Rates and mechanisms for the ring opening, ring closure and ring transformation reactions of the di-γ-lactone dihydrocanadensolide (DHC)

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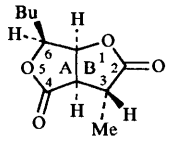
The title di-γ-lactone **1** ring opens in alkali to the monolactones **2–4** by three parallel routes: *via* hydrolysis to **2** and **3** and *via* β-elimination to give **4**. The last is probably an $(E1cb)_1$ process, though there is conflicting evidence and the mechanism is uncertain. The two hydrolyses are much faster than models would predict owing essentially to the $\Delta S^{\ddagger}$ term, and an unusual intramolecular interaction which results from steric crowding is invoked. While further hydrolysis of the monolactone **3** is straightforward, that of **2** probably goes *via* the δ-lactone **8**, whose rapid pre-equilibration with **2** has also been studied. This hydrolysis is characterised by a highly abnormal near-zero $\Delta S^{\ddagger}$ value which is tentatively explained as being due to exclusion of water from the transition state by intramolecular solvation. Rates for the reverse lactonisation process are unremarkable, but analysis of the activation parameters reveals evidence for ring strain in the formation of **1** which precisely balances the normal rate increase expected through approximation.

The di-γ-lactone dihydrocanadensolide (DHC) **1**, once thought to be a potential ulcer-healing agent,[1] was first isolated from



1

Penicillium canadense by McCorkindale *et al.*[2a] and from *Aspergillus indicus* by Birch and co-workers.[2b] Somewhat later, the stereochemistry of canadensolide [2a] was corrected by Kato *et al.*,[3] and the same correction follows for DHC. Because there was some risk of **1** coming into contact with alkali during formulation, and as lactones are known to be much more alkali-sensitive than normal esters,[4] the following kinetic investigation was launched. A preliminary account of this work has been presented.[5]

Results

Compound characterisation

Hydrolysis of **1** leads by various routes (Scheme 1) to four monocarboxylic acids (monolactones) and three dicarboxylic acids of which all but the hydroxy-dicarboxylic acid **5** have been isolated. Details are given in the Experimental section, while Tables 1–3 display the spectroscopic data essential for their characterisation.

Of the four monolactones, three show the expected addition of the elements of water, whereas the fourth retains the elemental composition of **1** itself. This is clearly the butenolide acid **4** formed in an elimination process (Scheme 1), as is shown by its unique vinylic proton at δ 7.46 (Table 1) along with the corresponding ν_{CH} and $\nu_{C=C}$ in its IR spectrum (Table 3). Its fragmentation under negative ion fast atom bombardment (FAB) conditions with loss of CO_2 (Table 1) provides supporting evidence, since a carbonyl-stabilised allylic anion can then result.

The other three are isomers and no one methodology will prove all structures unequivocally. The chemical shift assignments of Table 1 depend heavily on the further shifts produced by acylation using trichloroacetylisocyanate (Table 2), which unequivocally identifies the position of OH-substitution. This is similar for **3** and **8**, but clearly different for **2**, where its position at one end of the sequence of carbon atoms, each carrying a single hydrogen, identifies it as present in the side-chain. Supporting evidence comes from the close similarity between **1** and **2** with respect to the chemical shifts and coupling constants for these four CH groups, a similarity not echoed by **3**. Also, while for **2** and **8** the only significant mass ion is carboxylate $[M - H]^-$, **3** loses water to give **4** and thereafter follows the same fragmentation pattern, which is only explicable if OH in **3** is a ring substituent.

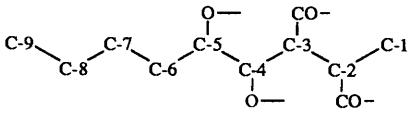
Identification of **2** and **3** as the isomeric γ-lactones that may result from hydrolysis of **1** is further confirmed by their near-identical IR spectra, with $\nu_{C=O}$ above 1770 cm^{-1} as expected[6] in solution. The much lower frequency of 1746 cm^{-1} (1718 cm^{-1} in the solid state) suggests[6] **8** as a δ-lactone, for which only one structure is possible. Its close structural relation with **2**, the same ring constituents with one extra carbon atom, is indicated by their very similar chemical shifts and coupling constants. Its mode of preparation, *via* the dicarboxylic acid **7** and not directly from **1**, helps to confirm this assignment. A lowered $\nu_{C=O}$ is also shown, as expected,[6] by the unsaturated γ-lactone **4**.

The ultimate product of hydrolysis of **1** should be the dicarboxylic acid **7**, and all spectroscopic and other evidence is in accord with this. Hydrolysis of the butenolide acid **4** is through two kinetically distinguishable steps (*vide infra*) to the keto-dicarboxylic acid **6**, identified by no protons at C-5 (nomenclature of Table 1), downfield shifts at C-4 and C-6, and the absence of alcohol ν_{OH} in its IR spectrum; unfortunately, ketone and acid $\nu_{C=O}$ are not resolvable. The intermediate acid **5** has not been isolated, but no other structure is plausible.

Structural computations

Ab initio computations were carried out at the 3-21G level of refinement, which should be adequate since d orbitals are not involved. The projection of Fig. 1 clearly shows the overall butterfly shape of DHC, with its nearly eclipsed central H–C–C–H unit (dihedral angle 31°) and the quite close approach of its two near-planar functional groups.

Table 1 NMR[a] and MS data for DHC and its reaction products



Compound	δ								m/z	
	C-1(3H)[b]	C-2(H)	C-3(H)	C-4(H)	C-5(H)	C-6(2H)	C-7/C-8(4H)	C-9(3H)	$[M - H]^-$	Other
1	1.40d	2.87dq	3.44dd	5.38dd	4.72dt	1.72–1.86m	1.33–1.55m	0.92t		
	7.6	*7.6, 1.3*	*1.3, 5.9*	*5.9, 3.8*	*3.8, 7.0*			*7.1*		
2	1.23d	3.20dq	3.36dd	4.62dd	3.99dt	1.52–1.66m	1.27–1.52m	0.90t	229	
	6.8	*6.8, 10.9*	*10.9, 8.7*	*8.7, 1.7*	*1.7, 6.7*			*7.0*		
3	1.50d	2.85–3.00m	2.85–3.00m	4.52dd	4.33ddd	1.67–1.84m	1.30–1.57m	0.92t	229	$-H_2O$,
	6.6			*4.2, 3.0*	*3.0, 6.4, 7.3*			*7.1*		$-CO_2$
4	1.41d	3.47qt	—	7.46t	5.03ddt	1.25–1.90m	1.25–1.90m	0.90t	211	$-CO_2$
	7.3	*7.3, 1.4*		*ca. 1.4*	*1.4,[c] 5.3, 7.0*			*7.1*		
6A[d]	1.11d	*ca.* 2.95	3.37m	*ca.* 2.49, 2.95	—	2.47m	1.51m, 1.29m	0.87t	229	
	7.2							*7.3*		
6B[d]	1.16d	2.80m	3.22m	*ca.* 2.54, 2.95	—					
	7.2									
7	1.24d	2.99dq	2.91dd	3.64m	3.58m	1.28–1.65m	1.28–1.65m	0.90t	247	$-H_2O$
	6.7	*6.7, 8.6*	*8.6, 3.7*					*7.0*		
8	1.17d	2.92dq	2.52dd	4.16dd	4.29ddd	1.62–1.89m	1.28–1.53m	0.91t	229	
	6.7	*6.7, 10.5*	*10.5, 2.6*	*2.6, 1.6*	*1.6, 5.3, 7.5*			*7.0*		

[a] Chemical shifts (ppm) in CD_3COCD_3 relative to TMS as internal standard. Coupling constants *J*(Hz) are italicised. [b] Atom numbering is based on the 'exploded' structure shown. [c] Shows allylic and homoallylic couplings. [d] Diastereoisomers.

Table 2 Chemical shifts after acylation with trichloroacetylisocyanate (TCAI)[a]

Lactone	Position[b]	δ	δ + TCAI	Δδ	Status[c]
2	C-2(H)	3.202	3.199	−0.003	δ
	C-3(H)	3.357	3.529	0.172	γ
	C-4(H)	4.620	4.953	0.333	β
	C-5(H)	3.989	5.277	1.288	α
3	C-2(H)	*ca.* 2.89	2.814	*ca.* −0.076	γ
	C-3(H)	*ca.* 2.89	3.217	*ca.* 0.327	β
	C-4(H)	4.519	5.799	1.280	α
	C-5(H)	4.335	4.666	0.331	β
8	C-2(H)	2.925	3.029	0.104	γ
	C-3(H)	2.524	2.637	0.113	β
	C-4(H)	4.157	5.388	1.231	α
	C-5(H)	4.289	4.586	0.297	β

[a] In $(CD_3)_2CO$. [b] See Table 1 for numbering key. [c] Relation of carbon atom in each structure to that (α) carrying OH.

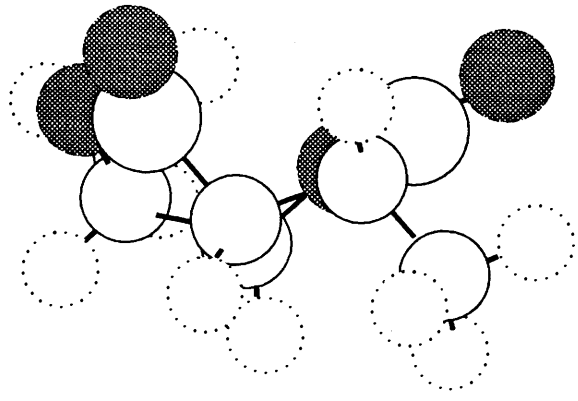


Fig. 1 A projection of the structure calculated for DHC (**1**), showing near-eclipsing of the central H–C–C–H linkage and the close approach of the two ester carbonyl groups. Oxygen atoms are indicated as filled circles.

Kinetics

All reactions, except where otherwise stated, were carried out in glass distilled water at 25 °C and I = 1.0 mol dm^{-3} with KCl. Except for **4**, none of these compounds has a usable UV spectrum, so that other means had to be employed to follow the reaction. Since acid is generated by the ring opening processes (Scheme 1), it was possible to measure $k_o = (k_1 + k_2 + k_3)$ by a pH-stat technique in which 0.1 mol dm^{-3} NaOH was added to an aqueous solution of **1** (*ca.* 2 × 10^{-3} mol dm^{-3}) so as to maintain a constant pH and the consumption of alkali was followed as a function of time. The reaction was followed for 2–3 half-lives within the range pH 8–11 according to temperature and was shown to be linear with respect to $[OH^-]$. The overall rate for the second hydrolytic step is 50–100 times lower than that for the first, so does not interfere. Parallel experiments were carried out in which samples, after adjustment to pH 7 to halt the reaction, were analysed for product balance by HPLC using a refractive index (RI) detector that had been calibrated against known concentrations of each component. A typical initial concentration of **1** for HPLC purposes would be 4–5 g dm^{-3}. This product balance was then combined with k_o to calculate the constituent rate constants k_1–k_3, each of which was converted to k_{OH} by extrapolation to pH = pK_w. By repeating the whole process at 35 and 45 °C, the activation parameters[7] that appear in the Tables were obtained.

A limited study of buffer catalysis for k_o employed borate, carbonate, *N*-methylmorpholine and *N*-methylpiperidine buffers in the pH range 7–10.5 at overall concentrations of up to 0.05 mol dm^{-3} and varying buffer ratios, the reaction being followed by pH-stat methods. This rather low limiting buffer concentration was an unfortunate (*vide infra*), but necessary, consequence of the pH-stat technique. Because of salting out of DHC at the higher buffer concentrations in water, the solvent was 16% aqueous methanol. Buffer pK_a values (8.28, 9.25, 7.50 and 9.80, respectively) were measured for this solvent. Graphs of $(k_{obs} - k_o)$/[Buffer] *vs.* mole fraction of free base x_B established that there is no contribution to the reaction rate from BH^+; *e.g.* no catalysis by HCO_3^- could be detected. The unavoidably low buffer concentrations confined rate acceleration to ≤50% and, while this still allowed for accurate values

Table 3 IR spectroscopic data for DHC and its reaction products[a]

Compound	ν_{CH}	ν_{OH}		$\nu_{C=O}$		$\nu_{C=C}$
		Alcohol	Acid	Lactone	Acid	
1	—	—	—	1764vs	—	—
2	—	3380ms	3050–2600mw br	1769s	1711s	—
		3530m	*3220mw br*	*1777vs*	*1746s*	
3	—	3435ms	3100–2600mw br	1742s	1692ms	—
		3470m	*3250mw br*	*1774vs*	*1742s*	
4[b]	3090w	—	—	1736s	1596s[c]	1645w
6[d]	—	—	3200–2500m br	—	1710s br[e]	—
7	—	3350m	2630m br	—	1688s br	—
8	—	3510m	3150–2600mw br	1718s	1695ms	—
		3470mw	*3220mw br*	*1746vs*		

[a] Nujol; *italicised* values are for solution in MeCN. [b] As Na salt. [c] Anion. [d] Liquid film. [e] Ketone C=O not resolved.

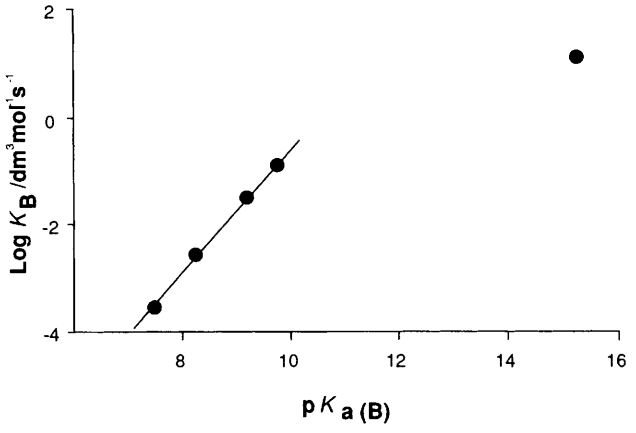


Fig. 2 A Plot of log k_B *vs.* p$K_{a(B)}$ for the hydrolysis of DHC (**1**)

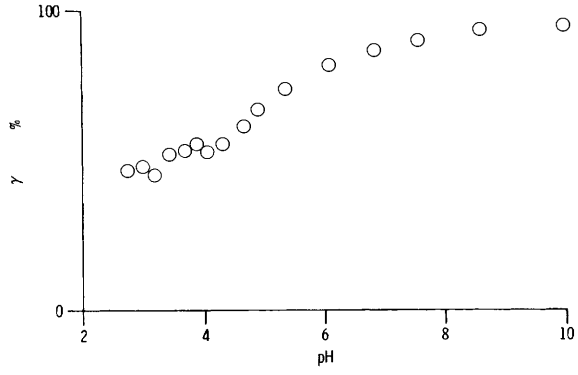


Fig. 3 A plot of % γ-lactone **2** *vs.* pH for the equilibrium **2**⇌**8**

of ($k_{obs} - k_o$), it made product analysis very difficult: k_3 contributes only *ca.* 6% to k_o, hence it is difficult to be certain that there is no contribution of k_B to k_1 or k_2. The graph of $k_B = (k_{obs} - k_o)/[B]$, which appears as Fig. 2, plots k_B for OH^- on the assumption that this relates to k_3 only.

The hydrolysis of **3**→**7** was followed by pH-stat methods alone. When, however, that of **2**→**7** was monitored in the same way its activation parameters appeared to be highly abnormal (*vide infra*), and furthermore, the hydrolysis of **8**→**7** was found to take place at a near-identical rate (k_{OH} = 0.73 and 0.63 dm^3 mol^{-1} s^{-1} at 25 °C). HPLC examination revealed that, at pH > 4, interconversion of **2** and **8** is fast. This process was followed at 25 °C by injecting equimolar amounts of **2** and **8**, from aqueous MeCN stock solutions, into buffer solutions at pH 2.7–10 and analysing the mixture by HPLC. Fig. 3 shows its equilibrium composition as a function of pH; at high pH, as is relevant to hydrolysis, **2** is present at *ca.* 94%. It had previously been observed that **2**, when isolated from fermentation broths, was always contaminated with **8**. The equilibrium constant K_δ = [**8**]/[**2**] for this interconversion at high pH was measured at four temperatures over the range 25–65 °C to obtain ΔH° and ΔS° for the process (Table 4).

Hydrolysis of **4**→**5** was followed by HPLC. This is a relatively slow reaction and is complicated in its later stages by the slow conversion of **5** to the ketone **6**, which makes the overall process irreversible. (The alcohol **5** has not been isolated, but is presumed to be the initial product detected by HPLC which then slowly disappears again.) The rate k_5 for this step has not been measured.

Since the dicarboxylic acid **7** is not a stable species except as its salts, its re-cyclisation to **2** + **3** ($k_{-6} + k_{-7}$) was studied by first hydrolysing **1** to **7** quantitatively *in situ*, HPLC being used to check that hydrolysis was complete. [The small amount (*ca.* 6%) of **4** and its reaction products present in the mixture was ignored, since these cannot regenerate **1**.] Cyclisation was carried out at a substrate concentration of *ca.* 0.02 mol dm^{-3} and 0.01 mol dm^{-3} $HClO_4$ and the reaction was monitored by taking samples which were analysed by HPLC. It was established that the reaction rate is linear with respect to [H^+] at pH < 3. The overall rate was measured by the decline in concentration of **7**, while its factoring into k_{-6} and k_{-7} depended on measuring the ratio of **2**:**3** in the early stages of the reaction (formation of *ca.* 5% **8** from **2** is fast so does not affect this calculation). This precaution was necessary since the second ring closure step is not much slower than the first. The ring closures of **2** and **3** to **1** under the same conditions were separately monitored by taking monolactone samples and titrating for residual acid with NaOH after dilution into 70% aqueous acetone in which hydrolysis is much slower. All these reactions were followed at 25, 35 and 45 °C and activation parameters were obtained. Since they do not go to completion, it was also possible to measure the equilibrium constant for lactone formation and calculate the corresponding acid-catalysed hydrolysis rate. Work in citric acid buffers at high temperatures (> 80 °C) gave some indication of a pH-independent lactonisation process for **2** and **3** at pH > 5, but accurate rates proved difficult to obtain and this investigation was not pursued.

The cyclisation of an equimolar mixture of **2** and **8** to **1** has also been studied. At 25 °C in 0.01 mol dm^{-3} $HClO_4$ alone, the half-life for the disappearance of **2** is *ca.* 6 h (*cf. ca.* 2 h at I = 1.0 mol dm^{-3}) while the concentration of **8** is barely affected, so k_{-1}

Table 4 Lactone and ester hydrolysis rates in water at 25 °C[a]

Substrate	k_{OH}/dm^3 mol^{-1} s^{-1}	$\Delta H^{\ddagger}$/10^3 cal mol^{-1}	$\Delta S^{\ddagger}$/cal mol^{-1} °C^{-1}
EtOAc[b]	0.11	10.7	−26.7
ICH_2CO_2Et[c]	16.2	6.18	−32.2
PhOAc[d]	1.3		
γ-Butyrolactone[e]	1.00	10.7	−22.6
Canrenone (**9**)[f]	0.29	10.8	−24.7
10[g]	1.35		
11[d]	85		
k_1	142	12.5	−6.9
k_2	28.2	12.1	−11.4
k_7	2.85	7.25	−32.3
k_6[h]	(0.73)	(19.3)	(+5.6)
δ-Valerolactone[e]	23.5	7.2	−28.1
k_8[h]	13.1	15.65	−0.9
$K_\delta = k_6/k_8$[h]	0.056	3.65[i]	+6.5[i]
12a[d]	824		
17a[j]	1900	6.4	−20
17b[j]	3400	5.9	−21

[a] 1 Cal = 4.184 J. [b] A. M. White and G. A. Olah, *J. Am. Chem. Soc.*, 1969, **91**, 2943. [c] E. K. Euranto and A.-L. Moisio, *Suomen Kemi.*, 1964, **37B**, 92. [d] E. Izbicka and D. W. Bolen, *J. Am. Chem. Soc.*, 1978, **100**, 7625. [e] Ref. 12. [f] Ref. 45. [g] In 20% EtOH; ref. 13. [h] See the text. [i] ΔH°, ΔS°. [j] Ref. 36(*b*).

Table 5 Rates and equilibria for lactone formation (k_f) and hydrolysis (k_h) in aqueous acid at 25 °C

Product	k_f[a]/10^{-3} dm^3 mol^{-1} s^{-1}	k_h[a]/10^{-4} dm^3 mol^{-1} s^{-1}	K_{eq}[b]
EtOAc[c]	0.0182	2.6	0.07
δ-Valerolactone[d]	2.2	360	0.061
—, 3-Me[d]	7.2	190	0.38
17a[e]	3.2	290	0.11
17a[f]			0.185[g]
17b[e]	0.46	240	0.019
γ-Butyrolactone[c]	1.43	2.33	6.14
	1.07[d]	3.7	2.9
	0.58[h]	2.2	2.6
—, 3-Me[d]	3.3	2.6	12.8
9[i]	*ca.* 10^2	< 10	> 10^2
16[f]			0.26[g]
10[c]	1.87 × 10^4	14.7	1.27 × 10^4
k_{-1} (**2**→**1**)	5.3	0.85	62.6[j]
k_{-2} (**3**→**1**)	9.2	2.5	36.6
(**8**→**1**)			53.3[j]

[a] k_f, $k_h = k_H \cdot$ [b] K_{eq} = [Lactone]/[Acid]. [c] In 20% EtOH: ref. 13. [d] Ref. 43. [e] Ref. 36. [f] Ref. 35. [g] K_δ = 0.71. [h] F. A. Long, W. A. McDevit and F. B. Dunkle, *J. Phys. Chem.*, 1951, **55**, 813, 829. [i] Ref. 45. [j] K_δ = 0.85.

is uncomplicated by any such interconversion (contrast k_6 above). Ultimately however, **8** is converted to **1** with $t_{\frac{1}{2}}$ *ca.* 4 days, and the final ratio **8**:**2**:**1** has been used to establish K_{eq} for both processes (Table 5).

One important fact established in the course of these experiments is that the interconversion of **1** and **7** can be carried out repeatedly without affecting the stereochemical integrity of either, ruling out any reaction mechanism that would involve this.

Data analysis

All measured processes involve simple linear relations: log *c vs. t*; log *k vs.* pH; log *k vs.* $1/T$. Hence all were handled by standard linear regression procedures. A partial check on accuracy is provided by the box equilibrium between **1**, **2**, **3** and **7**, for which $K_1K_6 = K_2K_7$ necessarily. Each is the product of four independently derived rate constants which can be solved to give $K_1K_6 = 1.60 \times 10^6\ [OH^-]^2/[H^+]^2$ and $K_2K_7 = 2.02 \times 10^6\ [OH^-]^2/[H^+]^2$ at 25 °C. The degree of agreement shown by this 'spot check' suggests that a reasonable level of accuracy was achieved.

Discussion

Lactonisation and lactone hydrolysis are well explored reactions with features of interest, many of which appear in the present study, along with others some of which are unusual and may be unique. We shall consider, in turn, the parallel alkaline hydrolysis reactions of DHC, the β-elimination process that accompanies these, further hydrolysis of the monolactones to the ultimate ring opened products and, where this happens, the acid-catalysed lactonisation process that returns in stages to DHC itself. These interlinked reaction sequences are set out in Scheme 1.

Hydrolysis of DHC dilactone (1)

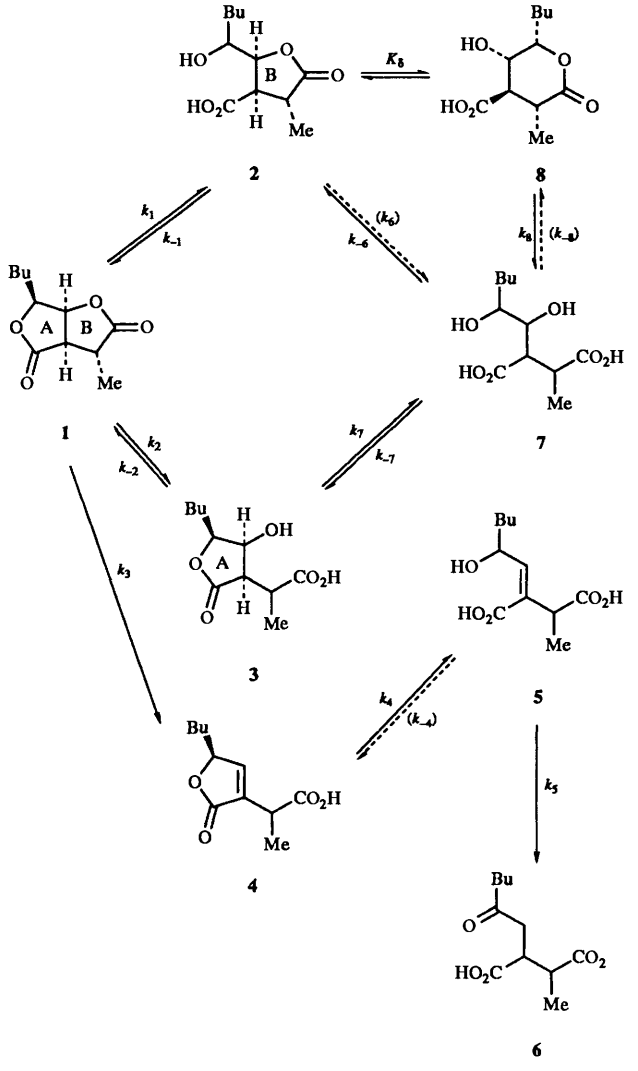
It has been established[8,9a] that the alkaline hydrolysis of esters in water involves uncatalysed addition of hydroxide ion in the rate-limiting step, since even alkoxide is a better leaving group than OH^-. For the hydrolysis of γ-butyrolactone, $\Delta V^{\ddagger}$ is about the value expected for partial bond formation, so that the transition state is reached before the ring-opening step.[10] Hence the greater reactivity of lactones than of normal (*trans*-) esters is due to ground-state destabilisation, as demonstrated by Huisgen and Ott,[4] who showed that an unstrained (14-membered ring) (*E*)-lactone is 800 times less reactive than an unstrained (7-membered ring) (*Z*)-lactone. It also follows that, since ring opening takes place after the rate-limiting step, relief of ring strain (except in terms of eclipsing interactions, *vide infra*) cannot be responsible for the rapid hydrolysis rates of small-ring lactones; this is attributed[4] to lone-pair repulsion in their highly disfavoured[11] *cis*-conformation.

Some values for ester and lactone hydrolysis are compared with those of Scheme 1 in Table 4. DHC (**1**) is extraordinarily reactive; k_1 and k_2 add up to 170 times the hydrolysis rate of γ-butyrolactone,[12] while ring A (k_1) opens even faster than the very activated lactone **11**. As seen above, this cannot be due to ring strain, as is further evidenced by the scarcely affected rate for the *cis*-fused lactone **10**.[13] Nor can it be caused by impaired conjugation, since both ester units appear substantially planar from *ab initio* calculations, and furthermore $\nu_{C=O}$ is quite normal (Table 3). We think two factors are involved. One is electronic: each ring will act as an electronegative substituent towards the other. We may attempt to estimate its magnitude in the following way. It is established[14] that the hydrolysis of aliphatic esters is controlled by inductive (σ_1) and steric (E_s) factors; from data given by Euranto,[15] we derive eqns. (1) and (2), in water at 25 °C, for RCO_2Et and $MeCO_2R$ respectively,

$$\log k_{OH} = -0.19\ (0.23) + 15.11\ (1.19)\sigma_1 + 0.62\ (0.18)E_s \quad (1)$$
$$(n = 8 \quad r^2 = 0.984 \quad s = 0.22 \quad F = 151)$$

$$\log k_{OH} = 0.74\ (0.30) + 10.63\ (0.94)\sigma_1 + 1.25\ (0.16)E_s \quad (2)$$
$$(n = 7 \quad r^2 = 0.984 \quad s = 0.20 \quad F = 126)$$

where σ_1 values are taken from Charton's compilation[16] and E_s, referenced to $H = 0$, from that of Unger and Hansch.[17] For the common species $MeCO_2Et$, these equations predict log $k_{OH} = -1.11$ and -1.00, respectively, whereas the observed value is -0.95. For $MeOCH_2CH_2CO_2Et$ and $MeCO_2CH_2CH_2COMe$ as models for the two independent corrections we now obtain $\Delta(\log k_{OH}) = 0.58$ and -0.28, respectively. This



Scheme 1

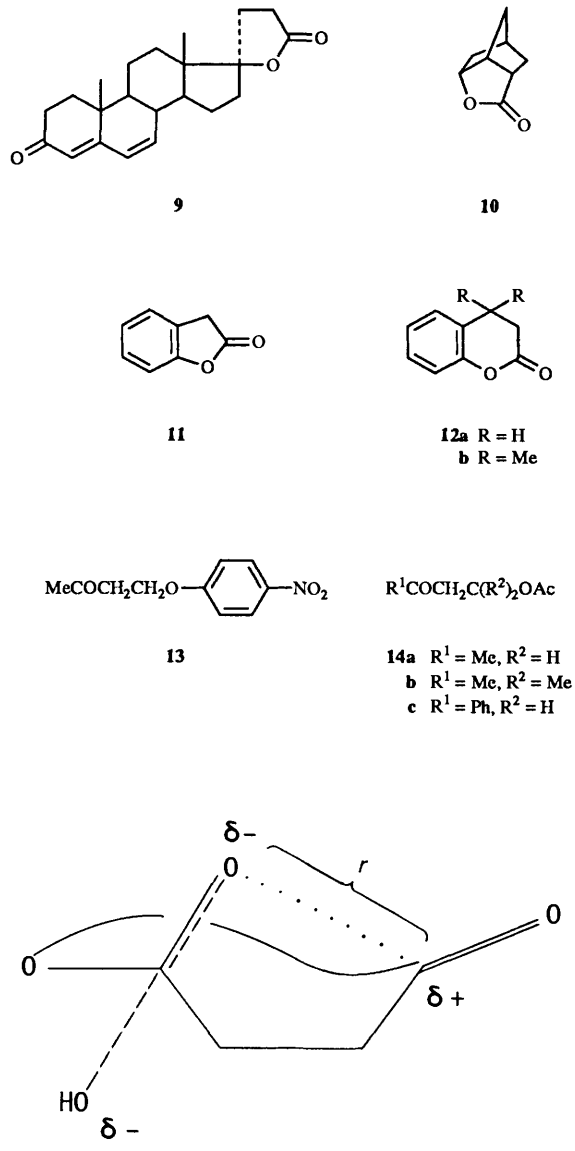


Fig. 4 A representation of the intramolecular close contact required in the transition state for the hydrolysis of **1** (either ring), based on *ab initio* calculation; see the text for calculated values of *r*

adds up to a mere two-fold acceleration in k_{OH} for the hypothetical compound $MeOCH_2CH_2CO_2CH_2CH_2COMe$ relative to $MeCO_2Et$ as a calibration standard. Even if (relative) steric factors are considerably attenuated in five-membered rings, compared with these linear models, as may well be the case, it seems improbable that this stereoelectronic factor can account for very much of DHC's exceptional reactivity. (On their own, the σ_I terms of these equations would predict a 30-fold rate acceleration). Note also that high ester reactivity is generally accompanied by a lowered $\Delta H^{\ddagger}$ but normal $\Delta S^{\ddagger}$ (*cf.* EtOAc and ICH_2CO_2Et in Table 4), whereas exactly the reverse is shown by k_1 and k_2.

We believe the second and major factor to stem from the forced juxtaposition of the two dilactone ester groups. Addition of hydroxide ion to either necessarily results in a C–O^- ••• C=O interaction within the van der Waals contact distance (Fig. 4); from *ab initio* calculations, we estimate *r* as *ca.* 2.8 Å.† While anhydride formation is precluded by the extreme rigidity of the system (and possibly by other considerations[18]),‡ this amounts to a form of internal solvation that is presumably responsible for the abnormally positive $\Delta S^{\ddagger}$ values, −6.9 and −11.4 cal mol^{-1} $°C^{-1}$ for k_1 and k_2 respectively; *cf.* −22.6 cal mol^{-1} $°C^{-1}$ in the case of γ-butyrolactone (Table 4). By contrast, $\Delta H^{\ddagger}$ is normal.

β-Elimination reaction

β-Eliminations[20] (Scheme 2) vary smoothly in mechanism between the limits of 'pure' E2, with irreversible deprotonation in which the steps are concerted so that $k_a \approx k_b$ with negligible return, and pre-equilibrium formation of carbanion C^- [eqn. (3), $k_{-a} \gg k_b$] followed by rate-limiting expulsion of the

$$k_{obs} = k_a k_b[B]/(k_{-a} + k_b) \quad (3)$$

nucleofuge:[21] the $(E1cb)_R$ mechanism.[22] In between comes the borderline E1cb or $(E1cb)_I$ mechanism[22,23] in which $k_{-a} < k_b$, *i.e.* carbanion formation is rate-limiting. The rates of all are linear with respect to [B], but while pre-equilibrium carbanion formation is a simple function of pH, E2 and $(E1cb)_I$ reactions are subject to general-base catalysis.[20] In general the transition

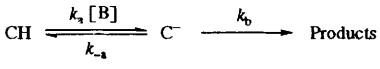
† The calculation is for the unsolvated molecule and probably exaggerates the closeness of this approach.

‡ In a study of crystal structures which display incipient nucleophilic attack precisely of this sort, Bürgi *et al.*[19] find *r* to vary from 2.7 (strong interaction) to 3.1 Å (weak interaction).

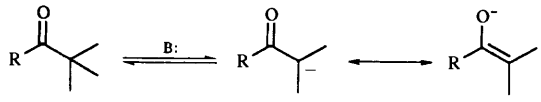
Table 6 Rates for β-elimination and carbanion formation in water at 25 °C

Substrate	k_{OH}/dm^3 mol^{-1} s^{-1}	$\Delta H^{\ddagger}$/10^3 cal mol^{-1}	$\Delta S^{\ddagger}$/cal mol^{-1} °C^{-1}	β_{cat}
$PhCH_2CH_2F$[a,b]	1.3×10^{-7}[c]	25.3	−5.4	
$PhCH_2CH_2Br$[b,d]	—			0.54
14b[e]	1.07[f]			0.46
14a[e]	8.67[f]			
14c[g]	8.82[c]			
13[h]	8.33			0.75[i]
$NCCH_2CH{=}CHCHTCN$[j]	0.205[k]	14.7	−12.4	0.96[i]
$Bu^tCT(CN)_2$[l]	2.48×10^5[k]			0.98[i]
k_3	11.33	16.2	+0.54	1.14[i]

[a] C. H. De Puy and C. A. Bishop, *J. Am. Chem. Soc.*, 1960, **82**, 2535. [b] E2 process. [c] k_{OEt} in EtOH. [d] R. F. Hudson and G. Klopman, *J. Chem. Soc.*, 1964, 5. [e] Ref. 26. [f] At 30 °C. [g] Ref. 23. [h] Ref. 25. [i] k_{OH} falls below regression line of k_B *vs.* pK_a (see the text). [j] Ref. 24(*a*). [k] For detritiation. [l] Ref. 24(*b*).



Scheme 2



15a **15b**

Scheme 3

state is later so β_{cat} rises as the $(Elcb)_R$ borderline is approached, but this is not entirely diagnostic: Table 6 lists, *inter alia*, E2 and $(Elcb)_I$ processes both with β_{cat} *ca.* 0.5. It is characteristic of high β_{cat} values that OH^- is a much less effective catalyst than the Brønsted slope would predict; this is found for simple carbanion exchange reactions (*e.g.* detritiations: [24] see Table 6) as well as for β-eliminations. For **13**, and more generally, Hupe and Wu[25] attribute this to the unfavourable energetics of desolvation for strong bases and show that alkoxides as well as OH^- exhibit this phenomenon. By contrast, no deviation is shown by OH^- in the case of **14b**[26] with $\beta_{cat} = 0.46$.

The present reaction,§ with β_{cat} *ca.* 1.1 and k_{OH} far short of the defining line for k_B (Fig. 2), appears on that criterion as an $(Elcb)_I$ process, much closer to $(Elcb)_R$ than to the E2 borderline. However several factors, mostly steric, argue against too easy acceptance of that proposition. Firstly, while enol anions are familiar examples of conjugated structures (Scheme 3), the normal predominance of canonical form **15b** is likely to be somewhat attenuated here by a kind of 'Bredt's rule'[27] restriction: **15b** involves double bond character at a bridgehead carbon atom. This should make anion formation (k_a) less favourable for RCO, while at the same time the nucleofugality[21] of OCOR′ (k_b) may well be enhanced by ring strain (contrast the nil effect of the latter on hydrolysis *per se*). Both changes would tend to move the transition state back towards the E2 borderline.[28] The near-zero value of $\Delta S^{\ddagger}$ for k_3 (Table 6), appropriate to a fission process,[29] is also consistent with some contribution from k_b to the overall rate. A near-zero $\Delta S^{\ddagger}$ is not a normal feature of simple deprotonations (Table 6).

Against this we have to set the roughly anticlinal alignment of the bridgehead H–C–C–O unit (Fig. 1), for which the E2 process is highly disfavoured.[20] A possible way out of this dilemma starts from one consequence of the above Bredt's rule restriction, namely that **15a** will contribute much more than usual to the carbanion structure. This, which is normal for CN- or $PhSO_2$-supported carbanions, results in a strongly marked shift from the $(Elcb)_I$ towards the $(Elcb)_R$ mechanism,[21] since k_{-a} is then greatly enhanced.[24b] In fact, the overall rate that results from these conflicting factors is hardly at all different from that for the unstrained molecule **14a**.[26] This fact itself is some evidence that ring strain, hence k_b, contributes little or nothing to the observed reaction rate. We therefore conclude in favour of the $(Elcb)_I$ mechanism, as indeed would be expected in this case.[23] A partial explanation for the near-zero $\Delta S^{\ddagger}$ may lie in the loosening effect, on this very rigid structure, even of proton loss, assuming that to be complete as $\beta_{cat} = 1.14$ implies. It may also be that steric crowding restricts carbanion solvation, at least relative to the reactants, which again should lead to a more positive $\Delta S^{\ddagger}$.

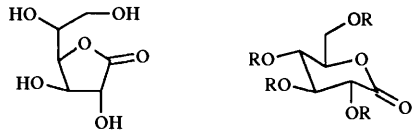
Hydrolysis of the monolactones

Hydrolysis of **3**→**7** (k_7) is 50 times slower than that of the corresponding ring in **1** (k_1), and in fact less than three times faster than for γ-butyrolactone itself (Table 4). The very negative $\Delta S^{\ddagger}$ may reflect repulsion between CO_2^- and the incoming hydroxide ion, as has been found to reduce the rate in a parallel context.[30] The hydrolysis rate of **2** is equally unremarkable, with a similar (40-fold) attenuation in k_6 relative to k_2. However, the activation parameters for this reaction are startling, with $\Delta S^{\ddagger} = 5.6$ cal mol^{-1} °C^{-1}. For an apparently simple addition–elimination reaction, such a value must be without precedent.

$$\mathbf{2} \overset{K_8}{\rightleftharpoons} \mathbf{8} \xrightarrow{k_8} \mathbf{7} \qquad (4)$$

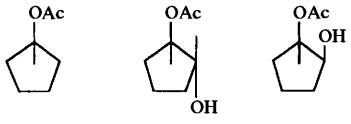
We have traced the origin of this phenomenon, and part of its explanation, to an alkali-catalysed equilibration between the γ-lactone **2** and the δ-lactone **8** which is rapid on the timescale of hydrolysis [Scheme 1 and eqn. (4)]. Such a process is known for D-glucono-γ-lactone **16** and the δ-lactone **17a** and has been much studied.[31–35] The mechanism of Scheme 4 was first suggested by Jermyn[31] and will equally fit the present case. Evidence in its favour comes from the observation by Woodman[32] that equilibration takes place in anhydrous dimethylformamide, so ring opening to gluconic acid is not entailed. The isomerisation process shows marked general-base

§ As explained above, our product analysis is not accurate enough to prove that buffer catalysis is confined to k_3, comprising only 6% of the total reaction; there might be a nucleophilic contribution to k_1 and k_2. However, in nucleophilic catalysis it is customary to obtain separate Brønsted relations for different classes of nucleophile,[8] and furthermore, there is no plausible mechanism for nucleophilic attack by borate ion. For both reasons, we are confident that k_B substantially represents catalysis of k_3.

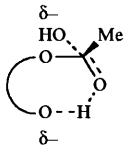


16

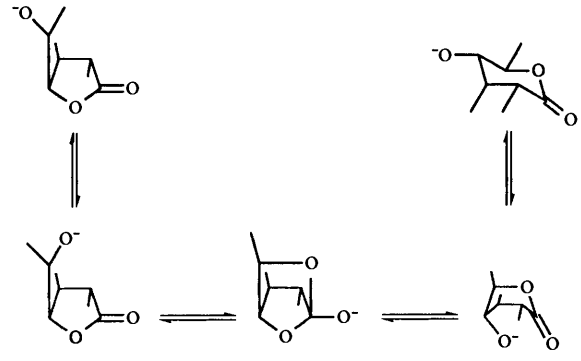
17a R = H
b R = Me



18 19 20



21



Scheme 4

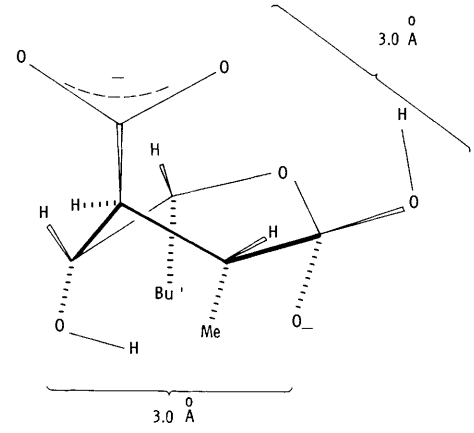


Fig. 5 A projection of the postulated structure for the tetrahedral intermediate in the alkaline hydrolysis of the δ-lactone **8**

catalysis[31-34] and is fast above pH 3.5;[33] for **2**⇌**8**, one would expect CO_2^- to be an effective intramolecular catalyst. The equilibrium itself is finely balanced: Mitchell and Duke[35] find, in acid, K = [Lactone]/[Acid] = 0.26 and 0.185 for the γ- and δ-lactones **16** and **17a**, respectively, from which K_δ = 0.71 [eqn. (4)]. We find K_δ = [**8**]/[**2**] = 0.85 under the same conditions, but with both lactones much more favoured *vs.* the free acid (*vide infra*). While K_δ for the gluconolactones is necessarily independent of pH, the carboxyl group present in **2** and **8** shifts the equilibrium very much on ionisation (Fig. 3); K_δ = 0.056 at high pH.

There is some dispute as to the hydrolysis mechanism. Pocker and Green[36] measured k_{OH}, $\Delta H^\ddagger$ and $\Delta S^\ddagger$ for **17a** and assumed no equilibration with **16** to occur. This is certainly incorrect, though with K_δ = 0.71 and an expected[4] much greater reactivity for the δ-lactone, their values cannot be greatly in error. Part of their evidence[36b] is the nearly equal hydrolysis rate for **17b** (Table 4), which cannot equilibrate, but this means little given a nearly equimolar mixture of **16** and **17a**. It does demonstrate, however, that the enormous k_{OH} value for **17a** cannot involve nucleophilic catalysis; we discuss this further below.

The rapid pre-equilibrium process of Scheme 4 leaves open the question as to what proportion of each lactone is involved in hydrolysis. By using IR for monitoring the products, Shimahara and Takahashi[34] have shown the δ-lactone **17a** to be responsible for substantially all of the hydrolysis reaction in that case. Here, where a 20-fold excess of γ-lactone is balanced by an 'expected'[4,12] 20-fold greater reactivity of the δ-lactone, we cannot be so certain, but nevertheless believe that eqn. (4) continues to apply. Our reason lies in the activation parameters, which remain nearly as abnormal for the derived k_8 as for the ostensible k_6 (Table 4), and do not remotely resemble those for k_7. The explanation for their abnormality which we propose below for k_8 could not possibly extend to k_6 (or k_7).

We believe alkaline hydrolysis of **8** to involve stabilisation of the tetrahedral intermediate (or transition state) by intramolecular general-acid–general-base catalysis as shown in Fig. 5. This differs from some previously discussed cases of neighbouring group participation[37] by carboxylate in ester hydrolysis[18,30,38] where the rate depends on [CO_2^-] not [OH^-] and in which, significantly, $\Delta S^\ddagger$ < −20 cal mol^{-1} $°C^{-1}$

Here we invoke a rigid intermediate wherein intramolecular solvation is enforced by the stereochemistry. Given an estimated[29] $\Delta S^\ddagger$ of *ca.* −18 cal mol^{-1} $°C^{-1}$ as the entropy loss for each water molecule incorporated into the transition state, the difference in $\Delta S^\ddagger$ between k_7 and k_8 is almost exactly that expected for 'squeezing out' two water molecules. The boat conformation of Fig. 5 is known[39] to be only slightly disfavoured for δ-valerolactone relative to the more usual chair form. A distant analogy is to be found in the hydrolysis of **18**–**21** studied by Bruice and Fife.[40] For **19** and **20** they postulate transition states of type **21** which involve intramolecular general-acid catalysis of hydroxide ion addition and whose stereochemistry closely resembles that of Fig. 5. Relative to **18**, $\Delta S^\ddagger$ is more positive by 12.6 and 22.8 cal mol^{-1} $°C^{-1}$ for **19** and **20**, respectively. A rise in $\Delta S^\ddagger$ of *ca.* 33 cal mol^{-1} $°C^{-1}$ for two simultaneous intramolecular interactions appears feasible.

Intramolecular catalysis for **19** and **20** is accompanied by a 20- to 30-fold increase in reaction rate. The hydrolysis of D-glucono-δ-lactone **17a** goes at a quite enormous rate (Table 4), and here Pocker and Green[36a] find evidence for both external general-acid and general-base catalysis. If external catalysis is possible then intramolecular catalysis is almost *de rigeur*; perhaps that is why their reaction is so fast. The difference in rate between **17a** and δ-valerolactone lies largely in $\Delta S^\ddagger$. Removal of the 3-OMe group from **17b** reduces k_{OH} by 20-fold.[36b] By contrast, **8** reacts more slowly than δ-valerolactone, reversing the behaviour of **3**, so that the k_8/k_7 ratio is only *ca.* 4.5, far less than is usual for this difference in ring size.[4,12] It seems probable, therefore, that the mechanism of Fig. 5 is not favoured by any large margin. In part, this could be precisely because it is 'enforced'; Fig. 5 implies a very late transition state,

Table 7 Rates of hydrolysis for unsaturated esters at 25 °C[a]

Substrate	$k_{OH}/10^{-3}$ dm^3 mol^{-1} s^{-1}	$\Delta H^{\ddagger}/10^3$ cal mol^{-1}	$\Delta S^{\ddagger}$/cal mol^{-1} °C^{-1}
EtOAc	6.98	14.1	−21.2
CH_2=$CHCO_2Et$	4.67	14.8	−19.8
MeCH=$CHCO_2Et$	0.625	15.9	−19.8
(*Z*)-MeCH=C(Me)CO_2Et	0.177	16.5	−20.7
k_4	1.45[b]	15.7	−18.8

[a] In 85% EtOH: J. D. R. Thomas and H. B. Watson, *J. Chem. Soc.*, 1956, 3958. [b] This work: k_{OH} in water.

which will help account for an unusually high $\Delta H^{\ddagger}$. The contrast here is with steric compression in the ground state, which is well known to be capable of very high rate accelerations (in the opposite direction).[41] In addition, perhaps the eclipsing interactions that help to make such a difference to the hydrolysis rates of γ- and δ-lactones[4,39,42] are to some extent relieved, or perhaps equalised, in these more complex structures.

Hydrolysis does not seem to have been studied for any butenolide, but the data of Table 7 for simple unsaturated esters suggest that k_4 and its associated $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values are unremarkable. In fact, these data do not show in any marked degree either the reduction in rate that might have been anticipated as a result of conjugation, or the expected rate enhancement for a lactone; perhaps, for **4**, these tend to cancel out. The alkali-catalysed process represented as k_5 is *ca.* 10 times lower than k_4 and has not been investigated.

Lactonisation

If ring opening lies beyond the transition state for lactone hydrolysis, lactone formation must involve rate-limiting ring closure, so that any ring strain should show itself here. This has been demonstrated,[41a] and it has further been shown,[41b] for ring substituted compounds of type **11**, that a reduction in hydrolytic rate of only 7–50 times accompanies an enhancement of up to 10^7 in the rate of lactonisation.

Some data on rates and equilibria for lactone formation in acid are assembled in Table 5. The above simple picture[41] is somewhat obscured by the rapid hydrolysis rates of six-membered ring lactones, as in alkali. Hence, while K_{eq} for five-membered lactone formation tends to be higher, this is not in general reflected in the lactonisation rate. Inside each class, and as reported elsewhere,[13,41,43] the effect of 'steric compression'[41,44] is particularly notable for *gem*-dialkylation, as in examples **9**[45] and **10**.[13]

The present results¶ are at first sight unremarkable, with all lactonisation rates very similar and, perhaps, rather lower than might have been expected, despite quite high K_{eq} values ($= k_{-1}/k_1$ and k_{-2}/k_2). This impression vanishes on inspection of the activation parameters (Table 8). On the limited evidence available (γ-butyrolactone is a notable absentee), $\Delta S^{\ddagger}$ *ca.* −20 cal mol^{-1} °C^{-1} appears as a typical value for lactone formation, more positive by 10–15 cal mol^{-1} °C^{-1} than that found for esters.[9b] This is echoed in the formation of monolactones **2** and **3**. However, their further ring closure to **1** is accompanied by an unusually favourable $\Delta S^{\ddagger}$, so precisely balanced by a less favourable $\Delta H^{\ddagger}$ that an almost exact cancellation in reaction rate results.

It is possible that here, at last, we have the evidence for ring strain in DHC (**1**). Pertinent data according to Scheme 5 are assembled in Table 9. Schleyer *et al.*[46] estimate a strain energy ($\Delta_s H$) for (*Z*)-bicyclo[3.3.0]octane (**23**), as a model for DHC, greater than that of (*Z*)-1,2-dimethylcyclopentane (**22**), as a model for either monolactone, by *ca.* 4 kcal mol^{-1}. This probably represents an upper limit to their relative strain energies since much of this comes from eclipsing interactions which are partly or wholly relieved when 2 × CH_2 is replaced by the ester moiety. On the hypothesis that incremental $\Delta H^{\ddagger}$ as adumbrated in Scheme 5 can be interpreted as $\Delta_s H$, we may perform the calculations of Table 9. The mean $\Delta\Delta H^{\ddagger}$ is in fact *ca.* 70% of $\Delta\Delta_s H$. It is possible on this evidence that ring **B** is more strained than ring **A**, as also suggested by K_{eq} (Table 5), though that may be to push the hypothesis too far. It is impossible to say whether strain is already present in the monolactones **2** and **3**, though their rather low formation rates, relative to their degree of substitution,[41,43] may suggest this.

As seen above, the unusually positive $\Delta S^{\ddagger}$ for DHC formation effectively equalises the rates. Page[47] estimates a rise in $\Delta_{rot}S$ of *ca.* 5 cal mol^{-1} °C^{-1} for each degree of freedom built into the system; factors of this sort ('approximation'[48]) largely account for the well known rate accelerations found for intramolecular reactions.[37] Lactone formation from **2** and **3** entails the loss of one less degree of freedom relative to **7**, hence $\Delta\Delta S^{\ddagger}$ *ca.* 8–11 cal mol^{-1} °C^{-1} is perhaps a little more than might have been expected. The final result for **1**, with K_{eq} (Table 5) very much where it might have been expected from the pattern of substitution in its precursors,[13,41-45] illustrates an almost classic cancellation of ΔH and ΔS in ΔG.

Table 8 Rates and activation parameters for ester and lactone formation in aqueous acid at 25 °C

Product	$k_H/10^{-3}$ dm^3 mol^{-1} s^{-1}	$\Delta H^{\ddagger}/10^3$ cal mol^{-1}	$\Delta S^{\ddagger}$/cal mol^{-1} °C^{-1}
$MeCO_2Me$[a,b]	59.3	9.4	−32.5
12b[c]	18.2	14.0	−19.5
9[d]	100	12.2	−20.0
7→**2** (k_{-6})	12.0	13.55	−21.8
7→**3** (k_{-7})	4.3	15.05	−19.0
2→**1** (k_{-1})	5.3	17.2	−11.2
3→**1** (k_{-2})	9.2	16.9	−11.2

[a] In MeOH. [b] H. A. Smith and C. H. Reichardt, *J. Am. Chem. Soc.*, 1941, **63**, 605. [c] Ref. 41(*a*). [d] Ref. 45.

Table 9 Enthalpies of ring closure processes[a]

	$\Delta H/10^3$ cal mol^{-1}		$\Delta H/10^3$ cal mol^{-1}	$\Delta\Delta H/10^3$ cal mol^{-1}
22[b]	8.85	**23**[b]	12.8	3.95
k_{-7}[c]	15.05	k_{-1}[c]	17.2	2.15
k_{-6}[c]	13.55	k_{-2}[c]	16.9	3.35

[a] See Scheme 5. [b] $\Delta H = \Delta_s H$; ref. 46. [c] $\Delta H = \Delta H^{\ddagger}$.

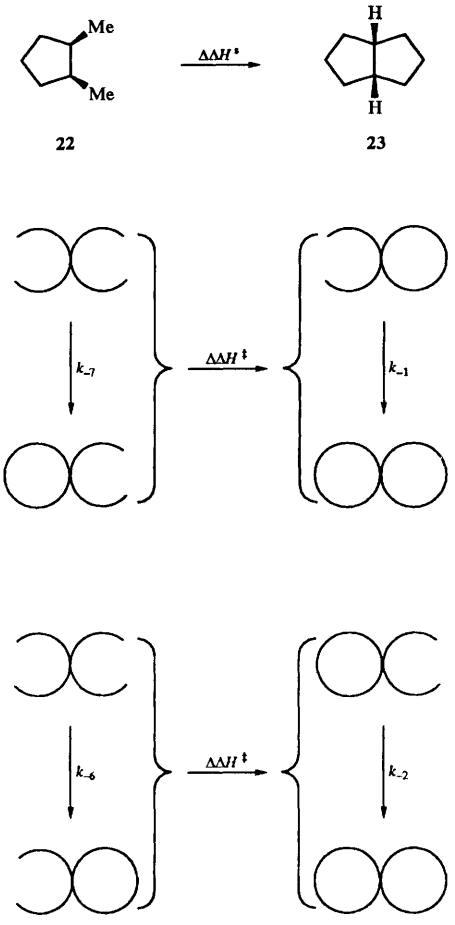
Conclusions

Alkaline hydrolysis of the dilactone (**1**) is remarkably fast, owing, we believe, to an unusual form of intramolecular solvation. An even more effective form may be responsible for the unprecedented near-zero $\Delta S^{\ddagger}$ found for hydrolysis of the δ-lactone **8**. Evidence for ring strain in **1** comes not from hydrolysis, but from ring closure, which is slower than might have been expected with unusual activation parameters, and perhaps from a ring fission process *via* β-elimination that accompanies hydrolysis. The apparent structural simplicity of **1** is belied by the complexity of its reactions.

Experimental

Melting points were taken in a Büchi 535 apparatus and are uncorrected. However, except for **4**, the hydrolysis products of

¶ The cyclisation of **7** to **8** has not been detected.



Scheme 5

DHC (**1**) are thermolabile and so the melting points tend to vary a little with the rate of heating. NMR spectra, which were recorded in $(CD_3)_2CO$ solution on a Bruker AC 250 instrument (250 MHz), appear in Table 1. Mass spectra were obtained on a VG ZAB-SE mass spectrometer using negative ion fast atom bombardment (FAB) ionisation and glycerine or *m*-nitrobenzyl alcohol as matrix. IR spectra (Table 3) were obtained on a Perkin-Elmer 580B IR spectrometer. Silica gel used for column chromatography was Fluka silica gel 60. Potentiometry was based on a Radiometer pH 64 pH meter equipped with Radiometer type B electrodes, an ABU 12 autoburette, a REA 300 pH-stat head, and a TTT 60 burette titrator interface. Consumption of electrolyte as a function of time, or pH as a function of titre, was recorded on a Radiometer REC 61 flat bed recorder with REA 100 interface. pK_a Values were measured in water by standard titrational techniques;[49] the overlapping pK_a values of **7** were disentangled using Noyes's method.[49]

RP-HPLC retention times were determined by means of a Waters model 6000A pump linked to a Rheodyne model 7125 injector and an octadecylsilane column; detection employed an RI detector *ex* HPLC Technology, or a hot wire detector *ex* Pye Unicam. Samples were injected *via* a 20 cm^{-3} injection loop into an aqueous eluent buffered at a pH chosen to minimise the reaction rate. Calibration lines were determined for each compound in terms of concentration *vs.* peak height or peak area.

Monolactone 3

The production of the dilactone DHC (**1**) by fermentation of *Penicillium canadense* strain no. 95493 (Commonwealth Mycological Institute, Kew, England) has been described.[50] However, when the culture medium from such a fermentation is extracted within the pH range 4–6, the monolactone **3** is the major product.

Typically, a culture filtrate (15 dm^3) at pH 5.8 was adjusted to pH 4 by addition of hydrochloric acid and extracted with ethyl acetate. The extract was dried at < 30 °C and the semi-solid residue (37.7 g) was triturated with ether, filtered and washed with diethyl ether to give *rel*-(2*R*)-2-[(3*R*,4*S*,5*S*)-5-butyl-4-hydroxy-2-oxotetrahydrofuran-3-yl]propanoic acid **3** (10.3 g). This compound was further purified by dissolving in a minimum volume of acetone at 20–25 °C and adding, with stirring, 5–10 times that volume of light petroleum (bp 60–80 °C). The resulting crystalline precipitate was filtered to give material mp 120–121 °C (Found: C, 57.7; H, 8.0. $C_{11}H_{18}O_5$ requires C, 57.4; H, 7.9%); *m*/*z* 229 ([M − H]$^-$, 83%), 211 (229 − H_2O, 7%) and 167 (211 − CO_2, 100%); titrated in 25% aqueous acetone as a monocarboxylic acid, pK_a 4.04.

Monolactone 2

To a stirred solution of **1** (1.44 g, 6.8 × 10^{-3} mol) in methanol (25 cm^3) was added 0.2 mol dm^{-3} aqueous sodium hydroxide (34 cm^3, 6.8 × 10^{-3} mol) at a rate such that the pH of the mixture stayed in the range pH 9–10 throughout this process (2 h). The resulting solution was concentrated at < 30 °C under reduced pressure to an aqueous residue, adjusted to pH 4 with hydrochloric acid and extracted with ethyl acetate. The extract was dried and the solid residue was recrystallised from acetone–light petroleum as described above to give *rel*-(2*S*,3*R*,4*R*)-2-[(1*S*)-1-hydroxypentyl]-4-methyl-5-oxotetrahydrofuran-3-carboxylic acid **2** (0.34 g), mp 120–121 °C (Found: C, 57.5; H, 7.7. $C_{11}H_{18}O_5$ requires C, 57.4; H, 7.9%); *m*/*z* 229 ([M − H]$^-$, 100%); titrated in 25% aqueous acetone as a monocarboxylic acid, pK_a 3.67.

Monolactone 4

The butenolide **4** was conveniently prepared by a similar route to that previously described.[51] DHC (1.0 g, 4.7 × 10^{-3} mol) in dry methanol containing sodium methoxide (0.24 g, 4.5 × 10^{-3} mol) was stirred at ambient temperature for 0.5 h. The reaction mixture was acidified to pH 2 with 2 mol dm^{-3} hydrochloric acid, concentrated to an aqueous residue under reduced pressure and extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate and the washings were acidified and re-extracted to obtain the acidic product. This fraction was further purified by silica gel chromatography in dichloromethane–methanol (9:1) to give *rel*-(2*R*)-2-[(5*S*)-5-butyl-2-oxo-2,5-dihydrofuran-3-yl]propanoic acid **4** as an oil (0.58 g) (Found: C, 62.0; H, 7.4. $C_{11}H_{16}O_4$ requires C, 62.2; H, 7.6%); *m*/*z* 211 ([M − H]$^-$, 80%) and 167 (211 − CO_2, 100%); titrated in 25% aqueous acetone as a monocarboxylic acid, pK_a 3.59.

Dicarboxylic acid 6

The monolactone **4** (0.56 g, 2.6 × 10^{-3} mol) was dissolved in a mixture of tetrahydrofuran (5 cm^3), methanol (5 cm^3) and 2 mol dm^{-3} aqueous sodium hydroxide (5 cm^3, 0.01 mol) and stirred at ambient temperature for 2 h. The resulting solution was acidified to pH 2 with 2 mol dm^{-3} aqueous hydrochloric acid and concentrated to an aqueous residue under reduced pressure. The deposited product was extracted into ethyl acetate and recovered to give 5-oxononane-2,3-dicarboxylic acid as a gum (0.54 g) shown by NMR (*cf.* Table 1) to be a mixture of diastereoisomers in the ratio 2:1; *m*/*z* 229 ([M − H]$^-$, 100%); titrated in 25% aqueous acetone as a dicarboxylic acid.

Dicarboxylic acid 7

DHC **1** (6.0 g; 0.028 mol) was suspended in 2 mol dm^{-3} aqueous sodium hydroxide (60 cm^3, 0.12 mol) and stirred at ambient

temperature for 18 h. The resulting solution was cooled to 0 °C and adjusted to pH 3.5 by dropwise addition of concentrated aqueous hydrochloric acid with vigorous stirring. The deposited solid was filtered, washed with ice cold water and vacuum dried at < 30 °C to give *rel*-(2*R*,3*R*,4*R*,5*S*)-4,5-dihydroxynonane-2,3-dicarboxylic acid (3.7 g). This product was further purified by recrystallisation from acetone–light petroleum as described above to give material mp 137–138 °C (Found: C, 53.4; H, 8.2. $C_{11}H_{20}O_6$ requires C, 53.2; H, 8.1%); *m*/*z* 247 ([M − H]$^-$, 100%) and 229 (247 − H_2O, 21%); titrated in 25% aqueous acetone as a dicarboxylic acid, pK_a 3.62 and 4.63.

Monolactone 8

To the dicarboxylic acid **7** (1.0 g) in tetrahydrofuran (20 cm^3), trifluoroacetic acid (0.2 cm^3) and a 4 Å sieve (2.0 g) were added and the mixture was stirred under argon at ambient temperature for 1 h. The mixture was filtered and the filtrate was dried under reduced pressure. The residue was shown by NMR spectroscopy to be a mixture of DHC **1** and the δ-lactone **8** in the ratio of 2:1. These products were separated by column chromatography on silica gel in dichloromethane containing a stepwise gradient of acetone. Fractions containing the more polar product were dried to give *rel*-(1*S*,2*S*,3*R*,4*R*)-2-butyl-3-hydroxy-5-methyl-6-oxotetrahydropyran-4-carboxylic acid **8** as a white solid, mp 92–93 °C (Found: C, 57.6; H, 8.0. $C_{11}H_{18}O_5$ requires C, 57.4; H, 7.9%); *m*/*z* 229 ([M − H]$^-$, 100%); titrated in 25% aqueous acetone as a monocarboxylic acid.

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