4-substituents. These correlations are shown in Table 2 and relate to compounds numbered 28–32 in Table 1. The reaction constant, ρ, is *ca* 1·9. The greater susceptibility indicated for the 1,4-naphthyl compared with the 1,3- or 1,4-phenyl system can be related to an increased relay of the polar effect by either an 'inductive' route *via* the fused benzo ring or an electrostatic field effect involving a larger low dielectric constant molecular cavity. The latter is much more likely.



Scheme 2.

Alkyl system

The results for the compounds numbered 37–39 in Table 1, H, CH_3 and CH_2CH_3, can be combined with those for the parent compounds numbered 1, 28 and 34, with the aryl substituents Ph and 1- and 2-naphthyl, to indicate the absence of any very significant steric 'bulk' or resonance effects on substitution at this 'distant' site on the reaction site. The polar effects of Ph, H, CH_3 and CH_2CH_3, measured as *para*-σ values, are $-0{\cdot}03$, $0{\cdot}0$, $-0{\cdot}17$ and $-0{\cdot}15$, respectively.[14] The order of reactivity is H > 1-naphthyl > Ph ≈ 2-naphthyl > CH_3 > CH_2CH_3. However, the rate ratio for the H to Ph substrate is only *ca* 1·9, which indicates that any steric 'bulk' effect must be minimal.

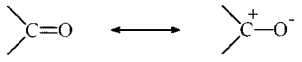
Correlation of rates and carbonyl stretching frequencies

Carbonyl stretching frequencies have been successfully correlated for limited series with substituent constants such as σ and σ^*.[15] Table 2 shows a very successful correlation between the rates of alkaline hydrolysis of the lactones and the carbonyl stretching frequences, ν_{CO}, in chloroform using the equation (2) below.

$$\log k_2 = a\nu_{CO} + \text{constant} \qquad (2)$$

The latter frequencies were unperturbed fundamental carbonyl stretching vibrations after deconvolution and band separation from Fermi resonance effects.[16] These ν_{CO} absorption bands observed in chloroform exhibit significant splitting arising from Fermi resonance. In tetrachloromethane solution, the compounds exhibit more or less single ν_{CO} absorption bands. The correlation between the reactivity and the carbonyl stretching frequencies in tetrachloromethane is poor, which probably arises from the nature of the carbonyl stretching vibration which remained perturbed in this solution.

The correlation between the reactivity and the carbonyl stretching frequencies in chloroform is remarkable in that it covers such a diverse range of substitution. Thus the rates of alkaline hydrolysis vary by a factor of *ca* 180 and the frequencies by a range of *ca* 20 cm^{-1}. The most important conclusion is that the factors controlling reactivity and carbonyl stretching frequencies must be the same. The relative stabilization of the transition to the initial state for alkaline hydrolysis by, in the main, electrostatic field effects must be duplicated in the stretching vibration. The latter has been represented by the canonical structures **7** and **8**.[17]



7 **8**

Electrostatic effects will alter the relative contributions of **7** and **8**. A reduction in the part played by structure **8** will increase the frequency, as is observed.

Table 3.Observed log k_2 values for the alkaline hydrolysis and calculated heats of formation of the phthalides, transition states for H_2O addition (**TS**) and derived activation enthalpies[a]

Compound No.[b]	Log k_2	ΔH_f(**TS1**)/kcal mol^{-1}	ΔH_f(phthalide)/kcal mol^{-1}	ΔH/kcal mol^{-1}	p (C=O)
1	0·009	−10·3	6·5	46·4	1·8610
2	−0·037	−16·8	0·3	46·1	1·8604
3	−0·148	−47·6	−31·0	46·6	1·8557
4	0·348	−55·1	−38·2	46·2	1·8631
5	0·439	−16·4	0·7	46·1	1·8637
8	0·867	−5·4	11·7	46·1	1·8721
10	−0·194	−17·8	−0·9	46·3	1·8605
11	0·137	−47·8	−31·0	46·4	1·8618
12	0·318	−55·7	−38·7	46·2	1·8656
13	0·545	−17·5	−0·5	46·2	1·8670
15	1·041	−8·6	8·8	45·8	1·8722
16	−0·316	−17·9	−1·1	46·4	1·8598
17	−0·217	−48·2	−31·6	46·6	1·8576
18	0·146	−55·9	−38·8	46·1	1·8641
19	0·358	−17·5	−0·3	46·0	1·8649
22	1·270	−9·0	8·6	45·6	1·8772
23	−0·618	−12·5	3·9	46·8	1·8547
24	−0·016	−48·3	−31·3	46·2	1·8601
28	0·059	9·9	27·1	46·0	1·8613
29	0·365	3·9	21·2	45·9	1·8648
32	1·477	14·5	32·7	44·9	1·8756
33	−0·550	9·4	26·3	46·3	1·8550
34	0·006	8·2	25·0	46·4	1·8606
35	1·365	15·6	33·6	45·3	1·8742
36	−0·254	7·3	24·9	45·6	1·8576
38	−0·398	−34·7	−17·8	46·3	1·8614

[a]1 cal=4·184 J.
[b]Numbers of compounds refer to Table 1.

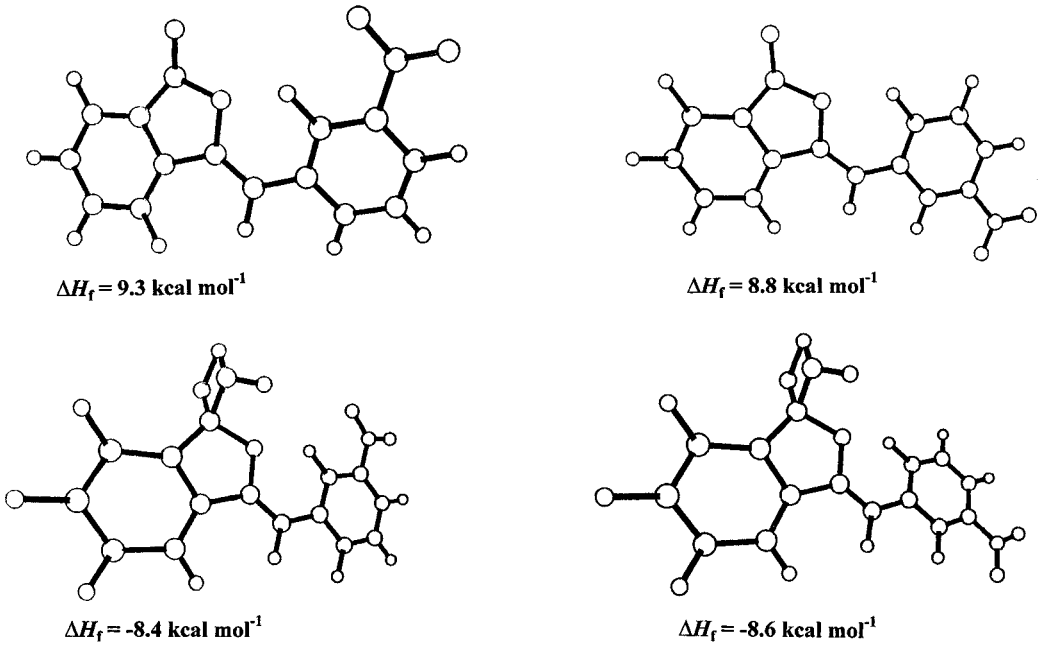
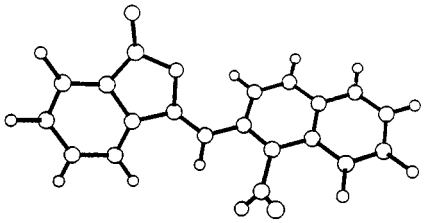


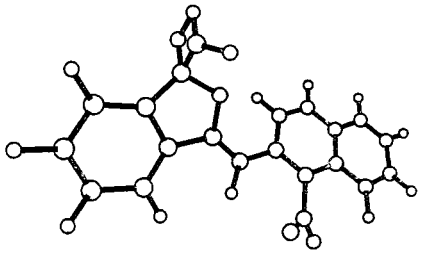
Figure 1. Computed conformations of compound 15 in Table 1 and the respective transition states

Computational studies

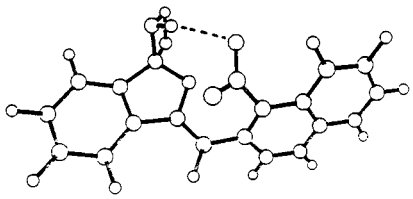
All calculations were made using the semi-empirical AM1[18] method with the VAMP program package.[19] Geometries were completely optimized by the eigenvector following method without any restrictions. Transition states were approximately located by the reaction coordinate procedure and subsequently refined by gradient norm minimization. All structures were characterized as true minima or transition states by force constant calculations. For transition states, in addition, downhill optimizations (intrinsic reaction coordinate calculations) along both directions of the normal mode corresponding to the imaginary frequency were completed. Solvent effects (H_2O) were approximated by the self-consistent reaction field (SCRF) method.[20]



$\Delta H_f = 33.6$ kcal mol^{-1}



$\Delta H_f = 16.3$ kcal mol^{-1}



$\Delta H_f = 15.6$ kcal mol^{-1}

Figure 2. Computed structure of compound 35 in Table 1 and the respective transition state

To model the alkaline hydrolysis of the lactones described in this paper, calculations based on the reaction of these lactones with water rather than hydroxide anion as a nucleophile were performed. The reasons for this are threefold: (i) small anions are generally poorly described by semi-empricial methods (more specifically, by any method using small basis sets, including *ab initio* calculations);[18] (ii) the addition of nucleophiles to carbonyl compounds in the gas phase occurs without any barrier and thus experimentally measured activation energies of such reactions in solution almost exclusively reflect the desolvation energies of the reactants[21] and in the calculations, therefore, a reasonable solvation shell would be needed; and (iii) in reaction path calculations involving the hydroxide anion, besides the presumed addition, deprotonation reactions or additions to the nearest positively charged centre may occur.[22] Using water instead of hydroxide anion as nucleophile will have two major drawbacks: (i) the calculated activation energies will be much too high since besides the addition of the nucleophile proton transfer also has to take place; and (ii) the activation energies for the second step in the proposed mechanism of the alkaline hydrolysis, *i.e.* ring opening to form the enol of 2-acylbenzoic acid **10**, shown in Scheme 2, will also be too high since in our experience the stability of the tetrahedral intermediates **9** is overestimated by AM1. However, it can be expected that the influence of substituents on activation energies will be correctly described. The results of these calculations (heats of formation of the lactones and the first transition state, in addition to activation enthalpies, ΔH_f(TS) $-\Delta H_f$(lactone) $-\Delta H_f(H_2O)$, are shown in Table 3. It can be seen from the latter that the calculated activation energies correlate reasonably well with the kinetic results, i.e. log k_2. For all *ortho*- and *meta*-substituted derivatives two conformations are possible. For compound 15 in Table 1, these two possible conformations of both the starting phthalide and the respective transition states are shown in Figure 1. In these cases the lowest energy conformation for both the starting lactone and the first transition state **TS1**, which in some cases are different, have been used. An especially illustrative example is provided by compound 35 in Table 1. Here the lactone only exists in a transoid arrangement of the nitronaphthyl moiety with respect to the exocyclic double bond due to electrostatic repulsion between the nitro group and the lactone oxygen atom. In the transition state, however, a cisoid conformation is stabilized by intramolecular hydrogen bonding to the added hydroxy group (see Figure 2 for computed structures). Intramolecular hydrogen bonding to the solvent, which is not accounted for by the SCRF approximation, might stabilize the transoid conformation. The calculated activation enthalpies appear to be sensitive to such effects. The substituent effect on the reactivity of the investigated phthalides appears to be

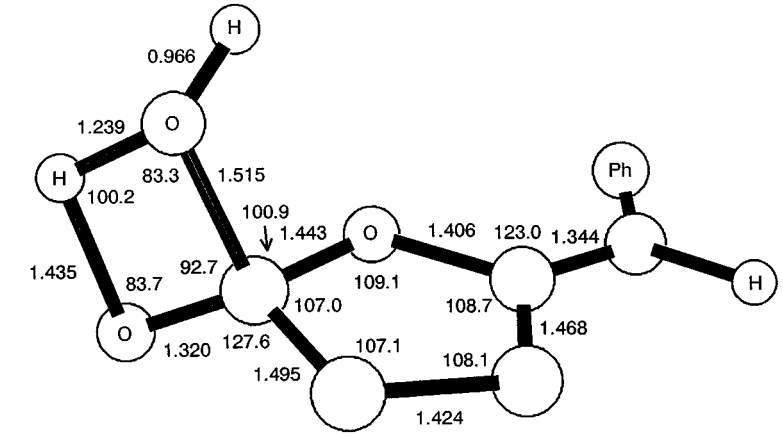


Figure 3. Pertinent geometrical features of **TS1**. Distances are given in Å and angles in degrees

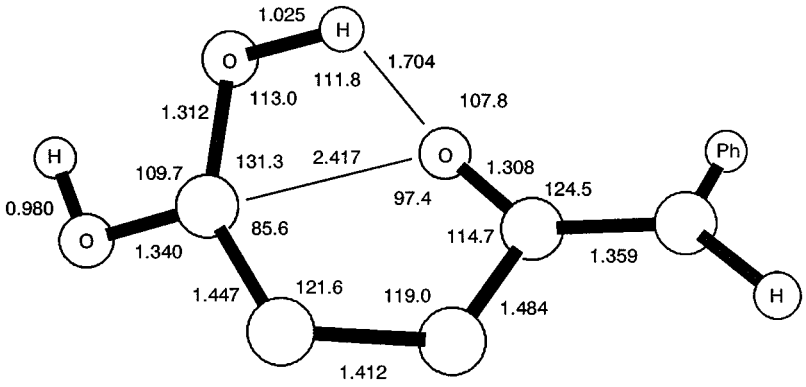


Figure 4. Pertinent geometrical features of TS2. Distances are given in Å and angles in degrees

determined to a large extent by the ground-state properties of the educt molecules. As can be seen from the results in Table 3, there is a good correlation between the kinetics of alkaline hydrolysis and the strength of the reacting carbonyl group as described by the respective bond order of *p*(C——O).

A typical example for the structure of **TS1** is given in Figure 3 (only pertinent atoms are shown). Addition of the water oxygen atom to the carbonyl carbon appears to be highly advanced [*R*(C—O) = 1·515 Å], accompanied by proton transfer {*R*[H—O(water)] = 1·239 Å, *R*[H—O(carbonyl)] = 1.435 Å}. To check the assumption of **TS1** being rate determining, calculations on some representative examples (compounds numbered 1, 3, 8, 11, 15, 22 and 23 in Table 1) of **TS2** were also performed. Activation energies relative to the corresponding tetrahedral intermediates (hydrates) **9** are slightly [46·3, 45·0, 45·2 kcal mol^{-1} for compounds 23, 1 and 11 in Table 1, respectively) to significantly lower (38·5, 40·3, 37·6, 39·0 kcal mol^{-1} for compounds 22, 15, 3 and 8 in Table 1) than activation energies for addition of the nucleophile to the phthalide carbonyl group. Given the above-discussed overestimation of the stability of tetrahedral intermediates, these results clearly indicate the addition of the nucleophile rather than lactone ring opening as the rate-determining step. Hence the calculations corroborate the experimental observations discussed earlier regarding the rate-determining step of this reaction. A typical structure of this second transition state is depicted in Figure 4. It is evident that the lactone ring is already completely opened whereas proton transfer from one of the geminal hydroxy groups to the lactone oxygen atom lags behind breaking of the C—O bond leading to a highly dipolar character of **TS2**.

EXPERIMENTAL

Materials. The preparation of the 3-(alkyl- and arylmethylene)-(*Z*)-1(3*H*)-isobenzofuranones was performed using published procedures.[23] 3-Methylene-(*Z*)-1-(3*H*)-isobenzofuranone was prepared using the method of Yale.[24] The purity of the lactones was monitored by IR and ^{1}H and ^{13}C NMR spectroscopy. Their melting points after repeated

recyrstallization and drying under reduced pressure (P_2O_5), were in good agreement with literature values.[23,24] The solvents were purified as described previously.[11]

Measurements. Rate coefficients for the alkaline hydrolysis of the lactones were determined spectrophotometrically by use of a Perkin-Elmer Lambda 5 UV–VIS spectrometer. The reactions were followed at the wavelengths shown in Table 1. The detailed procedure used was that described previously.[11] The substrate concentrations were *ca* $0{\cdot}5\times10^{-4}$ mol dm^{-3} and the base concentrations were from 6×10^{-4} to 4×10^{-2} mol dm^{-3}. The products of the reaction were found to be the anions of the corresponding carboxylic acids in quantitative yield[10] and were further confirmed spectrophotometrically by comparison of the spectrum of the acid in base with that of the reaction product.

IR measurements were made in chloroform or carbon tetrachloride as reported elsewhere.[16]

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