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Experimental Evidence for the Stereoelectronically Controlled Hydrolysis of Orthocarbonates

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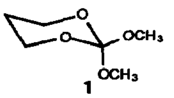
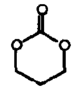
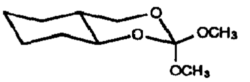
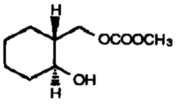
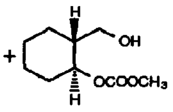
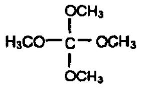
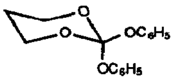
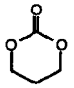
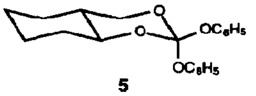
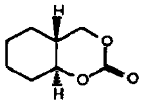
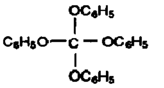
Abstract: *The acid hydrolysis of cyclic and acyclic orthoesters 1-6 is reported. The results obtained are explained by taking into account the principle of stereoelectronic control.*

The H_3O^+-catalyzed hydrolysis of tetraethyl orthocarbonate is about an order of magnitude slower than triethyl orthoformate.[1] Similar results were observed for the relative rate of hydrolysis of tetraphenyl orthocarbonate and triphenyl orthoformate, Sinnott *et al.*[2] concluded that this information could be used as evidence that neither a steric nor any transition state "stereoelectronic effect" is responsible for the lower reactivity of the orthocarbonates. We wish to report the acidic and basic hydrolysis of a series of cyclic and acyclic orthocarbonates which demonstrate that contrary to Sinnott's conclusion, stereoelectronic effects is one of the main factors controlling the relative rate of hydrolysis of orthocarbonates. The hydrolytic behavior of monocyclic and bicyclic dimethyl orthocarbonates **1** and **2** (see Table) were compared with tetramethyl orthocarbonate (**3**). A similar comparison was carried out with the corresponding phenyl orthocarbonates **4**, **5**, and **6**. Orthocarbonates **1**[3], **3**, **4**[4] and **6**[5] are known compounds. Starting from *trans* 2-hydroxymethylcyclohexanol,[6] its reaction with tetramethoxymethane (**3**) (*p*-TSOH cat., r.t., 48 h) gave orthocarbonate **2**,[7] whereas that with diphenoxy dichloromethane[8] (Et_3N, CH_2Cl_2, r.t., 3 h) provided diphenyl orthocarbonate **5**.[7]

Hydrolysis of the orthocarbonates was carried out in D_2O-CD_3CN with a catalytic amount of hydrochloric acid (0.1 N) and the results obtained by ^{1}H-NMR analysis are summarized in the Table. The relative rate was determined by carrying competitive experiments of a mixture of two orthocarbonates (either **1** with **2**, **3** or **4** or **4** with **5** or **6**). The two cyclic dimethyl orthocarbonates **1** and **2** are more readily hydrolyzed than the tetramethyl derivative **3**. Interestingly, monocyclic orthocarbonate **1** gave a 1:3 mixture of the corresponding cyclic and acyclic carbonates **7**[9] and **8**.[7] On the other hand, bicyclic orthocarbonate **2** gave a 1:1 mixture of the two acyclic hydroxy carbonates **9**[7] and **10**,[7] only trace amount of the corresponding cyclic carbonate **12** being observed. Tetraphenyl orthocarbonate (**6**) was found inert under these mild acidic conditions. The cyclic orthocarbonates **4** and **5** are less reactive than orthocarbonates **1** and **2**, and yield only their corresponding cyclic carbonates **7** and **12**[7] respectively.

As expected, the methyl orthocarbonates **1-3** and tetraphenyl orthocarbonate (**6**) were all found to be unreactive under aqueous basic conditions [orthocarbonate (0.01 mmol), NaOH (0.05 mmol) in D_2O-CD_3CN (2:3 ratio, 500 uL) at 25°C, 10 days]. On the other hand, and unexpectedly, the cyclic diphenyl orthocarbonates **4** and **5** were found to be hydrolyzed within 10 h under the same basic conditions yielding the corresponding diols and phenol. Accordingly, it was also found that orthocarbonates **4** and **5** are also readily converted into orthocarbonates **1** and **2** respectively by treatment with sodium methoxide in methanol at room temperature.

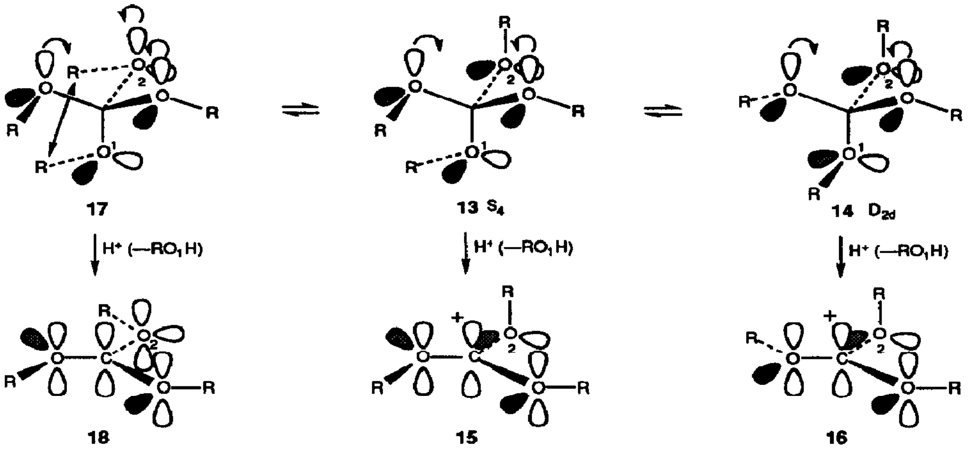
Table. Acid Hydrolysis of Orthocarbonates

Orthocarbonate	Relative rate	Products
 1	55	 7 +  $CH_3OC(=O)OCH_2CH_2CH_2OH$ 8 (1 : 3)
 2	55	 9 +  10 (1 : 1)
 $H_3CO-C(OCH_3)_2-OCH_3$ 3	2.2	 $CH_3OC(=O)OCH_3$ 11
 4	1	 7
 5	1	 12
 $C_6H_5O-C(OC_6H_5)_2-OC_6H_5$ 6	inert	

Discussion

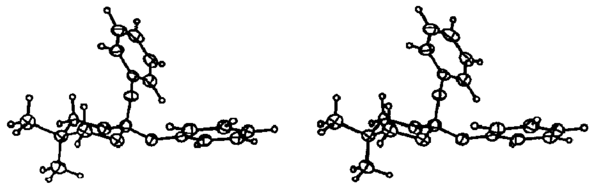
These results can be rationalized by taking into account the relative basicity of the alkoxy and phenoxy groups and the reactive conformation of the orthocarbonates while respecting the principle of stereoelectronic control.[10] The phenyl orthocarbonates are hydrolyzed at a slower rate than the corresponding methyl compounds in spite of the fact that the phenoxy is in principle a better leaving group than the methoxy group. Such results are best explained by invoking a rate determining protonation step during the hydrolysis reaction of the phenyl orthocarbonates.

Tetraphenyl orthocarbonates are known[11] to exist in conformations S_4 **13** or D_{2d} **14** which are sterically free. In **13** and **14**, there are only two oxygen atoms which have a lone pair oriented antiperiplanar to a potential leaving OR group. Thus upon protonation (for example O_1-R) **13** and **14** should give respectively the carbonate cations **15** and **16** in which the O_2R group has its oxygen lone pairs not conjugated. In other words, the lone pairs of the O_2R group cannot be used to expel the leaving O_1R group, consequently, the inductive effect of the C-O_2R bond should slow down the formation of the not fully conjugated cations **15** and **16**. Formation of ions **15** and **16** must therefore be high energy processes. In order to have three oxygen atoms with lone pairs properly oriented to eject a leaving OR group, the orthocarbonate must undergo rotation to produce other conformations like **17** which are strongly destabilized by a severe steric repulsion between two R

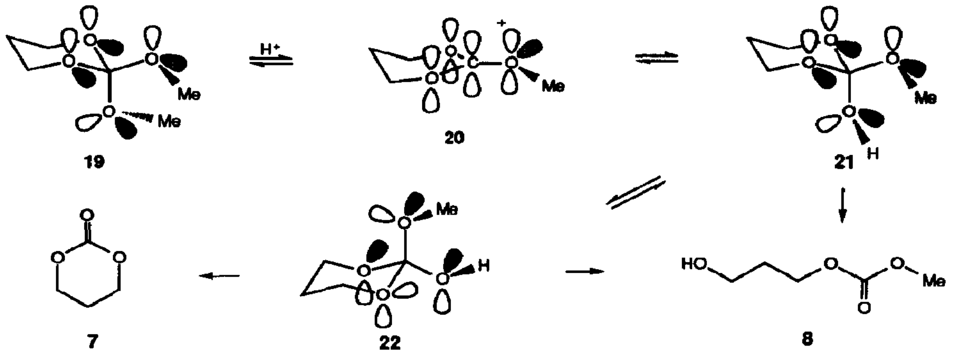


groups (see arrow).[11] Once a conformation like **17** is reached, appropriate protonation of the O$_1$R group will then produce the fully conjugated and thus more stable carbonate cation **18**. Thus, the hydrolysis of acyclic orthocarbonate is slowed down either by stereoelectronically disfavored processes such as **13** → **15** or **14** → **16** or by sterically disfavored processes such as **13** → **17** → **18**. Replacing the RO$_2$ group by H in **13** and **14** gives the corresponding orthoformate conformations which can yield the ions **15** and **16** (RO$_2$=H) with the help of two oxygen lone pairs. Acyclic orthoformate can thus be easily hydrolyzed in their ground state conformation in agreement with experimental results.

Examination of molecular models indicates that cyclic orthocarbonates must exist in a conformation equivalent to **19** which has minimal steric interactions between the two OMe groups and with the ring. This was confirmed by the X-ray analysis[12] of the crystalline 5,5-dimethyl-2,2-diphenoxy-1,3-dioxane (see stereo



ORTEP drawing). The larger rate of hydrolysis of the cyclic orthocarbonates are thus readily explained by the fact that the ground state conformation **19** has three oxygen atoms, each having an electron lone pair antiperiplanar to the axial OR group. It remains to explain on this basis the various reaction products. Upon protonation of the axial OMe group, monocyclic orthocarbonate **1** (≡**19**) must produce the fully conjugated cyclic carbonate cations **20** which upon reaction with water must give the hemiorthocarbonate **21** having an axial OH group. This intermediate **21** can undergo equilibration via chair inversion to give a mixture of **21** plus **22** having an equatorial OH group. After appropriate protonation, cleavage with stereoelectronic control (3 oxygens having each a lone pair antiperiplanar to the leaving group) of **21** and **22** can take place, intermediate **21** yielding only the acyclic methylcarbonate **8** and intermediate **22** giving both the cyclic and the acyclic carbonates **7** and **8** in accord with the experimental results.



In the case of bicyclic **2**, the tetrahedral intermediate will have a configuration corresponding to **21** which cannot undergo a chair inversion, thus only the acyclic carbonates **9** and **10** can be produced. The hydrolysis of orthocarbonates **4** and **5** must follow a course similar to that of **1** and **2** with the exception that once the tetrahedral intermediates are produced, only formation of cyclic carbonate takes place because the phenoxy group is the preferred leaving group. The acyclic phenyl carbonates **10** (CH_3=C_6H_5)[7] (produced by another route), was shown to be stable under the hydrolysis conditions indicating that the formation of cyclic carbonate **12** is a kinetically controlled process. Thus, in the case of bicycle **5**, the formation of carbonate **12** must take place from the breakdown of a tetrahedral intermediate having an axial OH group (*cf.* **21**, CH_3=C_6H_5) via a stereoelectronically controlled boat like transition state.

The unexpected hydrolysis under basic conditions of **4** and **5** can be explained by the fact that these two acyclic orthocarbonates exist in ground state conformations having three oxygen lone pairs antiperiplanar which can readily expel a very good phenoxy leaving group. These reactions are probably the results of SN_2 processes.

Sinnott's conclusion that there cannot be a transition state "stereoelectronic effect" responsible for the lower reactivity of the orthocarbonate was based on an incorrect statement[2] "in the S_4 conformation each C-O bond is antiperiplanar to an Sp^3 lone pair of electrons on each of the remaining three oxygen atoms". On the contrary, the S_4 (see **13**) can have only two such lone pairs.[11] This preliminary work which demonstrates clearly the importance of stereoelectronic effects in the hydrolysis of orthocarbonates will be followed by a more complete and detailed kinetic studies.[13]

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