Hydrolysis Enthalpy Changes for Selected Five- and Six-Membered Cyclic Esters
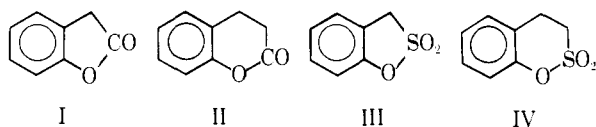
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Abstract: Enthalpy changes accompanying alkaline hydrolysis were measured by batch and flow microcalorimetry. The values obtained for 2-coumaranone and 3,4-dihydrocoumarin were −110.4 and −105.5 kJ mol^{-1}, respectively, while the value for phenyl acetate was found to be −96.9 ± 1.4 kJ mol^{-1}. For *o*-hydroxy-*α*-toluenesulfonic acid sultone the hydrolysis enthalpy changes were −181.8 and −83.7 kJ mol^{-1}. The 5-nitro derivatives of these sultones were also found to have hydrolysis heats very similar to those of their respective parent compounds. The relative hydrolysis enthalpy changes appear to reflect ring strain differences between the homologous lactones and sultones.

Introduction

Five- and six-membered lactones and sultones I–IV are believed to interact to different extents with *α*-chymotrypsin.[1,2] Evidence has been given to suggest that the 5-nitro derivatives of I, II, and III form covalent intermediates with *α*-chymo-

trypsin presumably with serine 195 hydroxyl.[2-5] In such a case the phenolic leaving group cannot leave the active site after transesterification occurs with the enzyme and is in position to act as a nucleophile and cause the esterified enzyme to revert to free enzyme and regenerated substrate. There is supportive evidence that this is indeed the case with the 5-nitro derivatives of I, II, and III and possibly also with the parent lactones and sultones.[2-5] Such a system is of interest from a thermodynamic point of view because of possible substrate ring strain which may be relieved on transesterification with enzyme. Though not much ring strain is expected for I and II, there is considerable evidence to suggest that III is strained relative to IV.[6] The purpose of the present work was to assess the magnitude of possible strain in the five- and six-membered lactones and sultones by comparison of their heats of alkaline hydrolysis.

Experimental Section

Materials. 2-Coumaranone (I) (Aldrich Chemical Co.) was recrystallized from CCl$_4$, mp 49°C (lit. 49 °C).

3,4-Dihydrocoumarin (II) (Aldrich Chemical Co.) was redistilled under vacuum.

o-Hydroxy-*α*-toluenesulfonic acid sultone (III) (Eastman Kodak) had mp 87 °C (lit.[7] 86.1–87.1 °C).

Phenyl acetate (MCB) was redistilled under vacuum.

β-*o*-Hydroxyphenylethanesulfonic acid sultone (IV) was synthesized by first converting *o*-methoxyphenylacetic acid (Aldrich Chemical Co.) to *o*-methoxyphenylethanol using the method of Nystrom and Brown.[8] The *o*-methoxyphenylethanol was converted to *o*-methoxyphenyl bromide by the method of Johnson and Smith[9] and this in turn was converted to the sodium salt of *o*-methoxyphenylethanesulfonic acid by refluxing with Na$_2$SO$_3$.[10] Further conversion to sultone IV was achieved by the method of Kaiser et al.[11] Sultone IV was twice chromatographed on neutral Al$_2$O$_3$ and recrystallized from anhydrous ethanol giving a melting point of 110–112 °C (lit.[12] 109–112 °C). Anal. Calcd: C, 52.14; H, 4.38; S, 17.41. Found: C, 52.05; H, 4.23; S, 17.19.

5-Nitro-*o*-hydroxy-*α*-toluenesulfonic acid sultone (V) was prepared from III by the method of Kaiser and Lo[13] and the product was twice recrystallized from anhydrous ethanol giving pale yellow crystals, mp 149.5–150 °C (lit.[13] 148.5–149.5 °C).

5-Nitro-*o*-hydroxyphenylethanesulfonic acid sultone (VI) was prepared by nitration of IV as described by Kaiser and Lo.[13] The product was twice recrystallized from ethanol, mp 153–155 °C (lit.[3] 154–155 °C).

Acetonitrile (MCB) was prepared by distillation of spectroquality grade compound in a nitrogen atmosphere over P$_2$O$_5$. All other organic solvents were of the highest grade commercially available.

All titration and calorimetric solutions using sodium hydroxide were prepared from saturated CO$_2$ free stock diluted into boiled degassed millipore filtered (Super Q) water. Stock solutions of cyclic esters were prepared in either acetonitrile, tetrahydrofuran, or dimethoxyethane.

Calorimetric Measurements. All batch calorimetry experiments were performed at 25.0 °C in a LKB batch microcalorimeter. Calorimetric measurements of compounds III, IV, V, and VI were performed with cyclic ester concentrations ranging from 1.0 to 0.1 mM. Reaction was initiated by mixing 2.0 mL of cyclic ester in degassed aqueous solution (1.0% CH$_3$CN) with 4.0 mL of CO$_2$-free NaOH (0.01–0.1 M) also containing 1.0% CH$_3$CN. The reference or control chambers contained the exact same solutions but without cyclic ester. Additional controls were performed to evaluate the heat of cyclic ester dilution, which was either negligible or very small in all instances. All calorimetric measurements reported here have been corrected for the heat of ester dilution. Base concentrations of 0.1 and 0.01 M were used to ensure that observed heats were independent of hydroxide ion concentration for hydrolysis of compounds I, II, III, V, and phenyl acetate.
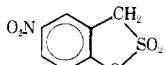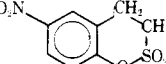
Batch calorimetry for hydrolysis of IV was performed by mixing 2 mL of 2 mM sultone containing 5% THF or 2% CH$_3$CN with 4 mL of 0.7 M LiOH in 5% THF or 0.9 M NaOH in 2% CH$_3$CN, respectively. Calorimetric values in the presence of either organic solvent were found to be the same. Several batch experiments with IV were performed with all solutions.

Some catalysis of the hydrolysis of IV by imidazole was found to occur in presence of strong base also containing 0.5 M imidazole.

A LKB flow microcalorimeter adapted for use by submersion in a Tronac 1040 temperature-controlled bath was used for all flow calorimetry measurements. Heats of hydrolysis for compounds I, II, III, V, and phenyl acetate were measured by flowing degassed aqueous solutions containing 1.0–0.1 mM ester in 1% CH$_3$CN against degassed 0.1 M NaOH aqueous solutions also containing 1% CH$_3$CN. Base line heats were determined by flowing base solution against 1% CH$_3$CN aqueous degassed solution. Resident time in the reaction mixing cell ranged from 45 s to 1 min and at this base concentration the hydrolyses were complete. Heats of dilution of esters were independently determined and corrections made to the observed hydrolysis heats. All solutions were delivered by means of Teflon loading coils and at no time were they in contact with surfaces other than glass, gold, or Teflon. Final concentrations were determined spectrophotometrically from the effluent. The effect of CH$_3$CN concentration was found to be negligible from calorimetric measurements of hydrolysis of V in 5% CH$_3$CN.

Heats of Ionization Measurements. The enthalpy changes of ionization were performed in the LKB flow microcalorimeter by shifting the pH of a solution containing hydrolyzed ester from a value two units above the pK_a to at least two pH units below the pK_a. Since heat of

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Table I. Enthalpy Changes for Alkaline Hydrolysis of Cyclic Esters at 25 °C

ester	$-\Delta H_{hyd}$, kJ mol^{-1}	measurements type and no.[d]	K_{OH^-}[b] (25 °C), M^{-1} s^{-1})
I	110.40 ± 0.92	8 (F)	85
II	105.55 ± 1.59	7 (F)	824
III	181.84 ± 0.88	9 (F, B)	37.4
IV	83.66 ± 1.55	4 (B)	0.0028
(V)	183.3 ± 3.2	5 (F) 1 (B)	1400
(VI)	88.5 ± 3.5	7 (B)	
phenyl acetate[20]	96.94 ± 1.77	9 (F)	1.3
ethylene sulfate	138.1[a]	(A)	0.0403[c]
dimethyl sulfate	114.25[a]	(A)	0.0021[c]

[a] Reference 28. [b] References 21, 22, and 6. [c] Reference 28, 10 °C; hydrolysis mechanisms of the two compounds differ from one another. [d] F = flow, B = batch, A = ampule calorimetry.

acid–base neutralization is the major contributor to the observed heat it is necessary to control or know this contribution precisely.

A single stock solution of CO$_2$-free 0.1 M NaOH was prepared and to equal volumes of the 0.1 M NaOH were added equal volumes of dimethoxyethane (control solution) and dimethoxyethane containing cyclic ester (sample solution), respectively. Several calorimetric runs were performed using a variety of dimethoxyethane concentrations ranging from 2 to 8% by volume. Solutions prepared as above were left at room temperature overnight so as to hydrolyze the cyclic ester. From eq 1 it is seen that 2 equiv of hydroxide is required for hydrolysis so that of the A equiv of OH$^-$ originally present, $A - 2B$ equiv are left on hydrolysing B equiv of the cyclic ester. The heat (Q) expected on adding sufficient acid solution (containing the appropriate percentage of dimethoxyethane) would be

$$Q = -\Delta H_{H_2O}[A - 2B] - \Delta H_{ion}[B] \qquad (a)$$

where ΔH_{H_2O} is the heat of ionization of water and ΔH_{ion} is the heat of ionization (deprotonation) of hydrolyzed sultone. The heat (Q') measured by titrating the control solution with the acid is represented by

$$Q' = -\Delta H_{H_2O}[A] \qquad (b)$$

In practice, the control heat of neutralization was used as the base line against which the sample solution was evaluated, giving a difference signal from which ΔH_{ion} can be calculated as in the equation
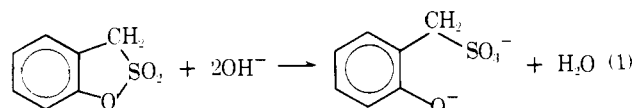
$$(Q' - Q)/[B] = 2[-13.6] + \Delta H_{ion} \qquad (c)$$

Sultone IV is the least soluble of all the cyclic esters used. The amount of IV in these experiments was fourfold lower than all other cyclic esters and because of the large neutralization correction factor the heats of ionization reported for this compound are the least reliable. For this reason we feel that the actual error of ionization heats for hydrolyzed IV is somewhat larger than indicated by the statistical error analysis in Table II.

Potentiometric Titrations. Several conditions were used to establish pK_a values for hydrolyzed esters III, IV, V, and VI. Most potentiometric measurements were performed by titrating the hydrolyzed ester originally at pH 12 with 0.1 or 0.01 M HCl. Some titrations of sultones hydrolyzed in 1 M NaOH were performed with 0.1 M HCl. One equivalent of phenolic group was quantitatively shown to titrate for each equivalent of cyclic ester hydrolyzed under the same conditions used in the calorimetry experiments. This confirmed that esters were completely hydrolyzed in such experiments. Titrations were performed under a nitrogen atmosphere at 25 °C. An A. H. Thomas high pH electrode with low sodium correction was used for all titrations. pK_a values were evaluated from Gran plots.[14]

Results

Hydrolyses of the five- and six-membered cyclic esters as well as phenyl acetate were performed for calorimetric measurements in strong base. All observed enthalpy changes reported are described by eq 1, which includes heat of neutralization to form water.[15]

$$\text{(structure)} \quad \text{CH}_2 \quad \text{SO}_2 \; + \; 2OH^- \longrightarrow \text{(structure)} \quad \text{CH}_2 \quad SO_3^- \; + \; H_2O \quad (1)$$

The slow rate of hydrolysis, especially of sultone IV, creates some difficulty in the calorimetric measurements. This is because of the relatively high dilution heat of the base necessary to bring about hydrolysis within a time frame suitable for batch microcalorimetry. In some instances it was possible to use alkaline conditions which hydrolyzed certain of the cyclic esters rapidly enough to measure the enthalpy change with flow calorimetry. Often, both flow and batch calorimeter measurements were made to corroborate the measurements. The calorimetric results for heats of alkaline hydrolysis of lactones, sultones, and phenyl acetate are listed in Table I. For comparison, enthalpy changes and rates of hydrolysis of ethylene sulfate and dimethyl sulfate are also included.

The most difficult calorimetric measurement of the series involved the hydrolysis of IV. For this compound, almost 1 M hydroxide was necessary in order to bring about hydrolysis in a reasonable time range for batch calorimetry. Because of the large correction for hydroxide dilution heat in experiments involving IV it was desirable to find alternative means of measuring the hydrolysis enthalpy changes. One approach used was to increase reaction rate by use of imidazole as a catalyst. The other was to measure hydrolysis enthalpy changes for the nitro derivatives V and VI (Table I).

The advantage of using the nitrated derivatives V and VI is that they hydrolyze far more rapidly than III and IV yet should have essentially the same characteristics in terms of ring strain and chemical nature of the hydrolyzed products. The relatively rapid rates of hydrolysis in the calorimeters and the results of these measurements are also included in Table I.

Imidazole was used to increase the rate of hydrolysis[16] of IV in some of the calorimetric measurements in alkaline solution (ca. 1 M OH$^-$). The hydrolysis enthalpy change observed for IV under these conditions was -113.15 ± 0.5, some 29 kJ mol^{-1} more exothermic than measurements in the absence of imidazole as catalyst. In all hydrolysis experiments a small amount of hydroxide ion is used in hydrolyzing IV (see eq 1) which makes the actual hydroxide ion concentration of the reaction mixture containing IV (sample) slightly different from the control without IV present. The difference in hydroxide between sample and control is quite small in terms of the total [OH$^-$] present and is negligible as far as OH$^-$ dilution heat is concerned. However, with imidazole present in sample and control (imidazole $pK_a = 14.44$, $\Delta H_{ion} = 73.6$ kJ mol^{-1}),[17] the small difference of hydroxide ion causes different extents of imidazole titration of sample and control and this contributes to the total observed heat. Thus, much of the 29

kJ mol⁻¹ discrepancy can be explained in terms of additional enthalpy contributions due to protonation of some of the imidazole present.

Since the observed hydrolysis enthalpy change is highly dependent on the ionization state of the final product it was necessary to characterize the hydrolysis products. The pertinent ionization and enthalpy data are included in Table II.

Discussion

Despite interest in quantitating ring strain differences in certain five- and six-membered cyclic esters very few measurements of enthalpy changes accompanying hydrolysis have been performed. For comparison, we have included in Table I the results of Kaiser et al.[18] on the alkaline hydrolysis of dimethyl sulfate. Although their measurements were with sulfate diesters instead of sulfonate esters, it is clear that the magnitudes of hydrolysis heats which were observed are roughly comparable to ours and, in fact, our enthalpy changes bracket their results.
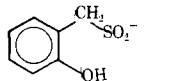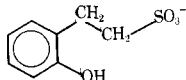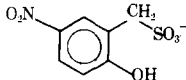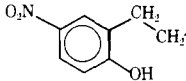
The combined rate and thermal data for hydrolysis of phenyl acetate and lactones I and II provide a rather detailed view of the energetics of hydrolysis. Enthalpy changes for hydrolysis of I and II are 13.5 and 8.6 kJ mol⁻¹ more exothermic than phenyl acetate hydrolysis, which indicates that the lactones may be strained relative to the acyclic ester. This interpretation is supported by the fact that rate constants for hydrolysis of I and II are about two orders of magnitude larger than for hydrolysis of phenyl acetate. The magnitudes of the rate and thermal data indicate clearly that strain differences between these cyclic and acyclic esters are by no means large.

Even smaller differences are noted in comparison of the data for the five- and six-membered lactones. Since II hydrolyzes about ten times more rapidly than I it has been suggested that II is slightly more strained than I.[6] Brown et al. reasoned that the trigonal carbon would distort the chain conformation of a six-membered lactone and the distortion would be relieved in the transition state.[19] The geometry of five- and seven-membered lactones on the other hand would not be relieved in the transition states and this would be reflected in lower rates of hydrolysis for these esters.

The implication of the rate data with regard to I and II is that II would exhibit greater steric strain in the ground state than I. The calorimetric data, however, suggest the opposite, i.e., that I is more highly strained (4.9 kJ mol⁻¹) than II relative to their respective hydrolysis products. The observations of enthalpy changes and rate data are not necessarily in conflict. If we accept both observations as correct then compound I will be more highly strained than II but the transition state for hydrolysis of II would be more easily achieved than the transition state for hydrolysis of I. Hence, hydrolysis of II would proceed faster than I while I would ostensibly be the more strained system. It should be noted that the differences in hydrolysis rates and enthalpy changes for I and II are actually rather minor, so small in fact that it becomes less and less meaningful to ascribe the differences entirely to strain.

While lactones I and II differ little in both rates and heats of alkaline hydrolysis, sultones III and IV appear to differ markedly. In alkaline solution, III hydrolyzes 10⁴ times faster than IV and about 10⁶ times as fast as the acyclic analogue, phenyl α-toluenesulfonate.[10,21,22] Furthermore, the crystal structures of III and IV show some bond angles in III to be as much as 5–8° smaller than in IV.[23] Table I indicates that sultone III is 96 kJ mol⁻¹ more exothermic than IV in terms of the observed heats of alkaline hydrolysis. These observations all support the conclusion that sultone III is strained relative to IV, but the calorimetric difference of 96 kJ mol⁻¹ indicates a much greater strain difference than predicted on the basis of alkaline hydrolysis rates. In comparison with other five- and six-membered ring systems the 96 kJ mol⁻¹ difference in hy-

Table II. pKₐ and Ionization Enthalpy Changes of Hydrolyzed Cyclic Esters in Basic Solution

hydrolyzed ester	pK_a (25 °C)	ΔH_{ion} (25 °C), kJ mol⁻¹
(structure: benzene ring with CH₂SO₂⁻ and OH)	10.09 ± 0.05	23.8 ± 1.1
(structure: benzene ring with CH₂CH₂SO₃⁻ and OH)	10.21 ± 0.03	4.0 ± 1.4
(structure: O₂N benzene ring with CH₂SO₃⁻ and OH)	7.08 ± 0.03	22.4 ± 1.2
(structure: O₂N benzene ring with CH₂CH₂SO₂⁻ and OH)	7.27 ± 0.05	9.96 ± 0.88

drolysis heats is remarkably large and a careful documentation of the calorimetric experiments seems prudent.

The sole products of hydrolysis under conditions used for calorimetry were confirmed by thin layer chromatography to be the expected open-chain acids.[24] Titrations of each of the hydrolyzed esters quantitatively gave a single titratable group in the basic region with pKₐ values characteristic of phenolic hydroxyl. The titrations deny any extraordinary contribution to the observed heats of hydrolysis from proton ionization and confirm that hydrolyses were complete.

Since calorimetric experiments on the hydrolysis of IV were the experimentally most difficult ones, our attention focused on validating these measurements. Attempts to catalyze the hydrolysis rate by use of imidazole led to somewhat more exothermic enthalpy changes than observed in the absence of catalyst. Small differences in titration of the imidazole in sample and control (reference chamber of batch calorimeter) are generated in the course of hydrolysis and we believe that this is responsible for much, if not all, of the discrepancy.[24] Even if this discrepancy is ignored the difference in hydrolysis enthalpy change of III and IV is still some 67 kJ mol⁻¹, a very substantial enthalpy difference. The extraordinarily high heat of ionization of imidazole (73.6 kJ mol⁻¹) in the pH range of the calorimetric experiments and the expected difference in hdyroxide ion concentration generated by sultone hydrolysis cause us to doubt the validity of the imidazole-catalyzed hydrolysis heats.

In an attempt to circumvent the problem of using 1 M base, the heats of hydrolysis of the 5-nitro derivatives of III and IV were measured. The rapid rates of alkaline hydrolysis for these derivatives permitted the use of much lower hydroxide ion concentration for the calorimetric experiments. Furthermore, the nitro derivatives are expected to retain much of the ring strain characteristics of the parent sultones, so little is sacrificed by using such compounds for comparative purposes. The enthalpy changes for hydrolysis of the nitrated sultones were essentially the same as those for the parent compounds (Table I). As a result, the difference in heats of hydrolysis between the pairs of five- and six-membered nitrated sultones was found to be about 96 kJ mol⁻¹, in agreement with that found with the parent sultones. These data strongly support the validity of the calorimetric measurements on the parent sultones and confirm the large differences in hydrolysis enthalpy changes exhibited by the five- and six-membered sulfonate esters.

The 10⁴ difference in hydrolysis rates of sultones III and IV falls several orders of magnitude short of the 96 kJ mol⁻¹ found from hydrolysis enthalpy changes. In the case of certain cyclic phosphodiester hydrolyses, not even qualitative agreement of rate and enthalpy data was observed.[25,26] Nonquantitative

agreement of these parameters is not surprising since they depend on quite different characteristics of the reactions. Heats of hydrolyses deal with enthalpy differences between reactants and products and are independent of reaction pathway while rate measurements are concerned with differences between reactants and transition states and are highly dependent on reaction mechanism. Kaiser and co-workers have concluded that alkaline hydrolysis of III occurs by hydroxide ion attack on the sulfur atom and that mechanisms involving carbanion and/or sulfene intermediates are not predominant pathways for hydrolysis of this compound.[6,26] The open-chain analogue of sultone III, phenyl α-toluenesulfonate, does appear by comparison to hydrolyze with formation of a sulfene intermediate and consequently has a different transition state for its hydrolysis.[27] This has led to the suggestion that the actual rate difference for hydrolysis of these two compounds is significantly greater than the observed factor of 10^6.[6] While no data exist concerning the predominant pathway for hydrolysis of IV, it is conceivable that this compound could behave much like phenyl α-toluenesulfonate. Neither hydrolysis rates, bond angles, nor hydrolysis enthalpy changes suggest any particular strain in sultone IV. So in this respect IV is more closely akin to the acyclic phenyl α-toluenesulfonate than to sultone III and could behave more like the acyclic analogue during hydrolysis. If this is the case then the 10^4 hydrolysis rate difference between III and IV could be deceptively small.

The rationale behind calorimetric studies of the type described here relies on the presumption that there are no essential solvation differences between homologous pairs of cyclic esters in solution and that the same is true for the resulting hydrolyzed products. We have no reason to suspect that the sultones or lactones invalidate that assumption. In fact, the lactone heats of hydrolysis confirm the predictions of little or no strain difference between these five- and six-membered cyclic esters.[6] It was also predicted that the five-membered sultones would have substantial strain in comparison to the six-membered homologue and this too was confirmed by the large difference (96 kJ mol^{-1}) in the heats of hydrolysis for these compounds. The magnitude of the difference in enthalpy change is surprisingly large and it remains to be seen whether other, as yet unidentified, factors may contribute to the enthalpy change. At this point only one factor is clearly identified as contributing and that is ring strain.

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(25) Assessments of strain suspected in cyclic esters by use of hydrolysis enthalpy changes are not always consistent with other predictors of strain. Gerlt et al.[26] have found that calorimetric hydrolysis enthalpy changes for certain six-membered phosphodiesters are more exothermic than those of the five-membered diesters even though the five-membered diesters hydrolyze 10^5 times faster than the six-membered analogues. Though possible explanations for the anomalies have been offered, it is clear that the manifestations of strain in terms of hydrolysis rates and enthalpy changes are poorly understood with these cyclic phosphodiester systems.
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