

## The Alkaline Stability of (5*Z*)-7-([2*RS*,4*RS*,5*SR*]-4-*o*-Hydroxyphenyl-2-trifluoromethyl-1,3-dioxan-5-yl)hept-5-enoic acid, ICI 185282.

### A Remarkable Intramolecular Hydride Transfer from a Trifluoromethyl Substituted Carbon Atom

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The kinetics of hydrolysis of (5*Z*)-7-([2*RS*,4*RS*,5*SR*]-4-*o*-hydroxyphenyl-2-trifluoromethyl-1,3-dioxan-5-yl)hept-5-enoic acid, ICI 185282 (**1a**), have been studied. At low pH the compound undergoes conventional acid-catalysed hydrolysis of the dioxane ring. However, under alkaline conditions, a second reaction is observed. Studies by NMR show that this process involves a quite unexpected intramolecular hydride transfer from a carbon atom carrying a strongly electron-withdrawing trifluoromethyl substituent. Additional studies on closely related compounds are reported and a mechanism involving a ring-opened quinone methide intermediate is proposed.

ICI 185282, (5*Z*)-7-([2*RS*,4*RS*,5*SR*]-4-*o*-hydroxyphenyl-2-trifluoromethyl-1,3-dioxan-5-yl)hept-5-enoic acid (**1a**) is one of a series of biologically active 1,3-dioxanylheptenoic acids.<sup>1,2</sup> These compounds act as antagonists of thromboxane A<sub>2</sub> (TXA<sub>2</sub>) which is responsible for undesirable effects such as bronchoconstriction, vasoconstriction and platelet aggregation which can cause problems in asthmatic conditions or circulatory disorders.<sup>3,4</sup>

As these compounds all possess a dioxane ring, they are potentially vulnerable to acid-catalysed hydrolysis at stomach pH values.<sup>5</sup> The effect of ring substituents at the 2-position has a considerable influence on the hydrolysis rate<sup>6</sup> and it is possible to greatly increase the acid stability by incorporation of electron-withdrawing groups. With a CF<sub>3</sub> substituent, the half-life for ICI 185282 (**1a**) at pH 2 at 25 °C is approximately 7 years compared with a few minutes for the equivalent 2,2-dimethyl species ICI 180080 (**1b**),<sup>3</sup> measured under the same conditions. ICI 185282 was therefore selected for further evaluation.

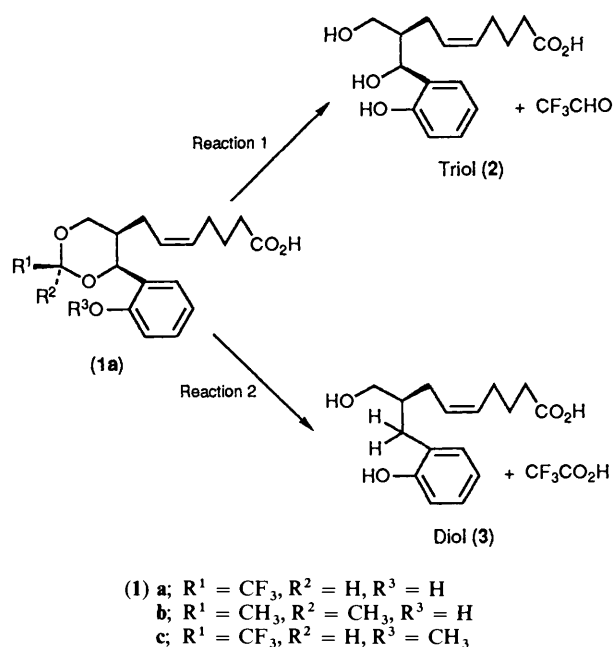
Because of the high acid stability, the initial evaluation was conducted at 91 °C. Although the reaction rates were relatively slow, the anticipated [H<sup>+</sup>]-dependent hydrolysis leading to formation of triol (**2**) was observed; (Scheme 1, Reaction 1). However, an additional reaction was observed at high pH. NMR investigation showed that the product is diol (**3**), formed by an apparent intramolecular hydride transfer from a carbon atom which is substituted with a strongly electron-withdrawing group (Scheme 1, Reaction 2). Details of this highly unexpected finding are given together with studies of the kinetics and the proposed mechanism.

#### Experimental

All reagents were analytical grade and were used without further purification.

<sup>1</sup>H NMR spectra were recorded at 200 MHz with a Bruker AM-200 spectrometer, and <sup>13</sup>C spectra at 100 MHz using a Bruker WM-400 spectrometer. Trifluoroacetaldehyde and trifluoroacetic acid were identified as reaction products using 376 MHz <sup>19</sup>F NMR spectra measured on a JEOL GX-400 spectrometer. Mass spectra were measured using an AEI MS 902 S spectrometer.

The kinetics of reaction were monitored by HPLC using a Perkin-Elmer ISS 100 autosampler combined with an Altex 110A pump, an LDC Spectromonitor III detector and LDC 308 computing integrator. A Rainin column was used. The eluant



Scheme 1.

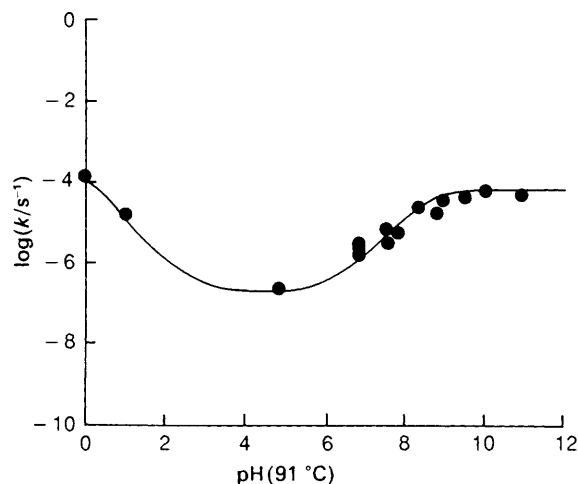
was 40% CH<sub>3</sub>CN-H<sub>2</sub>O, 0.1% H<sub>3</sub>PO<sub>4</sub> and the products were monitored at 222 nm: retention times of (**1a**), (**2**), and (**3**) were 41.6, 7.7, and 4.4 min, respectively. The hydrolysis of 185282 (**1a**) was also followed using an S5 ODS column eluting with 52% CH<sub>3</sub>CN, H<sub>2</sub>O, 0.1% H<sub>3</sub>PO<sub>4</sub> where the retention time was reduced to 9 min. Rate coefficients were calculated from HPLC integrals using a linear regression of standard ln concentration against time data sets. Acetate, phosphate, carbonate, and borate buffers μ = 0.1 were used to maintain pH control. pH measurements were made at 91 °C using a Radiometer PHM 63 meter.

**Preparation of Materials and Product Identification.**—(5*Z*)-7-([2*RS*,4*RS*,5*SR*]-4-*o*-hydroxyphenyl-2-trifluoromethyl-1,3-dioxan-5-yl)hept-5-enoic acid, ICI 185282 (**1a**) and the *o*-methoxy derivative (**1c**) were prepared and identified as previously described.<sup>1</sup>

An authentic sample of triol (**2**), (5*Z*,8*RS*,9*SR*)-9-hydroxy-8-

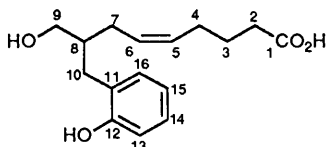
**Table 1.** Product ratios and rate coefficients for reaction of ICI 185282 (**1a**) at 91 °C.

pH	(3):(2)	$k/10^6 \text{ s}^{-1}$			% Yield triol (2)
		Loss of diol (3)	Loss of triol (2)	Loss of 185282 ( <b>1a</b> )	
10.8	7.0:1	—	—	62.5	11 (3 half lives)
9.8	7.4:1	—	—	73.1	6 (2 half lives)
9.4	4.5:1	12.9	—	46.7, 55.9	—
8.8	2.3:1	—	6.4	25, 35	—
8.4	—	9.4	—	28.2	—
7.5	0.2:1	2.5	—	4.97	—
6.8	0.15:1	—	—	3.52	29 (ca. 1 half life)
6.8	0.1:1	—	—	3.49	28 (ca. 1 half life)

**Figure 1.** pH profile for hydrolysis of ICI 185282 (**1a**) at 91 °C: ●  $\log k$  observed; —  $\log k$  predicted.

hydroxymethyl-9-(2-hydroxyphenyl)non-5-enoic acid, was prepared by acid-catalysed hydrolysis of 5(*Z*)-7-[2,2-dimethyl-4-(2-hydroxyphenyl)-1,3-dioxan-*cis*-5-yl]heptenoic acid, ICI 180080 (**1b**) prepared as previously described.<sup>2</sup> Compound (**1b**) was mixed with 0.02 mol dm<sup>-3</sup> HCl in 10% aqueous dioxane and heated for 1.25 h at reflux which gave the expected product (**2**). After extraction and purification, the structure was confirmed by NMR and mass spectrometry. This material was identical by UV and HPLC retention time with the product obtained from hydrolysis of (**1a**) in the present study.

(5*Z*,8*RS*)-8-hydroxymethyl-9-(2-hydroxyphenyl)non-5-enoic acid, diol (**3**) was identified from the NMR spectra of the product formed by hydrolysis of ICI 185282 (**1a**) in 0.5 mol dm<sup>-3</sup> NaOD. The data refer to this solvent.  $\delta_{\text{H}}$ (reference to H<sub>2</sub>O at 4.9) 7.2 (2 H, m, 14-H and 15-H) 6.78 (1 H, d, 13-H), 6.7 (1 H, t, 16-H), 5.7 (2 H, m, 5-H), 3.58 and 3.42 (2 H, AB of ABX 9-H), 2.8 and 2.7 (2 H, AB of ABX 10-H), 2.35 (2 H, t, 2-H), 2.2 (4 H, m, 4-H and 7-H), 2.0 (1 H, m, 8-H), and 1.8 (2 H, m, 3-H);  $\delta_{\text{C}}$ (external SiMe<sub>4</sub>) 184.0 (s, C-1), 31.1 (t, C-2), 26.1 (t, C-3), 26.8 (t, C-4), 131.5 (d, C-5), 131.1 (d, C-6), 28.6 (t, C-7), 41.8 (d, C-8), 63.6 (t, C-9), 37.4 (t, C-10), 129.3 (s, C-11), 165.0 (s, C-12), 114.5 (d, C-13), 129.3 (d, C-14), 118.6 (d, C-15), and 127.9 (d, C-16).



The NMR spectra provide evidence for a methylene group and not a methine adjacent to the phenol ring. The product

retained the phenol moiety, ( $pK_{\text{a}}$  10.08). Extraction of the neutralised reaction solution with CH<sub>2</sub>Cl<sub>2</sub> removed the product. The CH<sub>2</sub>Cl<sub>2</sub> was evaporated and replaced by methanol. The mass spectrum of this solution gave an  $m/z$  278 ( $M^+$ ) with an ion at  $m/z$  107 assigned to be the fragment ion  $o\text{-CH}_2=\text{C}_6\text{H}_4=\text{OH}^+$ . This supports the structural conclusions from NMR spectroscopy.

The formation of (**3**) combined with the identification of trifluoroacetic acid as the other product provides clear evidence of intramolecular hydride transfer.

## Results

Spectroscopic details for the identification of diol (**3**) as the major product at high pH are given in the Experimental section. The crucial piece of NMR evidence is the presence of a methylene group adjacent to the phenol ring. In one of the initial experiments the loss of (**1a**) in 0.5 mol dm<sup>-3</sup> NaOD at 91 °C was followed by NMR. It was particularly fortunate that the experiment was conducted in pure NaOD (rather than NaOH in D<sub>2</sub>O) because this provides clear evidence that the methylene moiety is formed quantitatively from a hydrogen atom present in the starting material (**1a**). There is no isotopic scrambling with the deuterium from the solvent indicating that the process is intramolecular. The most likely explanation is that a hydride transfer has occurred from the carbon atom adjacent to the trifluoromethyl group. As shown in Scheme 1, a consequence of hydride transfer would be the formation of trifluoroacetic acid and not trifluoroacetaldehyde as the other reaction product. The <sup>19</sup>F NMR spectrum of the final NaOD solution did indeed show a large peak for trifluoroacetic acid with a small doublet at -9.49 ppm (the position of the trifluoroacetic acid reference set at zero). By the use of a reference standard this was confirmed to be a small amount of trifluoroacetaldehyde present as a minor component.

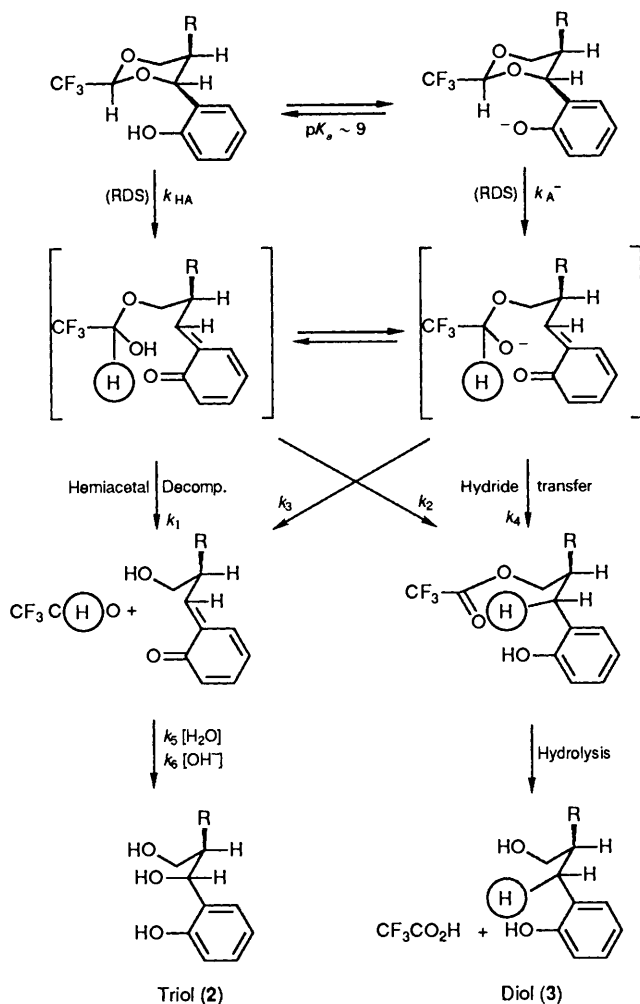
The pH profile for (**1a**) is shown in Figure 1. At low pH the expected acid-catalysed hydrolysis of the dioxane ring is clearly evident with a suggestion of a plateau at intermediate pH values. However, at higher pH values there is an acceleration in rate which reaches an upper plateau consistent with the reaction of an anionic species with a  $pK_{\text{a}}$  in the region of 9.1. This portion of the profile is absent when the hydrolysis study is conducted with (**1c**) where the phenol group of ICI 185282 is replaced by a non-ionisable *o*-methoxy group. This provides evidence that the process at high pH involves reaction of the (**1a**) anion.

There is some difficulty in fitting the data in Figure 1 to simple pH profile linked to a phenolic  $pK_{\text{a}}$ . A rate expression involving the anion alone would underestimate the observed rates in the pH 7–8 region. In addition, as shown in Table 1, at high pH the triol hydrolysis product (**2**) is formed as a minor component in parallel with the hydride-transfer product diol (**3**) in a ratio of ca. 1:7. At lower pH values this ratio is reversed and at pH 6.8 it is 10:1 in favour of triol (**2**). This quantitative analysis is slightly complicated because both the products (**2**) and (**3**) are unstable under low pH reaction conditions. However, the data are sufficiently reliable to show that although no diol (**3**) would be formed at pH 6.8 if the hydride transfer involved the anion alone, some of this species is produced. On the plateau at pH 4.8 many products are observed and it is not possible to quantify reliably diol and triol ratios because of further reaction.

Correction of the rate data for the product ratios would imply an apparent rate of production of diol (**3**) at pH 7 of approximately  $3 \times 10^{-7} \text{ s}^{-1}$ , rising to  $7 \times 10^{-5} \text{ s}^{-1}$  at pH 10; an increase in rate by a factor of roughly 200. In contrast, the rate of production of triol (**2**) would be roughly  $3 \times 10^{-6} \text{ s}^{-1}$  at pH 7 and  $1 \times 10^{-5} \text{ s}^{-1}$  at pH 10 (*i.e.* only a factor of 3). pH-Independent triol formation would be difficult to reconcile with OH<sup>-</sup> attack.

## Discussion

It is clear that any reaction mechanism must be able to reconcile both the pH rate profile and the product ratios. The mechanism which is proposed involves formation of quinone methide intermediates as shown in Scheme 2. Considering first the pH



Scheme 2.

profile in Figure 1, there are two plateaux between pH 4 and 11. As the rate-determining step, both for the neutral form [HA] and the anion [A<sup>-</sup>], is the opening of the dioxane ring, this can be accommodated by a rate expression given in equation (1),

$$k = k_{\text{HA}}[\text{HA}] + k_{\text{A}^-}[\text{A}^-] + k_{\text{H}^+}[\text{H}^+][\text{HA}] \quad (1)$$

where  $k_{\text{HA}}$  and  $k_{\text{A}^-}$  are the observed plateau rates at low and high pH and [HA] and [A<sup>-</sup>] are linked *via* the  $\text{p}K_{\text{a}}$  of the phenol. The solid line in Figure 1 is the theoretical curve using the values,  $k_{\text{HA}} = 2 \times 10^{-7} \text{ s}^{-1}$ ,  $k_{\text{A}^-} = 8 \times 10^{-5} \text{ s}^{-1}$ ,  $k_{\text{H}^+} = 1.26 \times 10^{-4} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ , and  $\text{p}K_{\text{a}} = 8.7$ .

It is possible to obtain a better statistical fit using a value of 8.5 for the  $\text{p}K_{\text{a}}$ . However, as the measured value by UV spectroscopy at 91 °C is  $9.0 \pm 0.3$ , these values have been disregarded. The rate coefficients quoted above are regarded as a 'best fit' within the limitations of the experimental data.

Product analysis shows that both diol (3) and triol (2) are produced at low and high pH from both the anion and the neutral species. This is necessary as diol (3) production at low

Table 2. First-order rate and activation parameters for reaction of (1a) in 0.1 mol dm<sup>-3</sup> NaOH.

$T/^\circ\text{C}$	$k/\text{s}^{-1}$	Activation parameters
91.0	$6.26 \times 10^{-5}$	$\Delta G^\ddagger = 25.76 \text{ kcal mol}^{-1}$
80.0	$2.75 \times 10^{-5}$	$\Delta H^\ddagger = 21.26 \text{ kcal mol}^{-1}$
70.0	$9.85 \times 10^{-6}$	$\Delta S^\ddagger = -15.10 \text{ cal mol}^{-1} \text{ K}^{-1}$
Extrapolation		Correlation coefficient = 0.9947
25.0	$8.13 \times 10^{-8}$	

$$\dagger 1 \text{ kcal mol}^{-1} = 4.184 \text{ kJ mol}^{-1}$$

Table 3. Rate coefficients for hydrolysis of hemiacetals  $\text{R}^1\text{R}^2\text{C}(\text{OH})\text{OR}^3$  used to predict a value for  $k_1$ .

R <sup>1</sup>	R <sup>2</sup>	OR <sup>3</sup>	$k/\text{s}^{-1}$ (25 °C)	Reference
CF <sub>3</sub>	Ph	OH	$2.2 \times 10^{-2}$ <sup>a</sup>	7
H	H	OH	$4.2 \times 10^{-3}$	8
H	H	OMe	$1.8 \times 10^{-3}$	8
H	H	OEt	$1.6 \times 10^{-3}$	8
CH <sub>3</sub>	H	OH	$5.1 \times 10^{-3}$	9
CH <sub>3</sub>	H	OMe	$2.0 \times 10^{-3}$	9
CH <sub>3</sub>	H	OEt	$1.5 \times 10^{-3}$	9
Ph	H	OMe	$5.18 \times 10^{-3}$ at 15 °C (Est. $1 \times 10^{-2}$ at 25 °C)	10
Ph	H	OEt	$2 \times 10^{-2}$ at 30 °C (Est. $1.5 \times 10^{-2}$ at 25 °C)	11
Bu <sup>i</sup>	H	OH	$3.4 \times 10^{-3}$	12
MeOC <sub>6</sub> H <sub>4</sub>	H	OEt	$1.8 \times 10^{-3}$	13
Ph	CH <sub>2</sub> Br	OMe	$< 3 \times 10^{-2}$	14

<sup>a</sup> Calculated from  $k_r = k_r K/55.5$ .

pH could not solely be from the anion. The apparent pH independent rate of formation of triol (2) is deceptive because it is based on correction of the observed rate for the ratio of the products. It does not reflect in any way the ratio between  $k_1$  and  $k_3$  in Scheme 2, as these occur after the rate-determining steps (RDS)  $k_{\text{HA}}$  and  $k_{\text{A}^-}$ . The values of the  $k_1:k_2$  and  $k_3:k_4$  ratios determine the relative product partitioning from the reaction intermediates (*i.e.* 10:1 and 1:7, respectively). Cross-comparisons are now allowed. It is possible that  $k_3$  and  $k_4$  could be several orders of magnitude greater than  $k_1$  and  $k_2$  but this would have no effect on the product ratios. Provided all the processes are fast relative to  $k_{\text{HA}}$  and  $k_{\text{A}^-}$ , these will have no influence on the overall rate. This is certainly the case; at 91 °C  $k_{\text{HA}}$  and  $k_{\text{A}^-}$  are relatively slow at  $10^{-6}$  and  $10^{-4} \text{ s}^{-1}$ , respectively. The temperature coefficients measured in 0.1 mol dm<sup>-3</sup> NaOH (Table 2) shows a roughly 800-fold rate retardation at 25 °C. Thus,  $k_{\text{HA}}$  and  $k_{\text{A}^-}$  at room temperature are in the region of  $10^{-10}$  to  $10^{-7} \text{ s}^{-1}$ , respectively.

In order to understand fully the mechanism of hydrolysis, it is necessary to estimate the two rates  $k_1$  and  $k_3$  in Scheme 2 and hence  $k_2$  and  $k_4$  from product ratios.  $k_1$  is the rate of loss of ROH from  $\text{CF}_3\text{CH}(\text{OR})\text{OH}$  and  $k_3$  is the rate of loss of  $\text{OR}^-$  from the equivalent anion  $\text{CF}_3\text{CH}(\text{OR})\text{O}^-$ . Although these figures are not directly available, it is possible to use linear free energy approximations to make reasonable estimates.

Water rate data from hemiacetal hydrolyses are summarised in Table 3. The values show little sensitivity to substitution pattern. The  $\rho$  value is roughly +1.7 for  $\log k_{\text{H}_2\text{O}}$  vs.  $\sigma_1(\text{R}^1 + \text{R}^2)$ . This is to be expected, as substitution effects will tend to cancel. Those which favour ionisation are counter-balanced by those reducing protonation in the intermediate. An estimate of the rate of  $\text{CF}_3\text{CH}(\text{OH})\text{OR}$  decomposition ( $k_1$  Scheme 2) can be made from the data using a Statgraphics<sup>15</sup> multiple-regression program. The data were found to fit equation (2)

**Table 4.** Hemiacetal anion decomposition rates  $k_-$  used in regression analysis to predict a value for  $k_3$ .

$pK_a$	$R_1$	$R_2$	$OR_3$	$k/s^{-1}$	$\log k_-$	Reference
13.27	H	H	OH	$3.90 \times 10^2$ <sup>a</sup>	2.59	8
13.47	H	H	OMe	$6.90 \times 10^2$	2.83	8
13.56	H	H	OEt	$4.72 \times 10^2$	2.67	8
13.57	H	CH <sub>3</sub>	OH	$6.32 \times 10^3$	3.80	9
13.77	H	CH <sub>3</sub>	OMe	$3.77 \times 10^4$	4.57	9
13.86	H	CH <sub>3</sub>	OEt	$3.40 \times 10^4$	4.53	9
13.88	H	Bu <sup>i</sup>	OH	$9.2 \times 10^3$	3.96	24
13.2	H	Ph	OH	$8.0 \times 10^3$	3.90	18, 19
12.8 <sup>b</sup>	H	Ph	OMe	$1.1 \times 10^5$	5.04	11, 21
10.0	CF <sub>3</sub>	Ph	OH	$6.4 \times 10^{-1c}$	-0.19	7
11.5 <sup>d</sup>	CH <sub>2</sub> Br	Ph	OMe	$1.2 \times 10^5$	5.07	14

<sup>a</sup>  $k_- = k_{OH^-} - Kw/Ka$ ; <sup>b</sup> From an estimate of the  $pK_a$  for Ph CH(OH) OMe,  $k_-$  can again be calculated. Ritchie<sup>7</sup> suggests that a  $\rho$  value of 6.5 gives a better prediction of hydrate  $pK_a$  values than the normal 8.5 of Fox and Jencks<sup>22</sup> for these hydrate systems. From Charton's  $\sigma$  values<sup>23</sup> and Ritchie's  $\rho$  value to correct for methanol gives  $pK_a = 15.54 - 6.5 \times (\sigma_{Ph} + \sigma_{OMe}) = 12.8$ . This value is in reasonable agreement with the value for *p*-Cl and *p*-NO<sub>2</sub> benzaldehyde hydrates calculated from Bell and Sorensen<sup>18</sup> ( $K_1K_w/K_2$ ) ca. 11.9 and 12, respectively. These figures can be corrected for a statistical factor (+0.3) and a correction for substitution giving values of 12.4 and 13.0, respectively. Thus the estimate of 12.8 is considered to be a reasonable approximation. Using this value  $k_- = 1.1 \times 10^5 s^{-1}$  for OMe<sup>-</sup> loss compared with  $8 \times 10^3 s^{-1}$  for OH<sup>-</sup> loss<sup>18,19</sup>; <sup>c</sup>  $k_r = k_t/K$ ; <sup>d</sup>  $pK_a$  calculated 11.51 using Ritchie's<sup>7</sup>  $\rho$  value and Charton's  $\sigma_1$ <sup>22</sup> data.

$$\log k_{H_2O} = -3.46 + 0.76 \sigma_1(R^1 + R^2) - \frac{0.09 \Sigma E_s + 2.37 \sigma_1(OR^3)}{0.09 \Sigma E_s + 2.37 \sigma_1(OR^3)} \quad (2)$$

from which  $k_1 = 6 \pm 4 \times 10^{-3} s^{-1}$ .

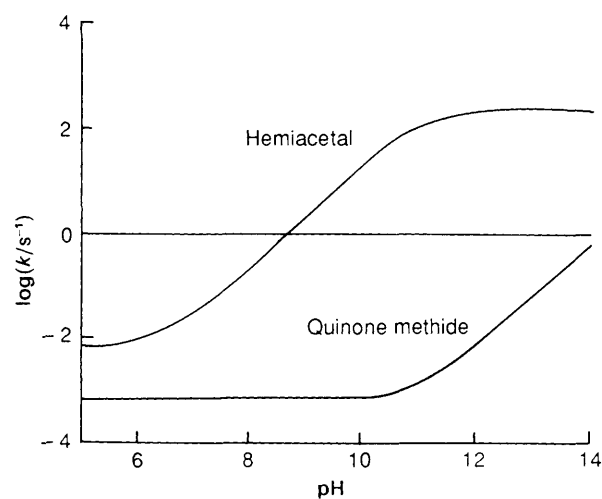
A value for the rate of elimination of OR<sup>-</sup> from the anionic species, ( $k_3$  Scheme 2) can again be estimated from literature information, but in this case there are greater difficulties. The closest direct model comes from the work of Ritchie<sup>7</sup> on hydroxide addition to phenyl trifluoromethyl ketone. From this data a value for  $k_r$  (loss of OH<sup>-</sup> from the tetrahedral anion) can be estimated as  $0.64 s^{-1}$ . This is relatively slow and presumably reflects the influences of the electron-withdrawing CF<sub>3</sub> substituent. However it is well known that the behaviours of aldols and ketals are quite different.<sup>16,17</sup> Bell and Sorenson,<sup>18</sup> Cox,<sup>19</sup> and McClelland<sup>20</sup> have shown that, for hemiacetals, the rate of breakdown is almost independent of  $\sigma_1$  values. Thus, correcting the ketal data for the absence of a phenyl group and a change from OH<sup>-</sup> to OR<sup>-</sup> as leaving group is not a simple task. It is clear that steric as well as inductive effects need to be taken into account.

The acceleration of rate caused by steric bulk and the reduction in rate due to electron-withdrawing substituents can be seen from the data in Table 4. Although the data set available is severely limited, an attempt has been made to fit the data to a three parameter equation. Using the Statgraphics<sup>15</sup> multiple regression program the equation (3) is obtained where

$$\log k_- = -5.81 - 5.12 \sigma_1(R^1 + R^2) + \frac{32.4 \sigma_1(OR^3) - 0.43 \Sigma E_s}{32.4 \sigma_1(OR^3) - 0.43 \Sigma E_s} \quad (3)$$

$R^1$  and  $R^2$  are the substituents on the ketone, OR<sup>3</sup> is the leaving group and  $E_s$  is the Taft steric parameter<sup>25</sup> using the high value for Ph.

The quality of the data fit is quite poor  $R^2 = 40\%$  reflecting the lack of discrimination in the initial data set. However, the equation can be used to calculate an approximate value for the rate of breakdown of the trifluoromethyl hemiacetal anion. Substitution of the appropriate coefficients into equation (3)



**Figure 2.** Predicted pH profiles at 25°C for hydrolysis of the trifluoromethyl hemiacetal and quinone methide intermediates shown in Scheme 2.

gives  $\log k_- = 2.48 \pm 1.4$  from which  $k_- = 300 s^{-1}$ . From the statistical error limits, the value could be a factor of 20 greater or lower. However, this gives us a rough value for  $k_3$  in Scheme 3 and hence, from the product ratio, a value for  $k_4$ , the rate of hydride transfer for the anion.

The predicted pH profiles for quinone methide solvation and hemiacetal decomposition are shown in Figure 2. The rates for trifluoroacetaldehyde hemiacetal decomposition are calculated from equation (4) where  $k_1 = 6 \times 10^{-3} s^{-1}$ ,  $k_3 = 300 dm^3$

$$k_{\text{hemi}} = k_1 + k_3 K_a / (K_a + H^+) \quad (4)$$

mol<sup>-1</sup> s<sup>-1</sup> and the  $pK_a$  for ionisation of the hemiacetal is 11.1 (calculated by using Ritchie's<sup>7</sup>  $\rho$  value).

The quinone methide hydration rates were calculated from equation (5) where  $k_5 = 7 \times 10^{-4} s^{-1}$  and  $k_6 = 0.7 dm^3 mol^{-1}$

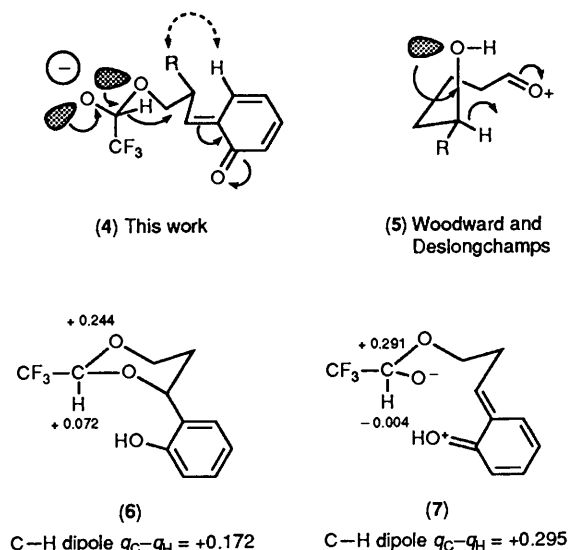
$$k_{\text{quinone}} = k_5 + k_6 [OH^-] \quad (5)$$

s<sup>-1</sup>.<sup>26</sup> Even allowing for the possibility of sizeable error in the estimate of  $k_3$  (up to 20-fold as previously described), it is clear that over the pH range of interest hemiacetal decomposition greatly exceeds the rate of quinone methide solvation. This provides evidence that the quinone methide hemiacetal intermediates in Scheme 2 decompose with loss of trifluoroacetaldehyde *via*  $k_1$  and  $k_3$  to give a second quinone methide, which then adds on water or hydroxide ions. These results demonstrate that triol (3) formation occurs after the hydride transfer-hemiacetal decomposition stage where  $k_1/k_2$  and  $k_3/k_4$  ratios determine the product composition. These observations are consistent with the product ratio observations which show no dependence of triol (3) formation on hydroxide ion concentration at high pH. The rate coefficient values for the mechanism shown in Scheme 2 are summarised in Table 5. These form a self-consistent group which is able to rationalise all the experimental observations. However the fundamental question of the mechanism of hydride transfer remains to be addressed.

Although the kinetics of the reaction can be explained by Scheme 2, it is necessary to consider whether the proposed hydride transfer is reasonable on mechanistic grounds. Related intramolecular hydride transfers are certainly known. Both Woodward<sup>27</sup> and Deslongschamps<sup>28</sup> have reported similar reactions. The reaction of (1a) is essentially a vinylogue of these known reactions. The unusual feature of the current study is the loss of hydride from a carbon atom bearing a strongly electron-withdrawing CF<sub>3</sub> group. This retarding influence is offset by a

**Table 5.** Summary of predicted rate coefficients for Scheme 2.

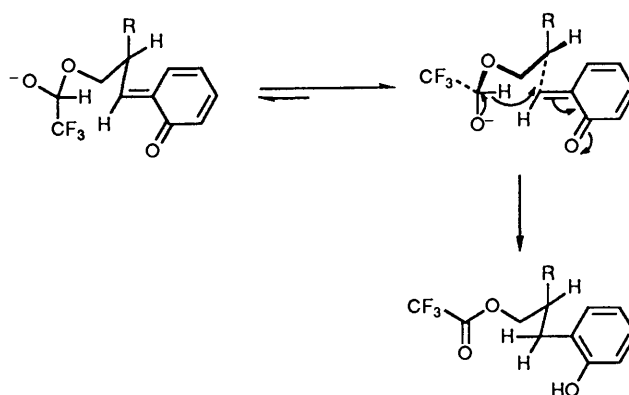
Reaction	Rate/s <sup>-1</sup> (25 °C)
Ring opening neutral species	$k_{HA} = 2 \times 10^{-10}$
Ring opening anion	$k_{A^-} = 1 \times 10^{-7}$
Hemiacetal decomposition neutral species	$k_1 = 6 \times 10^{-3}$
Hydride transfer neutral species	$k_2 = 6 \times 10^{-4}$
Hemiacetal decomposition anion	$k_3 = 3 \times 10^2$
Hydride transfer anion	$k_4 = 2 \times 10^3$
Quinone methide hydration	$k_5 = 7.2 \times 10^{-4}$
Quinone methide hydroxide	$k_6 = 7.5 \times 10^{-1}$ (dm <sup>3</sup> mol <sup>-1</sup> s <sup>-1</sup> )



number of factors [see structures (4) and (5)]: (a), an anionic oxygen atom (Woodward and Deslongchamps studies are done under acidic conditions); (b), two anti-periplanar oxygen atom lone pairs driving the hydride migration (Woodward and Deslongchamps have only one); (c) a very reactive quinone methide electrophile. It is worth re-emphasising that the overall reactions are relatively slow and require elevated temperature. Consideration of molecular models shows that once the first carbon-oxygen bond is severed (4), simple rotation around the remaining carbon-oxygen bond puts the hydride in a good orientation to transfer. Although this would not be expected to be particularly favoured, it is rather similar to some of Kirby's<sup>29</sup> studies of O<sup>-</sup> attack on C=C double bonds, where reactions which are not particularly favoured proceed simply because they have ideal structural orientation. MNDO calculations<sup>30</sup> of charge densities carried out on model structures (6) and (7) show that there is an increased C-H bond dipole when the dioxane ring has been opened and that the hydrogen atom of the anionic hemiacetal intermediate (7) is already carrying a net negative charge which would facilitate hydride transfer.

Consideration of the proposed chair-like transition state (4) for hydride transfer, suggests that this might be of relatively high energy for two reasons: (a), the structure as shown has two axial

\* Theoretically, it should be possible to distinguish between these alternative pathways using a deuterated derivative of (1a) since the monodeuterio diols (3) produced by deuteride transfer would be diastereoisomeric. However, this aspect of the study has not been pursued. In the absence of direct proof, the mechanism shown in Scheme 3 is energetically more attractive.

**Scheme 3.\***

substituents namely CF<sub>3</sub>, and R; (b), there is severe steric compression (A1,4 strain) between R and the *ortho* proton. If the open chain intermediate quinone methide were able to flip conformation, and undergo a rotation, then hydride transfer could occur *via* a lower energy intermediate *i.e.* with CF<sub>3</sub> and R equatorial and no A1,4 strain (Scheme 3). This is the mechanism which we favour.

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