DOI: 10.1002/ejoc.200700244

The Effects of Ring Size and Substituents on the Rates of Acid-Catalysed Hydrolysis of Five- and Six-Membered Ring Cyclic Ketone Acetals

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Keywords: Acetal / Hydrolysis / Cleavage reactions / Kinetics / Reaction mechanism

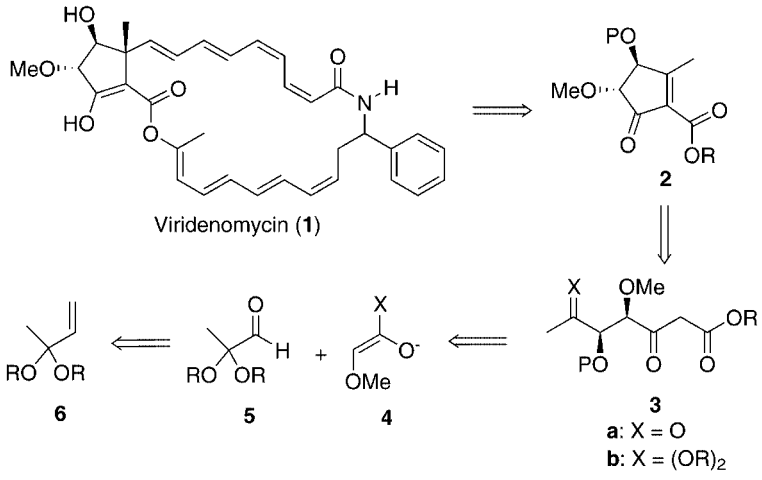
A series of sterically similar five- and six-membered ring cyclic diol-derived ketone acetals have been prepared and their rates of acid-catalysed hydrolysis examined. The rates of hydrolysis are substantially affected by acetal ring conformational stereoelectronic effects and resonance effects depending upon the substituents on the parent ketone; an A1 mechanism of hydrolysis explains the observed effects.

Introduction

As part of an ongoing project aimed at the construction of viridenomycin (**1**),[1,2] we envisaged that a cyclopentenone synthon **2** would be an ideal intermediate from which we could carry out a stereoselective Michael additions for assembly of the northern polyene section. In turn, the cyclopentenone **2** could be obtained by an intramolecular Knoevenagel condensation of the β-keto ester **3a**; the methyl ketone function of which could be derived by an acetal deprotection process. Hence, to access acetal **3b** from an aldol reaction involving a suitable enolate reagent **4**, an acetal aldehyde of type **5** was required. During the development of a synthesis of systems **5**, we discovered surprising differences in the stability of acetal-functionalised precursors to aldehydes **5**, and in this paper, we report these results and rationalise our findings (Scheme 1).

Results and Discussion

Acetal systems of type **5** have not been reported many times in the literature,[3] hence, it was decided that they would be conveniently prepared by ozonolysis of the corresponding vinyl acetals **6**, which are acetal derivatives of methyl vinyl ketone. Attempts to prepare examples of both 5- and six-membered ring acetals was planned using literature methods[4] from 3-chlorobutanone **7** involving acetal formation-elimination sequences, as shown in Scheme 2.



Scheme 1. Retrosynthetic analysis of the cyclopentanone core of viridenomycin.

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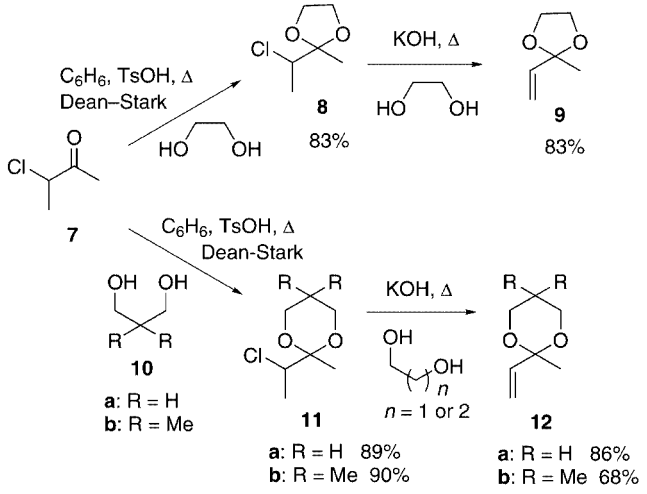


Scheme 2. Formation of 5- and 6-ring acetals **9** and **12**.

Initially, vinyl acetal **9** was prepared according to Scheme 2, however, the corresponding aldehyde resulting from the ozonolysis proved too volatile to isolate. Attention was therefore turned to the corresponding six-membered ring acetals **12** in the hope that the greater ring size might reduce the resulting aldehyde's volatility. Vinyl acetals **12a** and **12b** were prepared by analogous methods to **9**. However, upon isolation and characterisation of acetal **12a** it was noticed that it was unstable upon standing in $CDCl_3$, undergoing acid-catalysed acetal hydrolysis to give methyl vinyl ketone. This is in stark contrast to the five-membered ring acetal **9**, which had shown no such instability. Because of the marked difference in stability between acetals **9** and **12a**, further investigations and kinetic studies of the hydrolyses of each of several acetals were undertaken. In this paper, we report the results of these studies.

Acetal pairs **8** and **9**, and **11** and **12**, were accessed as described above and outlined in Scheme 2. The rates of the acid catalysed hydrolysis of each was carried out in a mixture of $[D_8]$THF and D_2O using various loadings of DCl and each of the reactions followed readily by ^{1}H NMR spectroscopy. In addition, the hydrolysis of vinyl acetal **9** was also carried out using H_2O/HCl in order to determine the kinetic isotope effect. The reactions were performed under *pseudo*-first order conditions (25 equiv. of D_2O) and the rate constants obtained by plotting ln[product] vs. time. Each of the rate constants for all of the acetal hydrolyses are summarised in Table 1.

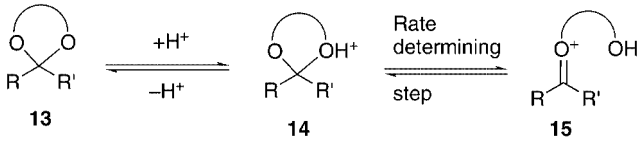
From the results in Table 1, there are several striking observations. Firstly, there is a considerable ring-size effect alone on the rate of hydrolysis for unsubstituted acetals, i.e. ethylene glycol vs. propylene glycol. Hence, comparing Entries 1 and 5, we see a clear transition from a stable acetal under the 50% acid conditions, to a system which does hydrolyse under these conditions. At first sight, comparing Entry 8 with these two Entries (1 and 5) seems to contradict this analysis, however, the 2,2-dimethylpropanediol acetal effectively behaves like ethylene glycol, i.e. the effect of the *gem*-dimethyl substituents is to flatten the normal chair

Table 1. Rate constants for the hydrolysis of cyclic acetals.

Entry	Acetal	Acid (loading/mol-%)	k_1/s^{-1}
1	**8**	DCl (50)	0
2	**9**	DCl (50)	$8.8 \pm 0.3 \times 10^{-4}$
3	**9**	DCl (5)	$6.4 \pm 0.1 \times 10^{-3}$
4	**9**	HCl (50)	$4.7 \pm 0.1 \times 10^{-4}$
5	**11a**	DCl (50)	$2.25 \pm 0.03 \times 10^{-6}$
6	**12a**	DCl (50)	$9.9 \pm 0.6 \times 10^{-3}$
7	**12a**	DCl (5)	$6.2 \pm 0.1 \times 10^{-4}$
8	**11b**	DCl (50)	0
9	**12b**	DCl (50)	$7.33 \pm 0.08 \times 10^{-4}$

conformation of the propylene glycol ester, such that it resembles the 5-ring acetal system and hence, it is also stable under these hydrolysis conditions. In addition, clear allylic effects[5] are observed, i.e. a comparison between acetal pairs in Entries 1 vs. 2, 5 vs. 6, and 8 vs. 9 highlights this effect; in the first pair, there is a large difference in the rate of hydrolysis (stable vs. 10^{-4}), compared with 10^3 difference for the second pair, and a repeat stable vs. 10^{-4} rate for the last. It is also interesting to note from Entries 2 vs. 3, and 6 vs. 7, that with a ten times reduction in acid concentration, there is ten-fold decrease in the rate of hydrolysis. The difference in rate between the five-membered ring vs. six-membered ring also remains essentially constant even under these less acidic conditions.

The graphic difference in reactivity moving from alkyl to allyl substituents supports the most plausible mechanistic interpretation, which is further supported by the observed kinetic isotope effect calculated from Entries 2 and 4 (Table 1), i.e. $k_H/k_D = 0.53$, which is similar to those previously reported and is entirely consistent with hydrolysis occurring by the A1 mechanism as outlined in Scheme 3.[6]



Scheme 3. General mechanistic scheme for first stages of the acid-catalysed ring opening of cyclic acetals.

Although it has been previously shown in rigid, bicyclic systems that the orientation of the oxygen lone pair relative to the protonated oxygen leaving group has a substantial effect on the stability of an acetal to hydrolysis,[7] to the best of our knowledge there are no such reports on the effects of ring-size in such hydrolyses. As discussed above, it appears that the conformation of the acetal ring is certainly an important factor in governing the observed reaction rates and therefore, stereoelectronic effects are the underlying major controlling influences that result from a combination of ring size, conformational and acetal substituents. For unsubstituted five vs. six-ring acetals, the flatter conformation of a five membered ring reduces the capability of the *pseudo*-equatorial oxygen lone pair to interact

with the σ* orbital of the protonated oxygen leaving group, i.e. in structure **14**. Hence, ring opening is either slow (vinyl-substituted) or non-existent (alkyl-substituted).

Addition of a *gem*-dimethyl substituent on the diol-derived section of the six-ring acetal mimics this effect, by flattening the chair conformation and causing misalignment of the equatorial oxygen lone pair to and σ* orbital of the protonated oxygen. Finally, the effect of an additional vinyl group (i.e. **13** R = $CH{=}CH_2$, Scheme 3) to the acetal carbon is to significantly speed up the ring-opening reaction which can be explained by lowering the energy of the forming oxonium ion **15** (R = $CH{=}CH_2$) due to conjugation with the alkene and the allyl cation stabilisation effect which occurs in these systems. The rate increase due to this effect alone is of the order of 10^3 or greater. Although such observations have been previously reported,[8] the combination of ring size, conformational and substituent effects show how important it is to ensure the correct choice of acetal for balancing stability with ease of acetal removal.

Conclusions

This study reinforces previous assertions[9] and unambiguous results[6b] that the acid-catalysed hydrolysis of cyclic acetals involves the formation of a protonated species **14**, followed by discrete bond cleavage to the oxonium ion **15** following an A1 mechanism. Although steric effects relating to R and R′ (on **13**) have also been studied,[10] these have little impact upon the series of compounds examined as part of this study, i.e. **8**, **9**, **11** and **12**, because all have sterically similar functional groups. In the case of these systems, acetal ring strain is also not expected to be major,[11] hence, the observed rates of hydrolysis are substantially affected by acetal ring conformational stereoelectronic effects in all cases, and by resonance effects[11] in the case of conjugated systems **9** and **12**. These conformational stereoelectronic effects (alignment of the equatorial or *pseudo*-equatorial lone pair with the σ* of the breaking C–O bond, see Figure 1) explain why a five-membered ring ethanediol-derived acetal strongly resembles a six-membered ring 2,2-dimethylpropane diol-derived acetal, and why the corresponding propanediol-derived acetals hydrolyse more readily than both of these.

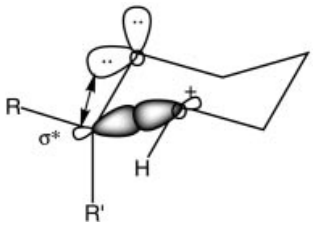


Figure 1. Equatorial lone pair to σ* interaction in a protonated cyclic acetal.

Experimental Section

General Experimental: All ^{1}H NMR spectra were recorded with either a 400 or 500 MHz spectrometers. ^{13}C NMR spectra were recorded at 100 or 125 MHz. Chemical shifts are expressed as parts per million downfield from the internal standard TMS. Column chromatography was performed on silica gel, 60 mesh. TLC was performed on plastic backed silica gel plates with visualisation achieved using a UV lamp or by using a potassium permanganate stain. All other materials were purchased directly from standard chemical suppliers and used without further purification, unless stated otherwise.

2-(1-Chloroethyl)-2-methyl-1,3-dioxolane (8): A solution of 3-chloro-2-butenone (23.2 mL, 0.23 mol), ethylene glycol (12.4 mL, 0.22 mol) and *p*TsOH·H_2O (170 mg, 0.89 mmol) in benzene (330 mL) was heated to reflux in a flask equipped with a Dean–Stark system. After 21 h the mixture was cooled, the benzene evaporated and the crude product purified by kugelrohr distillation to give the product (27.4 g, 83%) as a clear oil. All spectroscopic and analytical properties were identical to those reported in the literature.[4]

2-Methyl-2-vinyl-1,3-dioxolane (9): Compound **8** (10.5 g, 70 mmol) was added to a solution of potassium hydroxide (24 g, 0.43 mol) in ethylene glycol (50 mL) at 130 °C, and the mixture stirred at 125 °C under argon. After 3 h the temperature was increased to 160 °C and product distilled from the reaction mixture to give the product (6.62 g, 83%) as a clear oil. All spectroscopic and analytical properties were identical to those reported in the literature.[4]

2-(1-Chloroethyl)-2-methyl-1,3-dioxane (11a): A solution of 3-chloro-2-butenone (23.2 mL, 0.23 mol), 1,3-propanediol (**10a**, 16.5 mL, 0.23 mol) and *p*TsOH·H_2O (1.0 g, 5.2 mmol) in benzene (330 mL) was heated to reflux in a flask equipped with a Dean–Stark system. After 20 h the mixture was cooled, the benzene evaporated and the crude product purified by kugelrohr distillation to give the product (33.2 g, 89%) as a clear oil. B.p. 100 °C at 1 Torr. IR (film): $\tilde{\nu}_{max}$ = 2960, 2872, 1480, 1449, 1372, 1247, 1153, 1057 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.43 (s, 3 H, Me), 1.45 (d, ^3J = 6.8 Hz, 3 H, Me), 1.48–1.57 (m, 1 H, CH_2), 1.76–1.86 (m, 1 H, CH_2), 3.77–3.97 (m, 4 H, 2 × CH_2O) and 4.12 (q, ^3J = 6.8 Hz, 1 H, CHCl) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 15.7, 19.2, 25.2, 59.9, 60.2 and 99.4 ppm. MS (ES$^+$): *m*/*z* = 167 [M + H$^+$, ^{37}Cl], 165.0677 [M + H$^+$, $C_7H_{14}O_2{}^{35}Cl$, requires 165.0677, 100%].

2-Methyl-2-vinyl-1,3-dioxane (12a): To a stirred solution of potassium hydroxide (14.4 g, 0.26 mol) in 1,3-propanediol (30 mL) at 125 °C was added **11a** (7.10 g, 43.2 mmol) and the mixture stirred at 125 °C. After 2 h the temperature was increased to 165 °C and the product distilled from the reaction mixture and separated from water to give product (4.73 g, 86%) as a clear oil. B.p. 123 °C at 760 Torr. IR (film): $\tilde{\nu}_{max}$ = 2962, 1645, 1403, 1369, 1249, 1191, 1143, 1086 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.38 (s, 3 H, Me), 1.94–2.06 (m, 2 H, CH_2), 3.78–3.98 (m, 4 H, 2×CH_2), 5.36 (dd, ^3J = 10.8, ^4J = 1.2 Hz, 1 H, =CHH), 5.39 (dd, ^3J = 17.6, ^4J = 1.2 Hz, 1 H, =CHH) and 5.80 (dd, ^3J = 17.6, ^3J = 10.8 Hz, 1 H, $CH{=}CH_2$) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 25.8, 29.0, 61.2, 99.2, 118.1, 138.9 ppm. MS (ES$^+$): *m*/*z* 129.0911 [M + H$^+$, $C_7H_{13}O_2$, requires 129.0910], 99, 79 and 60 (100%).

2-(1-Chloroethyl)-2,5,5-trimethyl-1,3-dioxane (11b): A stirred solution of 3-chlorobutanone (23.2 mL, 0.23 mol), 2,2-dimethyl-1,3-propanediol (24 g, 0.23 mol) and *p*TsOH·H_2O (1.0 g, 5.2 mmol) in benzene (330 mL) was heated to reflux in a round bottomed flask equipped with a Dean–Stark apparatus. After 23 h the mixture was cooled, the benzene evaporated and the resulting oil dissolved in

Et_2O (250 mL). The solution was washed with satd. aq. $NaHCO_3$ (150 mL), water (150 mL) and brine (150 mL), dried ($MgSO_4$) and evaporated to give product (40.3 g, 90%) as a yellow oil. IR (film): $\tilde{\nu}_{max}$ = 2980, 1473, 1396, 1329, 1311, 1213, 1080 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.83 (s, 3 H, CMeMe), 1.06 (s, 3 H, CMeMe), 1.43 (s, 3 H, $MeCO_2$), 1.51 (d, ^3J = 7 Hz, 3 H, MeCH), 3.44 (d, ^3J = 11.5 Hz, 1 H, CHH), 3.46 (d, ^3J = 11.5 Hz, 1 H, CHH), 3.59 (t, ^3J = 12 Hz, 2 H, CH_2) and 4.11 (q, ^3J = 7 Hz, 1 H, CHCl) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 15.2 (CMeMe), 19.3 (CMeMe), 22.4 ($MeCO_2$) 22.9 (MeCHCl), 30.1 (CMe_2), 60.5 (CHCl), 70.6 (CH_2), 70.8 (CH_2) and 99.3 (CO_2) ppm. MS (CI^+): *m/z* (%) = 195 [M^+, ^{37}Cl], 193 (100) [M^+, ^{35}Cl,], 159, 129. HRMS (ES^+) 193.0989 [M + H^+], $C_9H_{18}ClO_2$, requires 193.0990.

2,5,5-Trimethyl-2-vinyl-1,3-dioxane (12b): To a stirred solution of potassium hydroxide (28.8 g, 0.50 mol) in ethylene glycol (60 mL) at 120 °C was added 11b (8.63 g, 44.4 mmol) and the temperature increased to 160 °C. After 23 h the mixture was cooled, diluted with water (300 mL) and extracted with Et_2O (3 × 150 mL). The combined organic phase was washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated to give product (4.79 g, 68%) as a pale yellow oil. IR (film): $\tilde{\nu}_{max}$ = 2689, 1645, 1472, 1396, 1369, 1239, 1089 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.70 (s, 3 H, CMeMe), 1.16 (s, 3 H, CMeMe), 1.40 (s, 3 H, $MeCO_2$), 3.32 (d, ^3J = 11 Hz, 2 H, 2×CHH), 3.58 (d, ^3J = 11 Hz, 2 H 2×CHH), 5.32–5.39 (m, 2 H, CH_2), 5.75 (dd, ^3J = 17.6, ^3J = 10.8 Hz, 1 H, CH=CH_2) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 22.1 (CMeMe), 22.8 (CMeMe), 28.7 ($MeCO_2$), 30.2 (CMe_2), 71.6 (2×CH_2), 98.8 (CO_2), 118.0 (CH_2=CH), 138.6 (CH_2=CH) ppm. MS (EI): *m/z* = 157, 141, 129, 71, 43. HRMS (ES^+) 157.1222 [$C_9H_{17}O_2$, M + H^+, requires 157.1223].

General Procedure for Acetal Hydrolysis: The appropriate acetal (0.23 mmol) was dissolved in [D_8]THF (0.75 mL) and observed by ^1H NMR spectroscopy. D_2O (0.100 mL) and the appropriate amount of DCl in D_2O (0.010 mL) were added (giving acid concentrations of 0.16 M and 0.016 M for 50% and 5% loadings respectively), the mixture shaken and the hydrolysis followed over time at 293 K by ^1H NMR spectroscopy.

Supporting Information (see also the footnote on the first page of this article): All kinetic NMR spectroscopic data is available.

Acknowledgments

We are grateful to the Engineering and Physical Sciences Research Council (EPSRC) for a DTA award to J. P. K. and to the EPSRC mass spectrometry service at the University of Wales, Swansea.

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Received: March 19, 2007
Published Online: May 15, 2007

