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The Relative Rate of Hydrolysis of a Series of Acyclic and Six-Membered Cyclic Acetals, Ketals, Orthoesters, and Orthocarbonates

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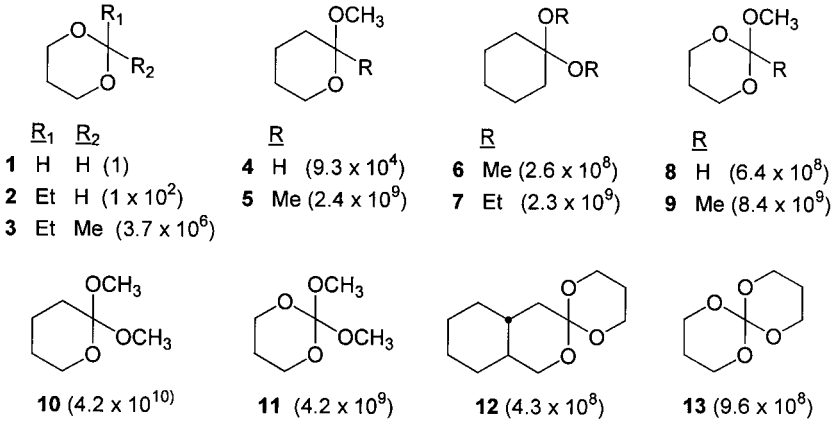
Abstract—The relative rate of hydrolysis of these compounds is rationalized by considering the influence of steric, inductive and stereoelectronic effects on the hydrolysis reaction mechanism.

A better understanding of the hydrolytic behaviour of acyclic and cyclic acetals, ketals, orthoesters and orthocarbonates is important for mechanistic reasons[1] and can be useful in organic synthesis either for the design of stereocontrolled processes or for the selection of appropriate hydroxyl and carbonyl protecting groups.[2] We wish to report the relative rate of hydrolysis of the series of acetal related compounds **1**–**13** described in Scheme 1 (relative rates are indicated in parentheses) and to provide a simple qualitative explanation for the observed results. Interestingly, there is an enormous difference in rates up to 10^{10} times, between **1** and **10**. The hydrolysis of acyclic compounds **14**–**22** has been previously reported[3,4] and their relative rate, compared to compound **1**, is shown in Scheme 2. These relative rates can be explained according to the following stereoelectronic model.

Cyclic compounds **1**–**3**, **12** and **13** are hydrolysed via an endocyclic C–O bond cleavage which corresponds to the reverse of an intramolecular process, and will be discussed separately. An exocyclic C–O bond cleavage can be safely assumed to take place with all the other cyclic compounds (i.e. **4**–**11**). Therefore, the hydrolysis of **4**–**11** corresponds to the reverse of a bimolecular process as in the acyclic structures represented in Scheme 2. In all these compounds, the leaving group is either methanol or ethanol, but since the relative rate has been measured in some cases with both alkoxy groups (**6/7**; **14/15**; **17/18**; **21/22**), a direct correlation can therefore be made between all these compounds.

Generally speaking, there is an increase in hydrolysis rate with a higher degree of substitution at the central carbon of each functional group. For instance, when a hydrogen atom



Scheme 1.

Keywords: acetals; ketals; orthoesters; orthocarbonates; stereoelectronic effects; hydrolysis.

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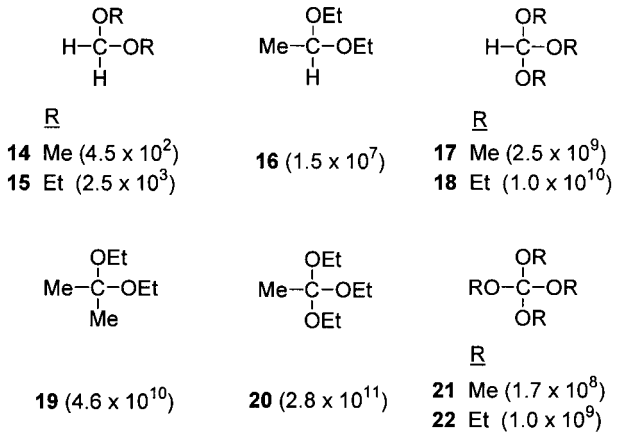


Scheme 2.

is replaced by an alkyl or an alkoxy group, an important rate acceleration is observed. This can be explained by a steric decompression factor as the tetrahedral intermediates collapse to the trigonal counterpart or by the fact that the rate of hydrolysis increases with the stability of the corresponding alkoxy carbenium ion intermediate, which in turn is directly related to the relative stability of the final hydrolysis product. Thus, the relative rate follows the order formaldehyde (CH_2O)<aldehyde (RCHO)<ketone (RCOR)< ester (RCOOR). At first sight, carbonates ($CO(OR)_2$) appear to be an exception to this trend. For instance, orthocarbonate **22** is hydrolysed at a slower rate than orthoester **20**.

It should be pointed out that all acyclic and cyclic compounds (except orthocarbonates in some cases, vide infra) can take a conformation with the necessary antiperiplanar oxygen lone pair orientation to the OR leaving group,[5,6] i.e., one for acetal, two for orthoester and three for orthocarbonate. On that basis, stereoelectronic effects could influence both the protonation as well as the C–O bond cleavage steps. Thus, the anomeric effect in the starting compound should directly influence the basicity of the potential leaving group.[6] Also, once an alkoxy group is protonated, it becomes a much better leaving group and the corresponding stabilizing anomeric effect should increase considerably in that protonated intermediate. This is supported by ab initio calculation which gives a stabilizing anomeric effect of 1.0 kcal/mol for dihydroxy methane and about 6 kcal/mol for protonated dihydroxy methane.[7] The experimental data in Schemes 1–2 show that the ethoxy compounds are hydrolysed (cf. **6/7**; **14/15**; **17/18** and **21/22**) 4 to 9 times faster than the corresponding methoxy derivatives because the ethoxy group is more basic (more readily protonated than the methoxy group) and therefore a better leaving group.

The highest energy level on the reaction coordinates of the hydrolytic process need not be the same for all compounds shown. For instance, in acetals (including formaldehyde) it is well established that the slow step is the cleavage of the protonated acetal, not the initial protonation.[8] Since aldehydes have one alkyl group and formaldehyde none, the larger rate observed for compound **16** by comparison with **15** is simply due to the fact the former leads to a more stable alkoxycarbenium ion.[9]

There is also a large difference of rate ($\sim 10^3$) between alkyl acetal **16** and ketal **19**. This can be explained by the facts that the two alkyl groups in ketal **19** increase the basicity of the OR leaving group due to electron donation. The ejection of ethanol from the protonated ketal is thus easier in **19** than in **16**. Also, the alkoxycarbenium intermediate derived from ketal **19** should be more stable than the one derived from **16** (ab initio calculation shows that CH_3COCH_3 is more stable than the isomeric CH_3CH_2CHO by about 7 kcal/mol).[10] Qualitatively, the hydrolysis of diethyl ketal **19** shows that the slow step is the formation of the alkoxycarbenium ion where the protonation step and the breaking of the C–O bond are considered as a single step.[11] AM1 calculation suggests that protonated ketal species is the highest energy point on the hydrolysis reaction coordinates for the ketals, thus favouring a concerted protonation-cleavage process.[12] Interestingly, orthoester **20** (which has the same degree of substitution as **19**) has a slightly higher rate and it has been established that the slow step in alkyl orthoester hydrolysis is the initial protonation.[9,13]

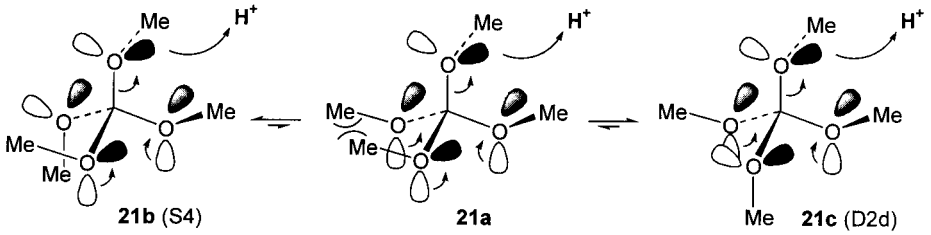
Orthoesters are readily hydrolysed because there are two oxygen lone pairs that can increase the basicity of the leaving group and facilitate the hydrolysis. Since orthoester **20** has one additional alkyl group, its rate is increased compared to orthoformate **18**.

The cyclic compounds are now examined. Compounds **4** and **5** represent the cyclic versions of acyclic acetal **16** and acyclic ketal **19**. Cyclic ketals **6** and **7** have the same degree of substitution as ketal **5** and the rates are in the same range. The same is true for orthoesters **8** and **9** which are cyclic versions of orthoformate **17** and orthoester **20**, respectively.

As mentioned previously, acyclic orthocarbonate **22** (and also **21**) appears to be an exception to the general trend as it is hydrolysed at a slower rate than orthoester **20**.[14] In principle, three oxygen lone pairs can be antiperiplanar to the fourth alkoxy group in an orthocarbonate, this should lead to an increase in basicity and facilitate the protonation as well as the ejection of the leaving group. The resulting trialkoxycarbenium ion should also be highly stabilized through electronic delocalization.

However as previously discussed,[14] conformations of acyclic orthocarbonates (cf. **21a**, Scheme 3) that have three oxygen lone pairs antiperiplanar to a C–O bond are very high in energy due to severe steric repulsion between two methyl groups. Indeed, such acyclic orthocarbonates are known to exist in the ground state[15] conformations **21b** (S4 symmetry) and **21c** (D2d symmetry) which both have only two oxygen lone pairs antiperiplanar to a potential OR leaving group. This should lead to a reduction in basicity of the OR leaving group due to the inductive effect of the third oxygen which does not have an antiperiplanar lone pair. On that basis, it is not surprising that **22** hydrolyses slower than **20**.

To obtain further support for this explanation, the relative rates of hydrolysis of compounds **10**, **11**, and **21** were compared. Cyclic orthoester **10** hydrolysed 10 times faster than cyclic orthocarbonate **11** which in turn hydrolyses 25



Scheme 3.

times faster than acyclic orthocarbonate **21**. Due to its cyclic nature, orthocarbonate **11** can take conformation **11a** (Scheme 4) with three antiperiplanar oxygen lone pairs without severe steric interactions. Its hydrolysis should normally be faster than that of cyclic orthoester **10** which has only two antiperiplanar lone pairs (cf. **10a**). However, 6-31G** calculations[16] on the relative stabilities of the various conformers of **10** and **11** reveal that both **10a** and **11a** are not the favored conformers. Rather **10b** was more stable than **10a** by 0.2 kcal/mol, another conformer, **10c**, was also found but was less stable than **10a** by nearly 1 kcal/mol. In the case of the orthocarbonate **11**, **11b** was more stable than **11a** by about 1 kcal/mol. The most stable conformation **10b** is prone to endocyclic stereoelectronic effects assisted protonation and cleavage (two lone pairs are antiperiplanar to the leaving group). This process (reverse of intramolecular process) is entropically disfavoured. On the other hand, the exocyclic cleavage can occur readily on the conformer **10a** which is only 0.2 kcal/mol higher in energy than **10b**, **10c** also leads to the exocyclic (entropically favoured) cleavage. It comes out that protonation of **10b** slowers down slightly the speed at which the orthoester **10** gets hydrolysed. The same effect is dramatically emphasised in the case of the orthocarbonate **11**, because in that case the conformer **11b** which undergoes endocyclic cleavage (three lone pairs are antiperiplanar to the leaving group) accounts for 84% of the mixture of conformers. Therefore, protonation and cleavage of the exocyclic axial methoxy group (Re-inter process) is very disfavoured, only a small percentage (~16%) of the ground state conformers are ready to undergo exocyclic cleavage which is much less than for the orthoester **10**. It may seem surprising that the conformer **11b** is so much stabler than **11a**, because the steric effects are similar is both conformations. But, interestingly, the X-ray structure of cyclic ozonide **23** shows that it exists in a solid state conformation where the $O–CH_3$ group points towards the ring as in **11b**.[19] This unexpected behaviour may be due to a stronger exo anomeric effect[6,20] of the OCH_3 group in **11b**. On that basis, one can understand why cyclic orthocarbonate **11** would be more reactive than acyclic orthocarbonate **22** but less reactive than cyclic orthoester **10**.[†]

Tricyclic orthoester **12** and bicyclic orthocarbonate **13** were also compared. For the first time, an orthocarbonate is not hydrolysed slower than an orthoester. Since, orthocarbonate **13** is now fixed in a conformation (**13a**) (Scheme 5) with three oxygen lone pairs antiperiplanar to the leaving group, it is perhaps not surprising that its hydrolysis is slightly faster than **12** which has only two antiperiplanar lone pairs (cf. **12a**). These results further confirm the above rationalisation although the difference of rate between **12** and **13** is not very large. This may be due to the fact that adding a fourth oxygen atom reduces the oxygen basicity of orthocarbonates due to the inductive effect. Indeed, with such a high rate of hydrolysis, one can probably assume that protonation is part of the initial rate determining step for these orthocarbonates. On a statistical basis, compound **13** has two C–O bonds that can be cleaved with full stereoelectronic control (3 antiperiplanar lone pairs) (cf. **13a**). However, the same statistical arguments holds also for orthoester **12** (cf. **12a**), thus, only the inductive effect remains to explain the slight difference of rather between **12** and **13**.

It remains to explain the relative rates of hydrolysis of cyclic acetals **1**–**2** and ketal **3**. As expected, their relative rate increases with the degree of substitution at the central

[†] In our discussion about the hydrolysis of orthoesters and orthocarbonates we assumed that the population of ground state conformers significantly dictates the hydrolysis reaction kinetics. One referee raised the point that this matter should be clarified; here is our answer to this issue:

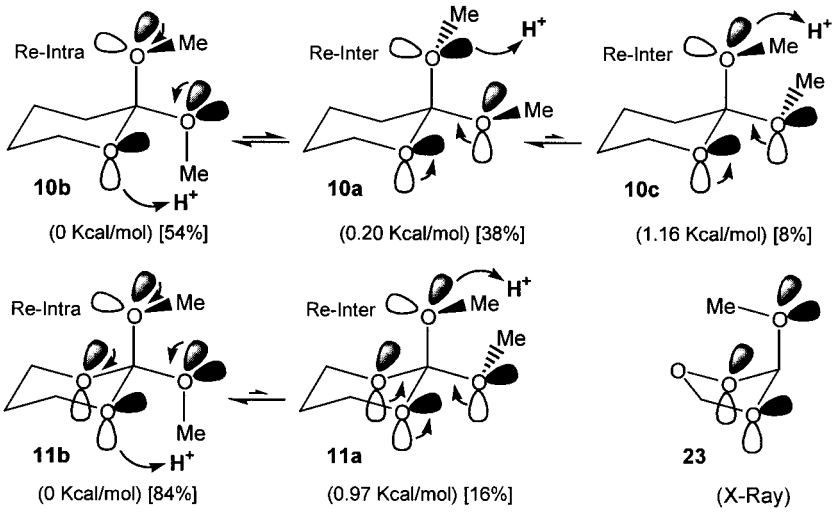
When dealing with various conformers of a molecule leading to separate products, two extreme situations can be considered:[17]

1. The conformational barriers are substantially lower than the reaction barriers; this case is known as the Curtin–Hammett principle. According to this principle, the population of products is determined by the difference between the free energies of transition states.
2. The conformational barriers are substantially higher than the reaction barriers; this case is known as the situation of conformational equilibrium control. In this limiting case the ratio of products is equal to the ratio of the population of the starting states.

The hydrolysis of gem polyoxygenated species follows two mechanisms according to the number of oxygen atoms at the central carbon center:

1. The slow step in acetals hydrolysis is the bond breaking step. Those molecules are not very basic and it is always possible for the protonated species to lose their proton; therefore the neutral species can equilibrate freely and the Curtin–Hammett principle applies. On the other hand it is worth noting that the protonated species cannot equilibrate because the anomeric effect energy has a very high value of 6 kcal/mol [7].

When orthoesters and orthocarbonates are put in acidic aqueous mediums of various strength, they become protonated and the bond cleavage takes place in a concerted fashion. Those molecules are very basic and all the different conformers having the proper number of antiperiplanar or synperiplanar lone pairs (2 for orthoesters and 3 for orthocarbonates) should display equal proton affinity. There exist experimental facts[9,13,18] which indicate that protonation and cleavage occur in one single step; as a result equilibrium of the various equally very basic neutral species under acidic conditions is unlikely. Nevertheless, even if the protonated species still had some very short lifetime as high energy intermediates, then they would be unable to equilibrate because they have geometries which prevent the various OR groups from rotating freely: When protonation of the most basic oxygen atom occurs, all the remaining oxygen atoms and the central carbon can be considered as sp2 hybridized, the C–OR bonds become like double bonds. Therefore, under acidic conditions, the Curtin–Hammett principle does not hold for orthoesters and orthocarbonates; instead the conformational equilibrium control applies. Consequently, the relative energies of the various equally basic neutral conformers before the very fast protonation step becomes meaningful.



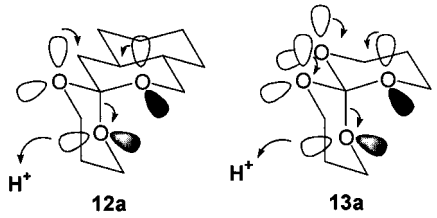
Scheme 4.

carbon. However, their rates are much smaller than the other compounds having a similar degree of substitution, i.e. **14** (or **15**), **4** and **5** (or **6**) respectively. This is due to the fact that with compounds **1**–**3** cleavage of the ring must take place (endocyclic cleavage). Being the reverse of an intramolecular process, their rates of cleavage are lower due to an entropy factor as well as an enthalpy factor both of which disfavoured the opening of the 6-membered ring. Indeed, since the transition states for these hydrolysis reactions are late, their geometry should resemble that of the resulting oxycarbenium ion. On that basis and as previously discussed,[12] in six-membered case, there is a severe steric strain associated with the fact that the cleaving C–O bond must remain parallel with the developing π system of the alkoxycarbenium ion. A similar conclusion can be drawn by comparing **12** and **13** with **10** and **11** respectively. Indeed **12** and **13** are hydrolysed more slowly as they represent the reverse of an intramolecular process.

Experimental

The infrared (IR) spectra were taken on a Perkin–Elmer 1600 series FTIR. Nuclear magnetic resonance (NMR) spectra were recorded on a Brüker AC 300 instrument. Mass spectra (MS) were obtained on a ZAB-IF spectrometer. Flash chromatography was performed on silica gel Merck 60, 230–400 mesh.

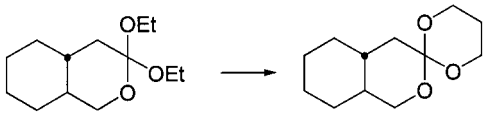
Compounds **1**,[21a] **2**,[21b] **3**,[21c] **4**,[21d] **5**,[21e] **6**,[21f] **7**,[21g] **8**,[21h] **9**,[21i] **10**,[21j] **11**,[21k] and **13**[21l] are known in literature.



Scheme 5.

Synthesis of cyclic orthoester 12

To a stirred solution of 3,3-diethoxy-octahydro-isochromene[22] (0.51 g, 2.3 mmol) and 1,3-propanediol (0.228 g, 3.0 mmol) in dichloromethane (5 mL) was added TFA (15 μL). The resulting solution was stirred for 20 h at room temperature. The solvent was removed and the residue was purified by flash chromatography (hexane/ethyl acetate/triethylamine=20/80/1) to give compound **12** (0.333 g, 68%) as an oil.



IR (neat): 2923, 1450, 1381 cm^{-1}; ^1H (C_6D_6): 4.26–4.181 (m, 1H), 4.00–3.91 (m, 1H), 3.64–3.56 (m, 3H), 3.22 (t, J=10.0 Hz, 1H), 2.03–0.83 (m, 14H). ^{13}C NMR ($CDCl_3$): 10.38, 67.86, 59.27, 58.19, 41.06, 36.61, 32.38, 27.09, 25.83, 25.70, 24.54. MS (*m/e*): 212 (M^+).

Relative rate of hydrolysis

The kinetic hydrolyses of the compounds described in Scheme 1 were carried out in an NMR tube at 25°C and followed by ^1H NMR spectroscopy. The disappearance of compounds in the hydrolysis follows first order kinetics. The observed rate constants $k1$ were evaluated from the stops of semilogarithmic plots of the integrations of the selected NMR peaks against time. The relative rates were obtained by comparing their observed rate constants $k1$ determined by carrying competitive hydrolysis of a mixture of two compounds (0.05–0.1 mmol) in D_2O–CD_3CN (1/4, 0.5 mL) in the presence of hydrochloric acid. Study[23] has shown that the variations of $k1$ with increase of hydrochloric are linear and the second order rate constants $k2$ can be described as $k1=k2\times[H^+]$. The acid concentration is 2×10^{-4} M for the hydrolysis of compounds **3**–**13** and 0.5 M for the less reactive compounds **1** and **2**.

Considering the large differences of hydrolytic rates,

selected pairs of compounds were used for competitive hydrolysis as shown in the following table:

Pairs of compounds	**1**	**2**	**4**	**6**	**8**	**11**
	2	**4**	**6**	**3, 5, 7, 8, 11**	**12, 13**	**10**

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