SECTION 6

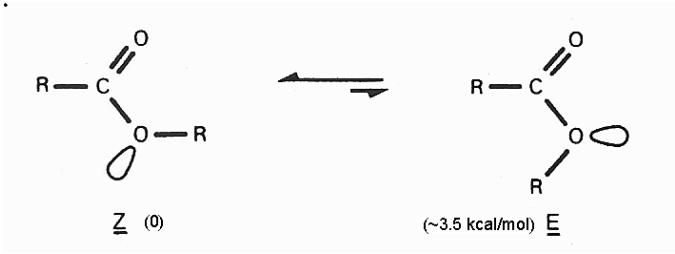
Stereoelectronic Effects (S.E.)

and Reactivity of Esters and Related Functions

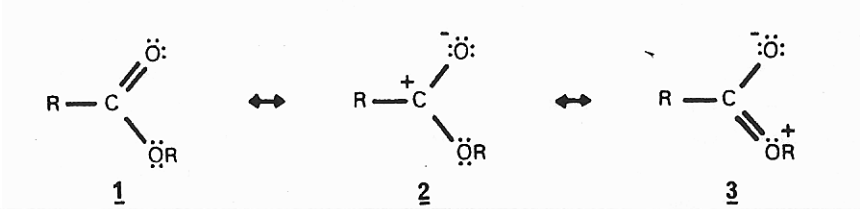
(2018)

Esters and Related Functions

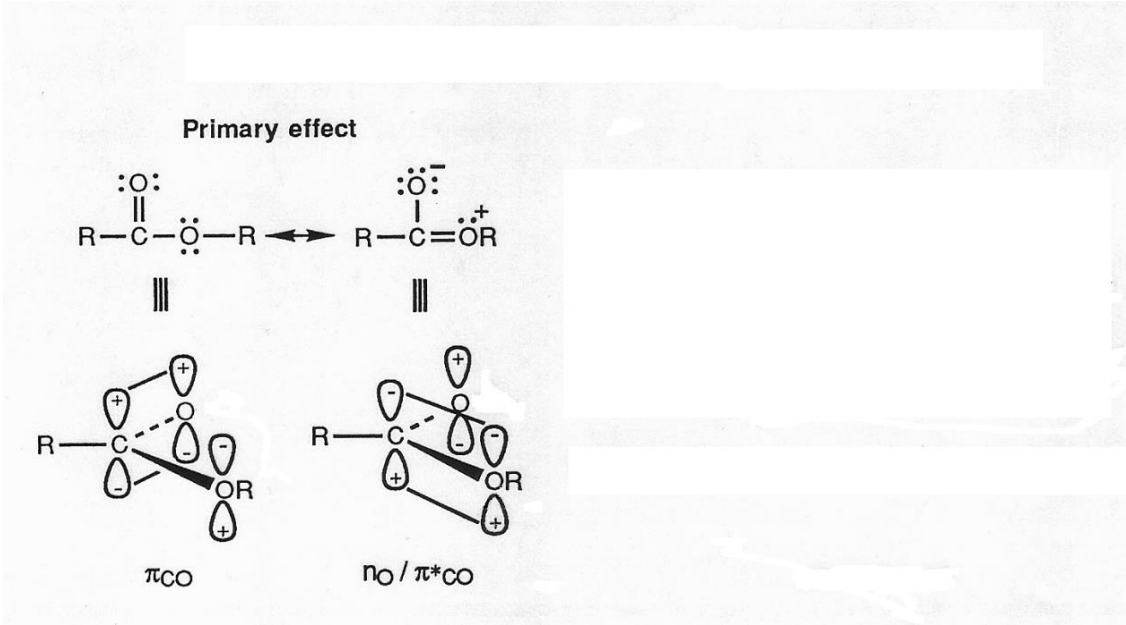
2 conformations



Primary Stereoelectronic Effects

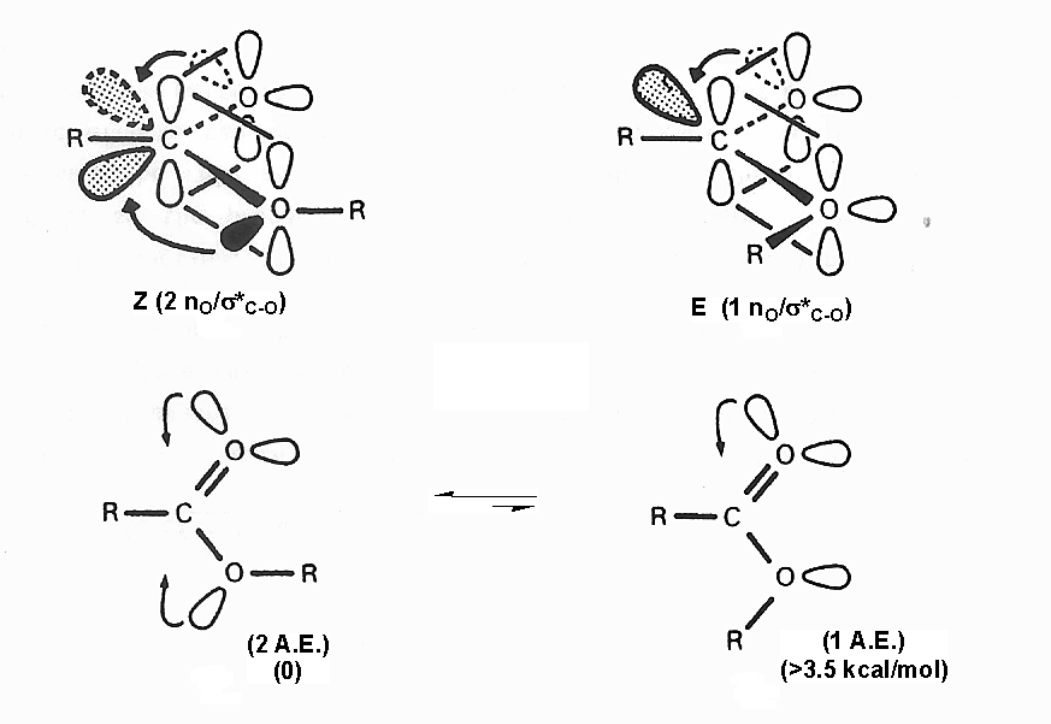


Resonance Structure and Stereoelectronic Effect in Ester

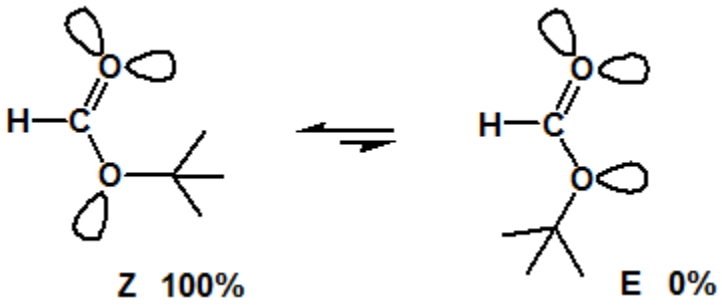


N. S. True, R. K. Bohn. *J. Phys. Chem.* **1978**, *82,* 478-479.

Secondary Stereoelectronic Effects and Relative Stability of Esters



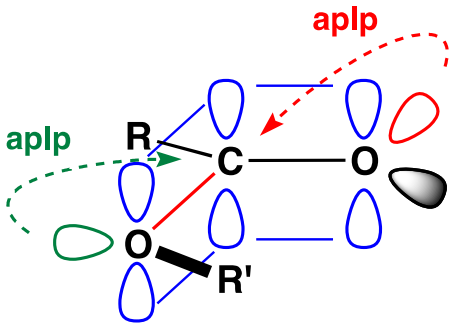
even *t*-butyl formate:

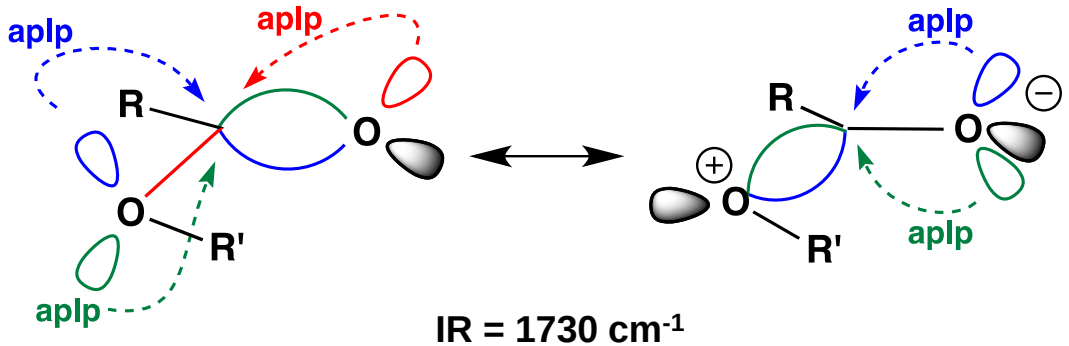


N. S. True, R. K. Bohn. J. Phys. Chem. 1978, *82*, 478-479.

τ *versus* σ-π in *Z*-ester and *E*-ester (lactone) and Justification of the Relative Importance of Resonance Structures

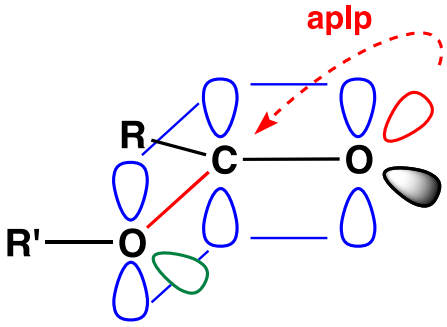
Z-esters:

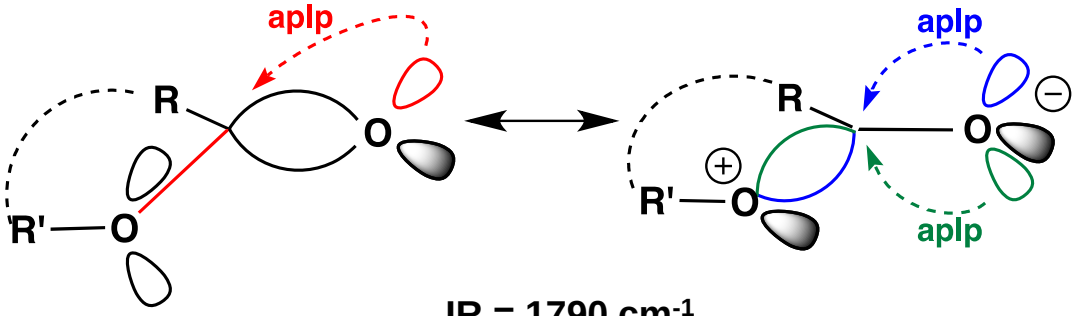




IR = 1730 cm^{-1}

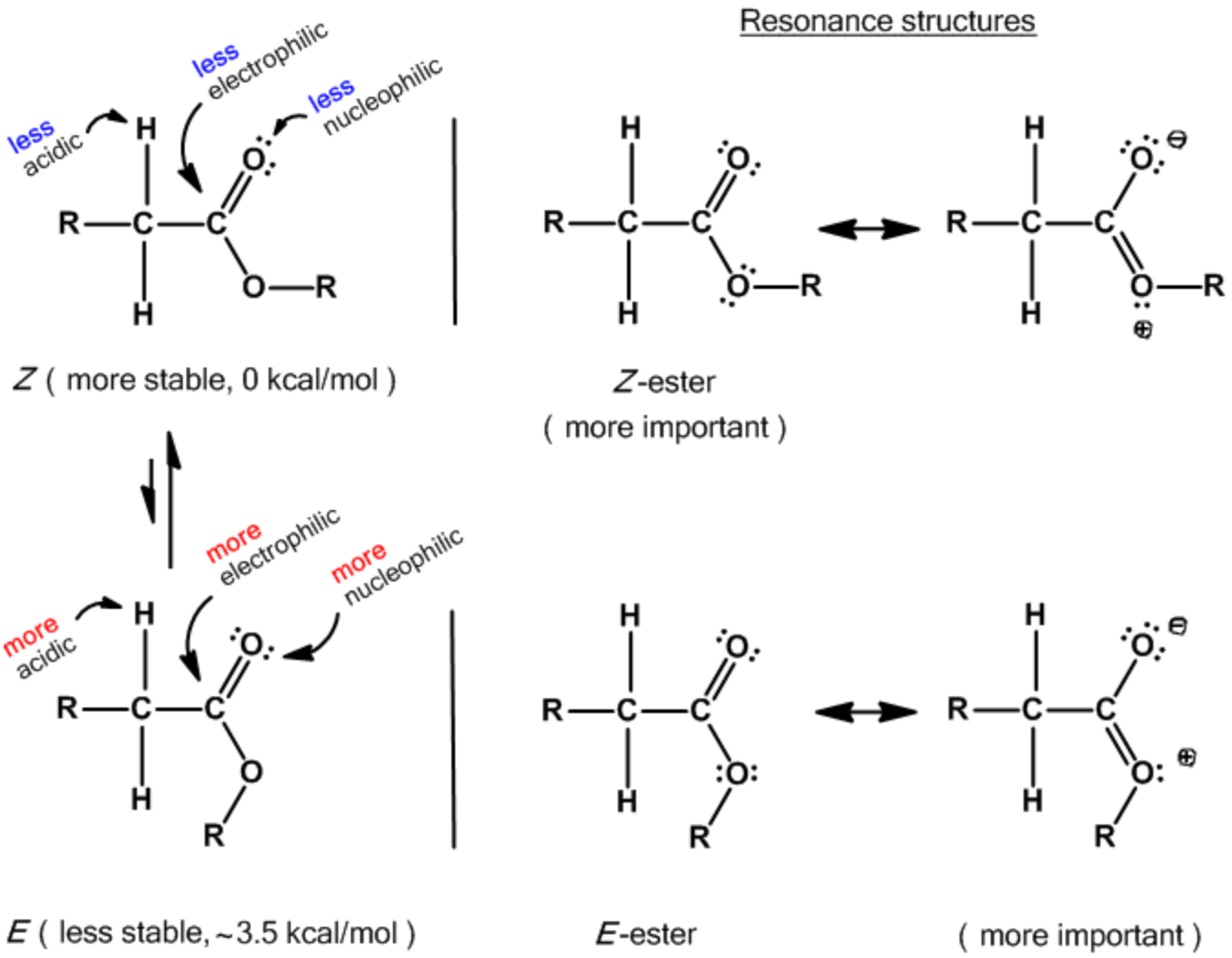
E-esters/lactones:



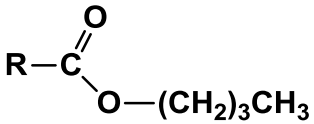


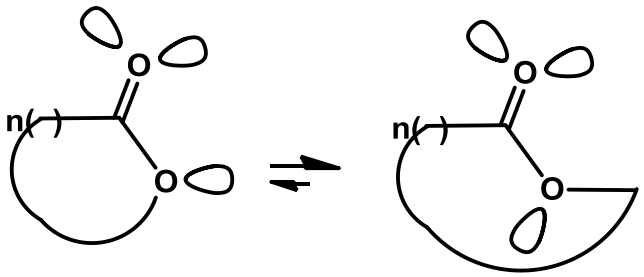
IR = 1790 cm^{-1}

Comparison Between *Z* and *E*-esters



LACTONE: RATE OF HYDROLYSIS 1N NaOH / Dioxan-H_2O (60:40)

	Ring size	Rate
γ-butyro lactone	5	1480
valero lactone	6	55000
	7	2250
	8	3530
	9	116
	10	0.22
	11	0.55
	12	3.3
	13	6.0
	14	3.0
	16	6.5
		8.4

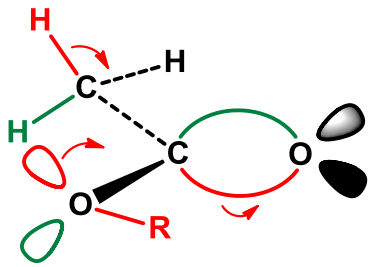


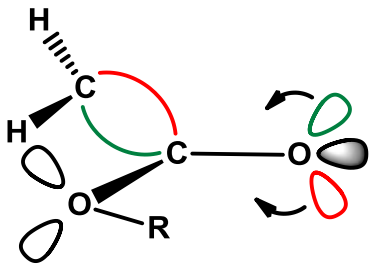
E (cis) ⇌ *Z (trans)*

R. Huisgen and H. Ott. Tetrahedron 1959, *6,* 253-267.

CH Acidity in *Z* and *E*-esters

Z ester

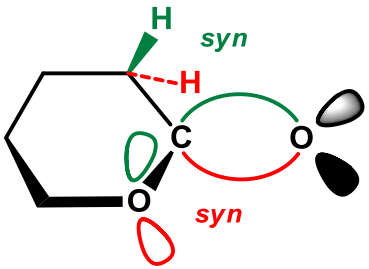




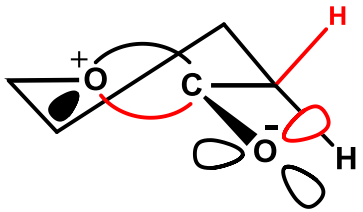
Z 1 (2n-τ*)

2 (2n-τ* (CH_2) weak)

E ester



(syn) E 3 (O σ-τ*)



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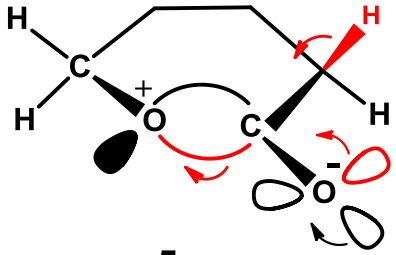
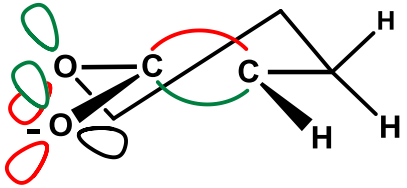
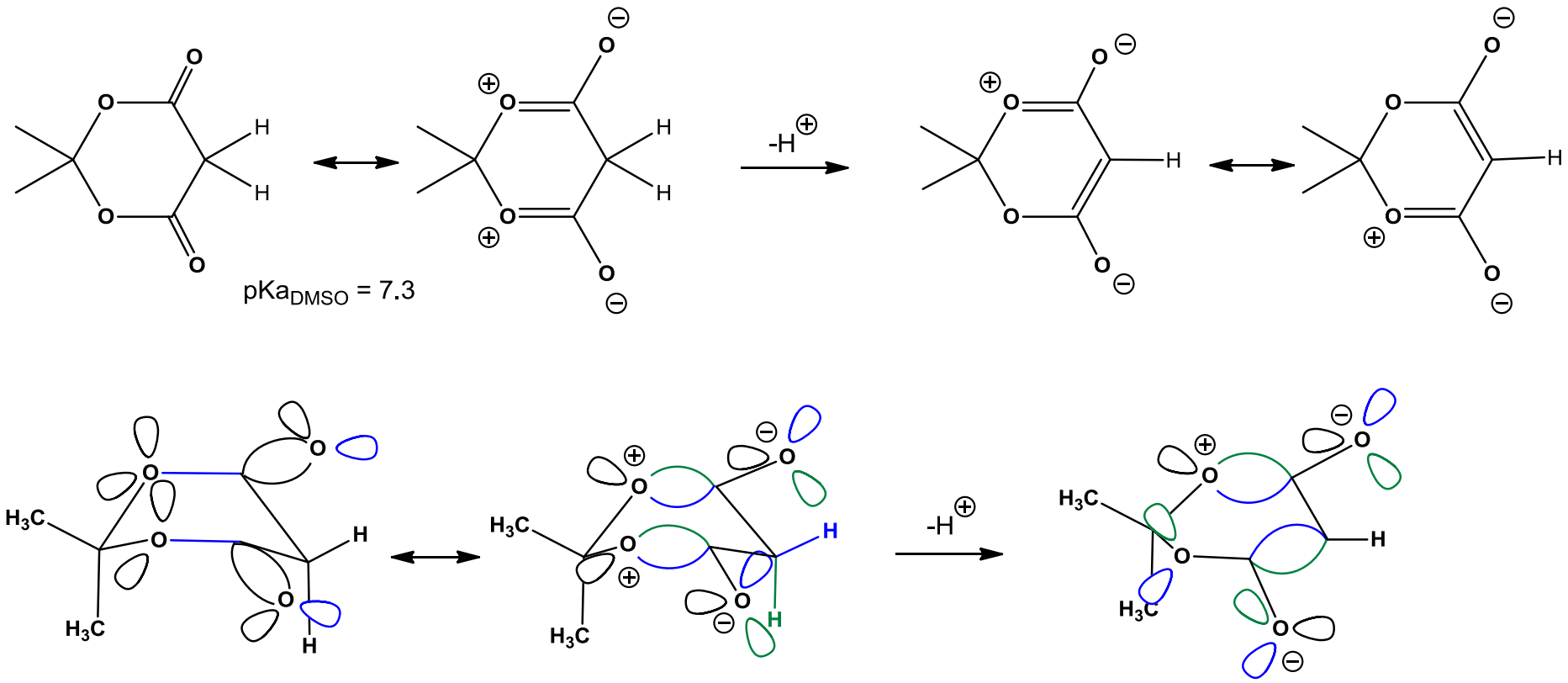


5



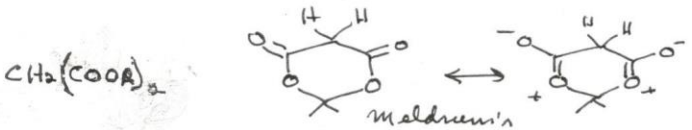
4 (4n-τ* (CH_2) weak)

Meldrum's Acid



E. M. Arnett, S. G. Maroldo, S. L. Schilling, J. A. Harrelson,
***J. Am. Chem. Soc.*, 1984, *106*, 6759.**

PKA of C–H

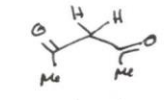


$CH_2(COOR)_2$

13.3

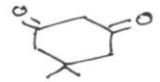
Meldrum's

4.83



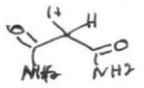
2,4-pentadien

13.2

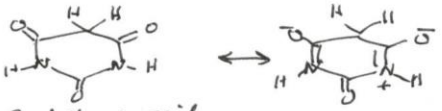


dimedone

11.2

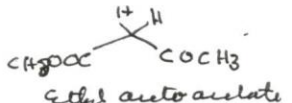


12.5



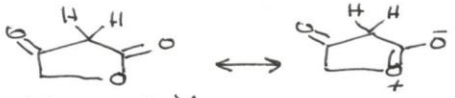
Barbituric acid

4.01



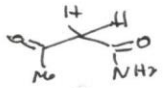
Ethyl acetoacetate

10.7



tetronic acid

3.7



tetramic acid

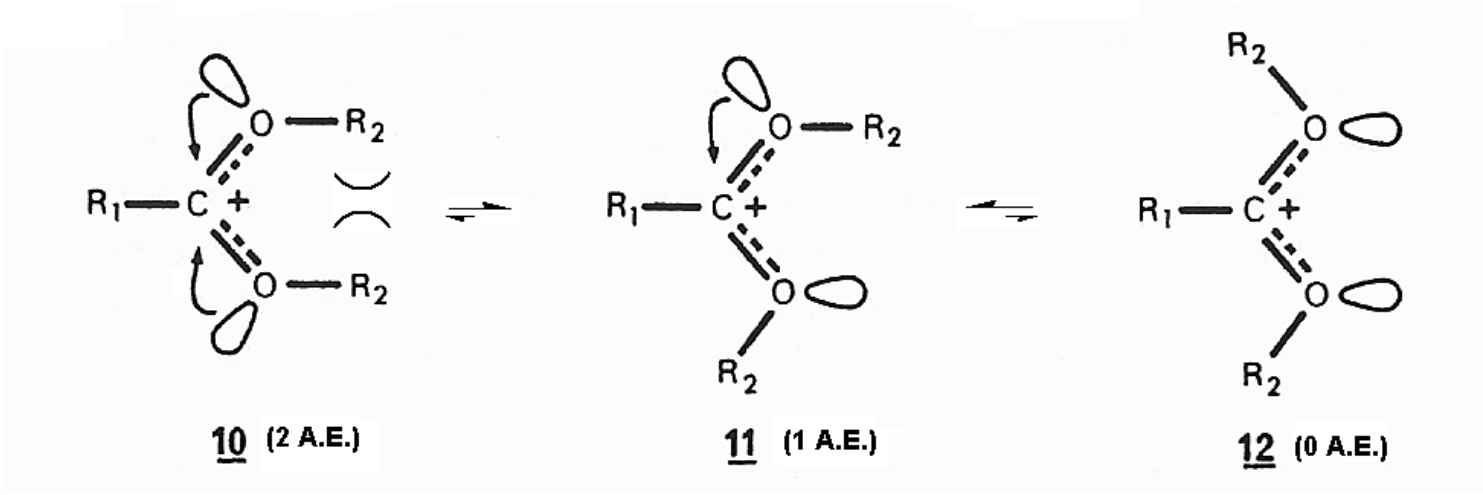
6.4

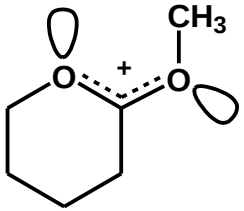
1) D. Villemin et al Eur. Chem. Bull. 2016, 5(7), 274-279

2) P. G. Seybold et al Int. J. Quant. Chem. 2009, 109, 3679-3684

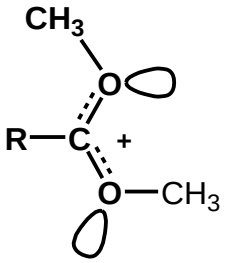
3) A. L. Perez et al J. Chem. Educ. 2000, 77(7), 910-915

Relative Stability of Dialkoxy-carbonium Ion





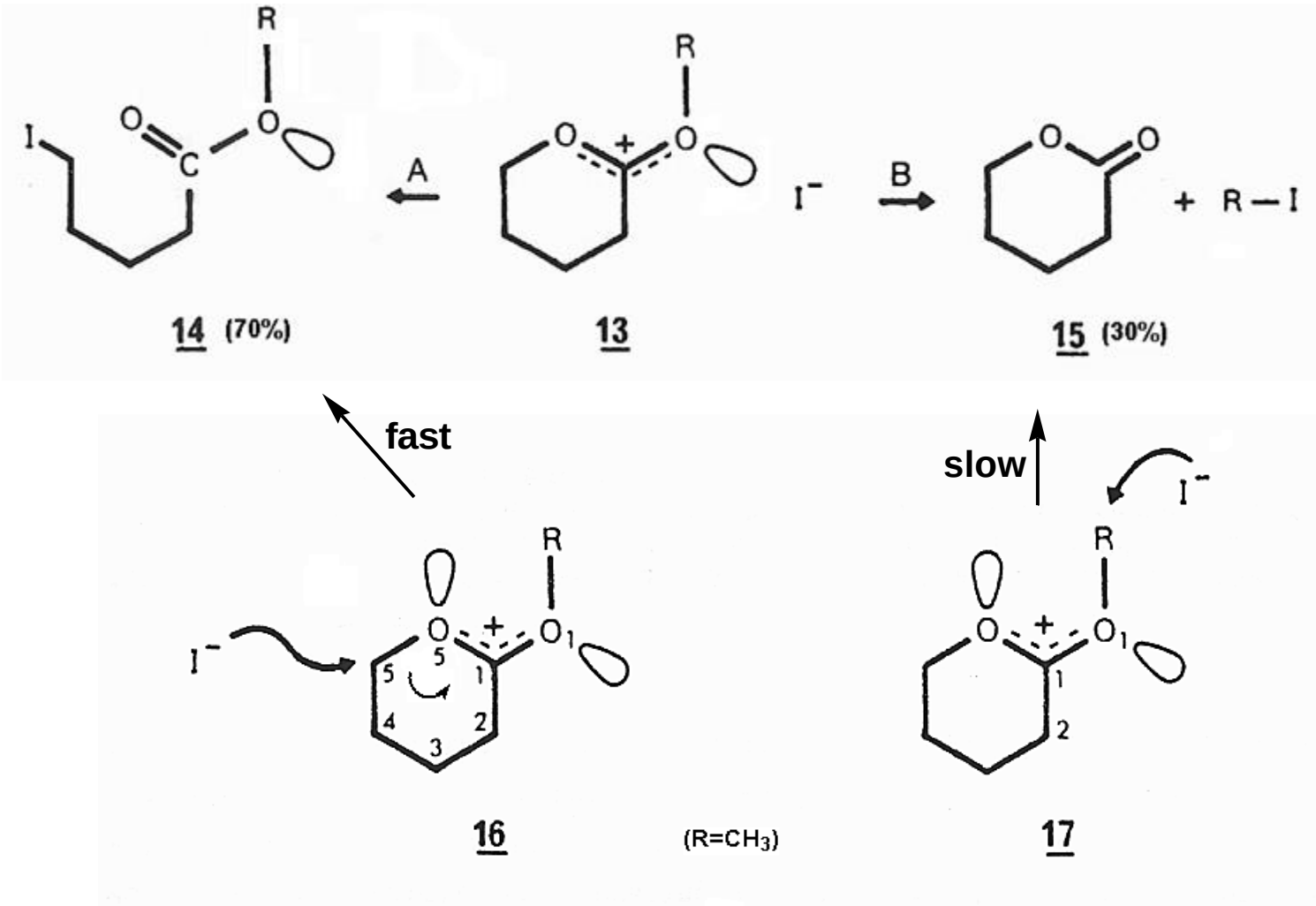
X-rays



(NMR)

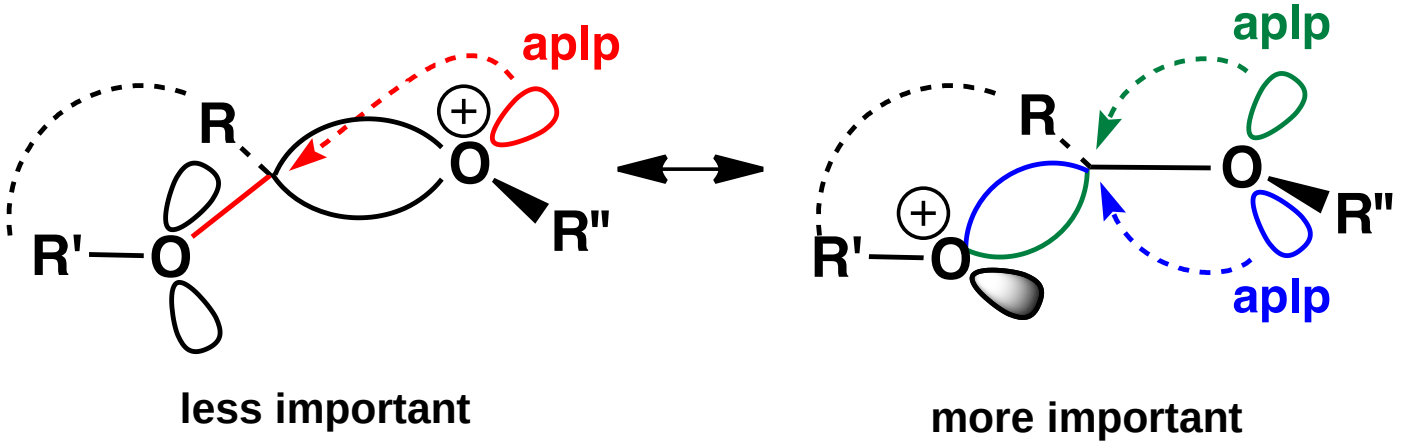
Experimental Evidence for Secondary Stereoelectronic Effects

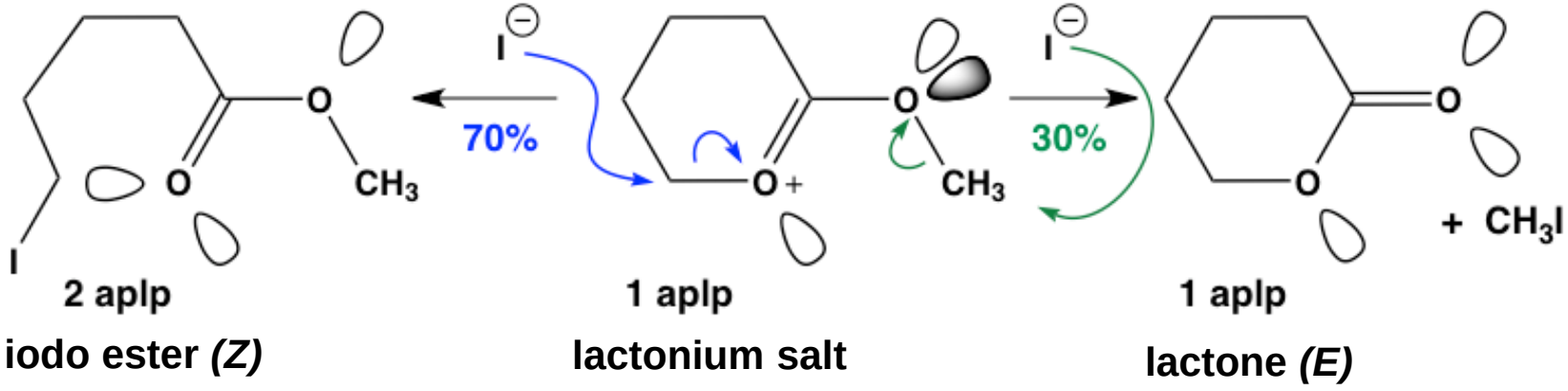
Iodide Displacement on Lactonium Salt



SN_2 on secondary carbon faster than primary one due to SE control

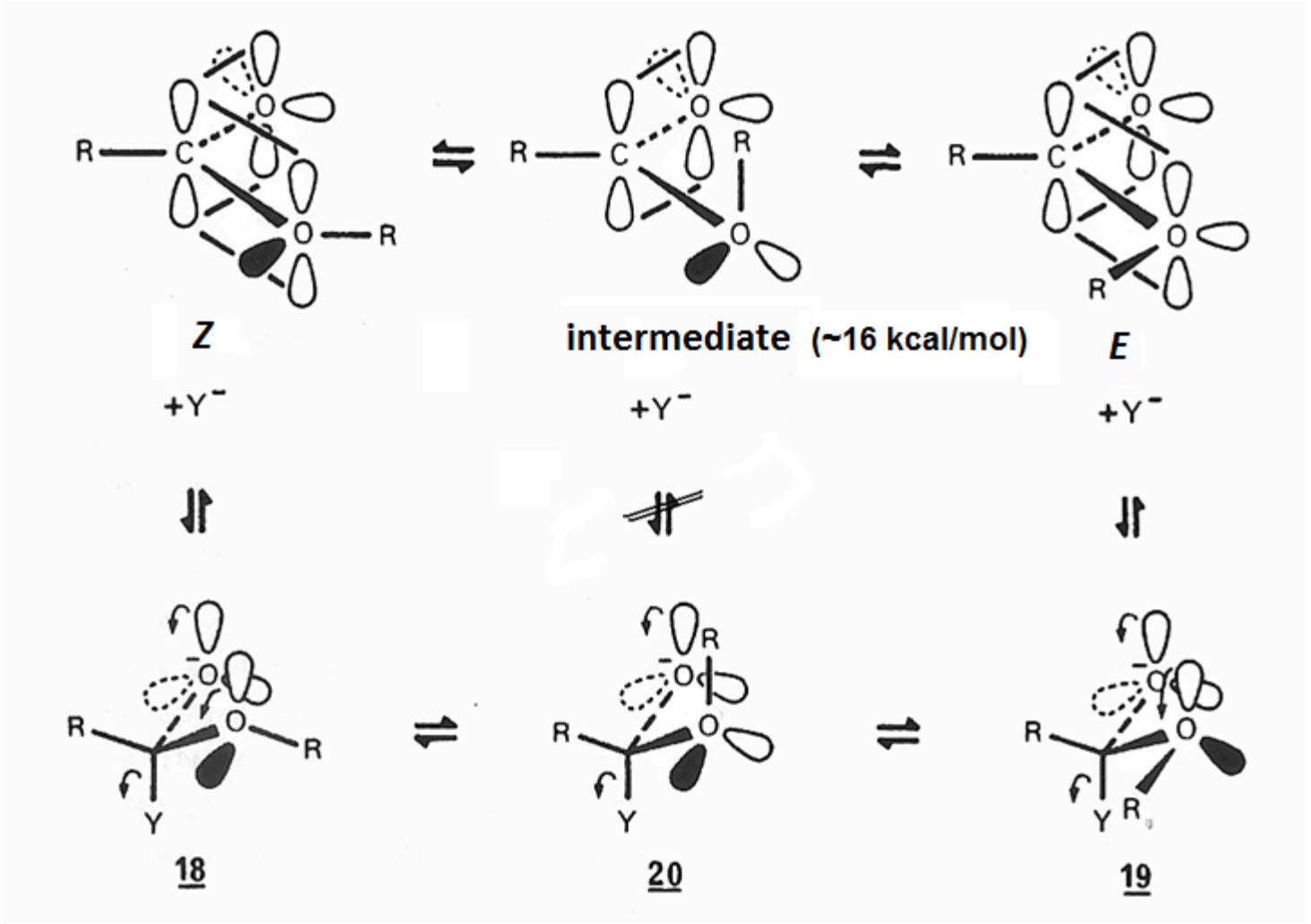
Resonance Structures in Lactonium Salt





N. Beaulieu, P. Deslongchamps, *Can. J. Chem.*, 1980, *58*, 164.

Stereocontrolled Cleavage of Hemiortoester Tetrahedral Intermediate

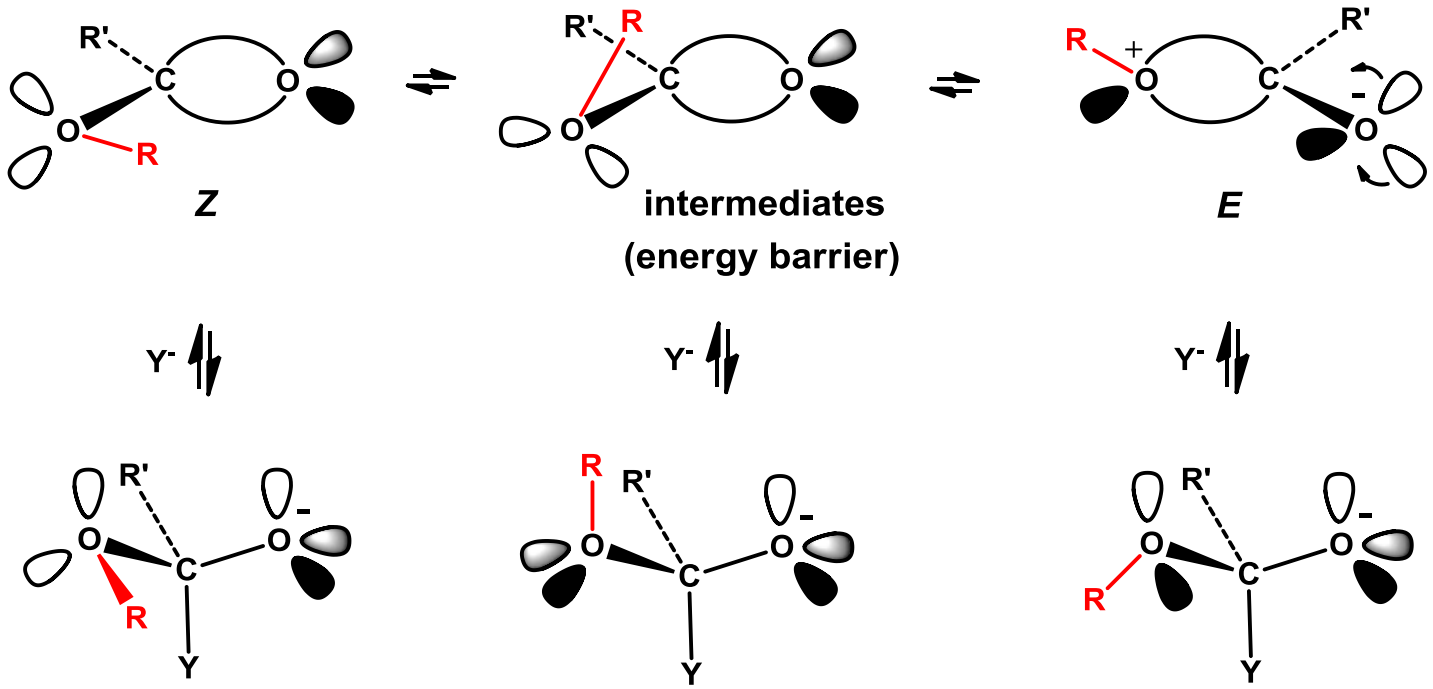


primary (2 A.E.)
secondary (2 A.E.)

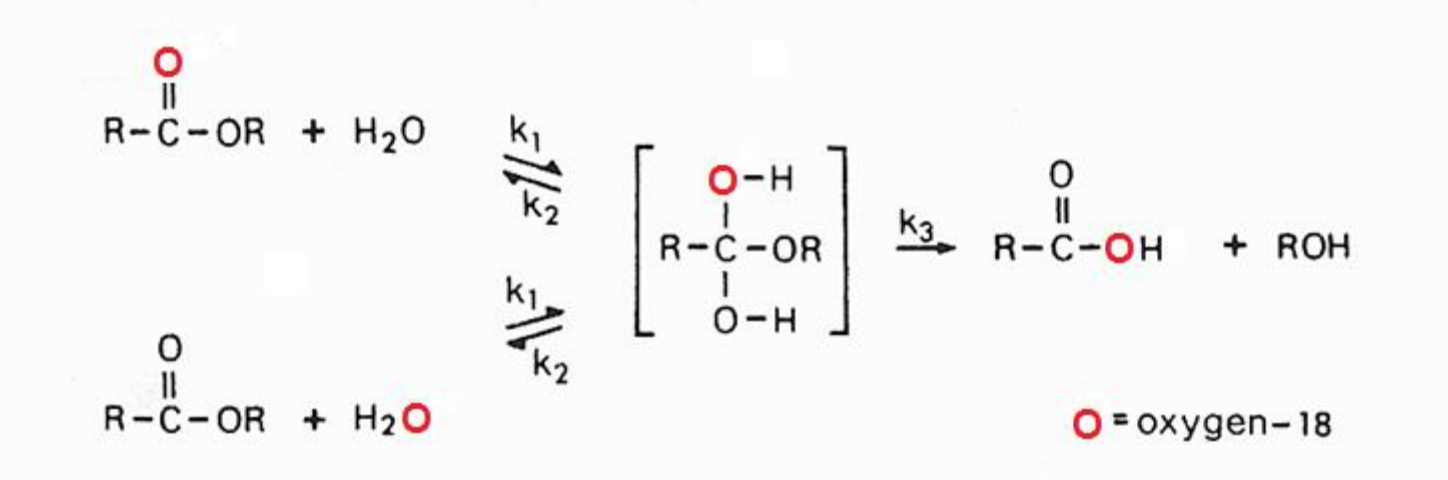
primary (1 A.E.)
secondary (2 A.E.)

primary (2 A.E.)
secondary (1 A.E.)

τ Bond and Hemiorthoester Cleavage

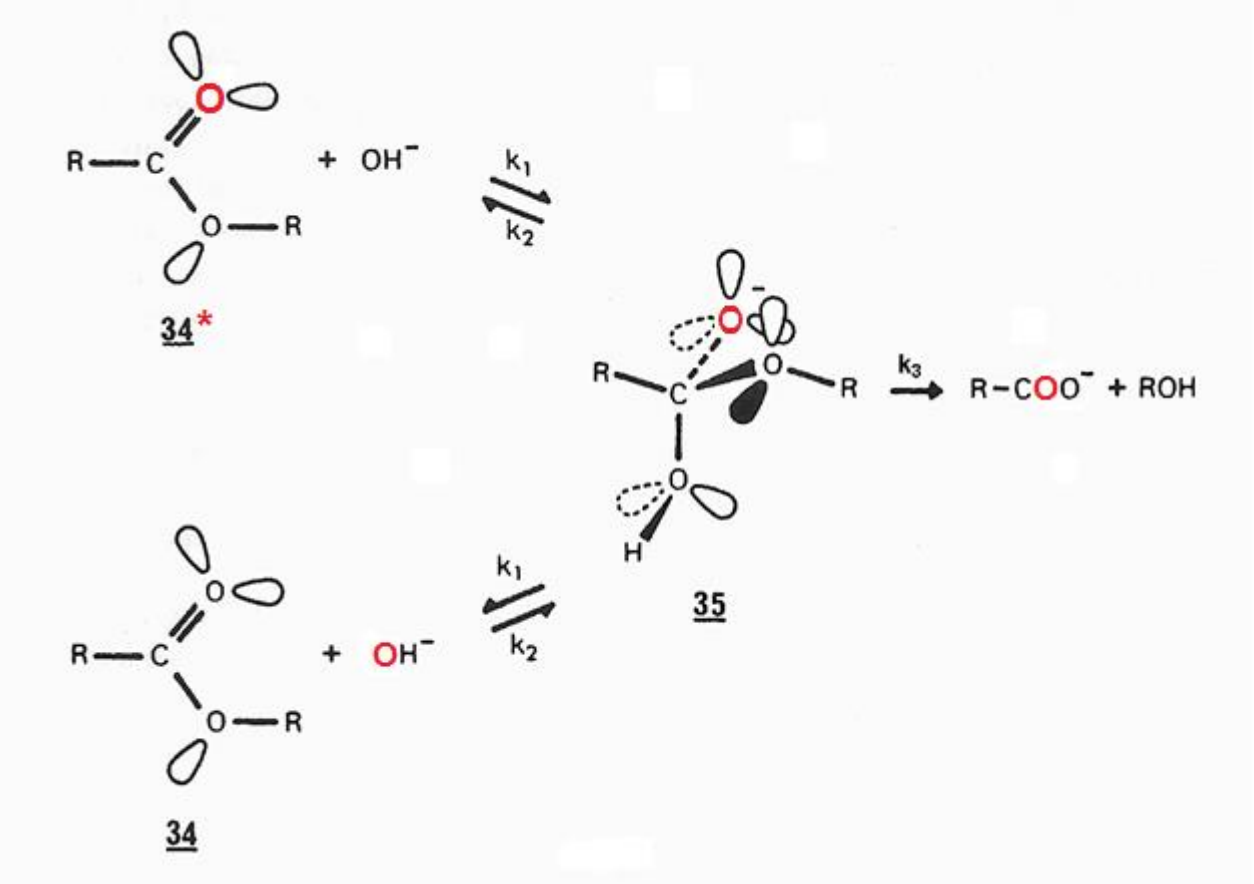


O^{18}-Exchange Concurrent to Hydrolysis in Ester and Lactone



Z-ester undergoes O_{18} exchange as $k_2 \approx k_3$

O^{18}-Exchange Concurrent to Hydrolysis in *Z* Ester



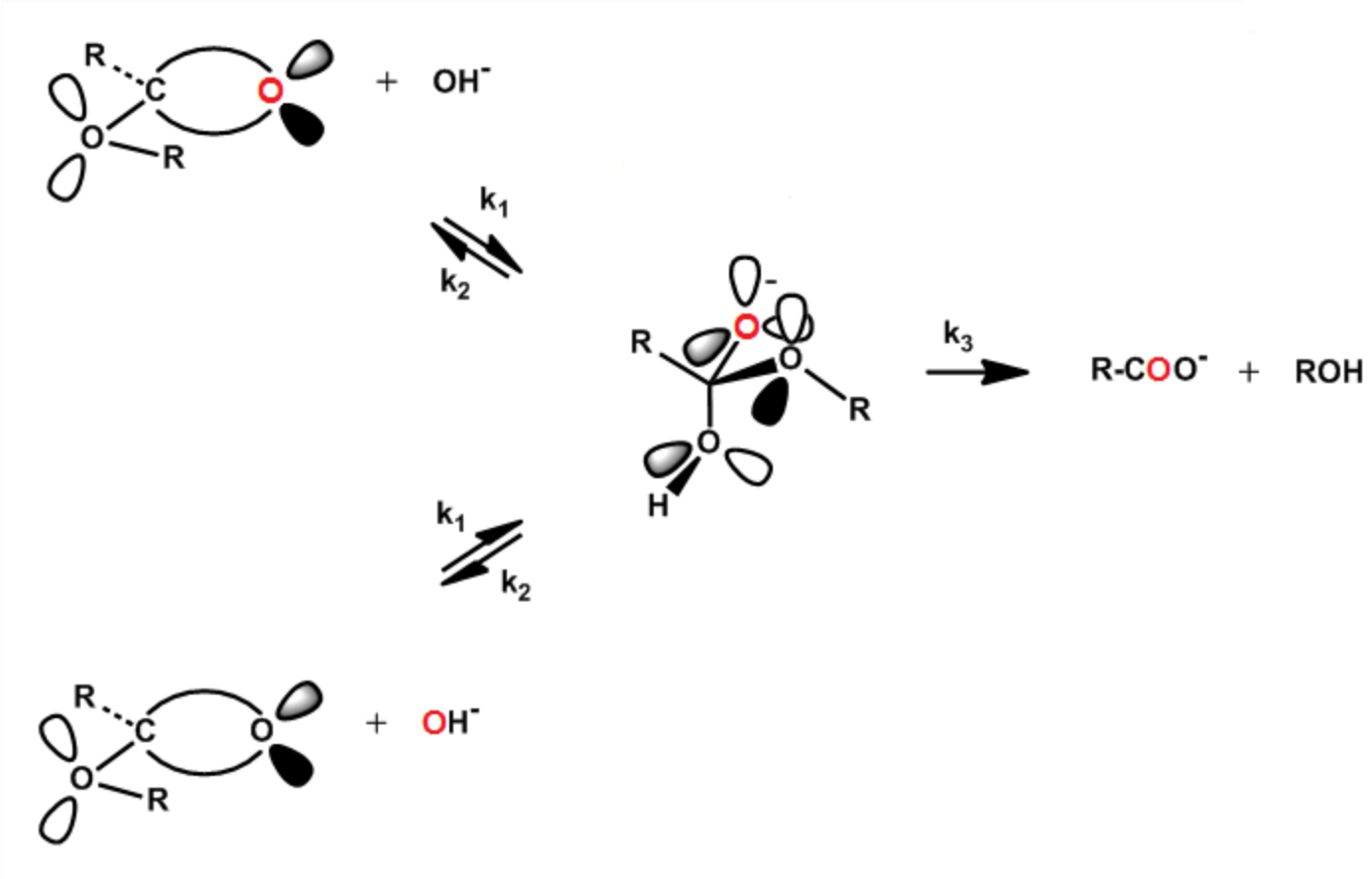
In both k_2 and k_3, cleavage takes place with

2 secondary stereoelectronic effects (or 2 A.E.)

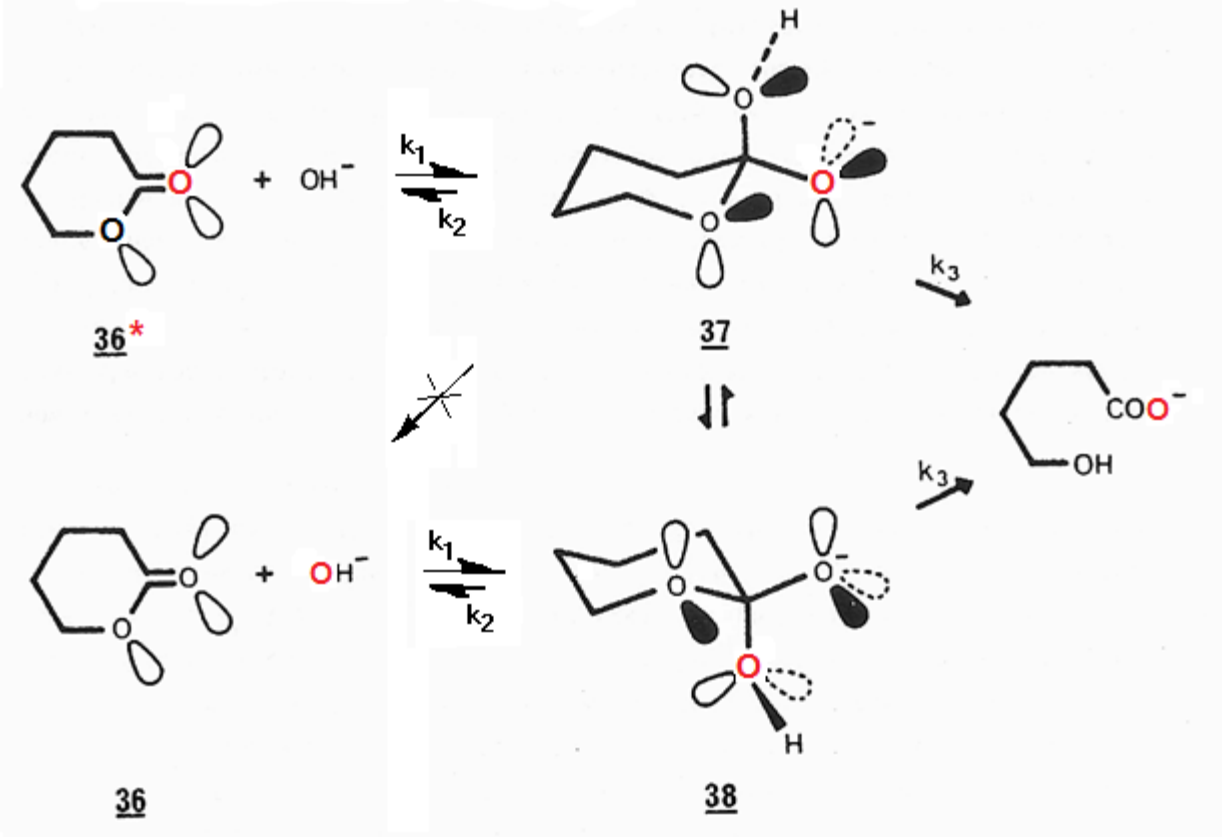
(1) Groupe partant semblable

(2) Transfert de protons à la vitesse de diffusion

τ Bond and Z Ester Hydrolysis



Lactone (*E*-ester) do not undergo O^{18}-Oxygen Exchange Concurrent with Hydrolysis



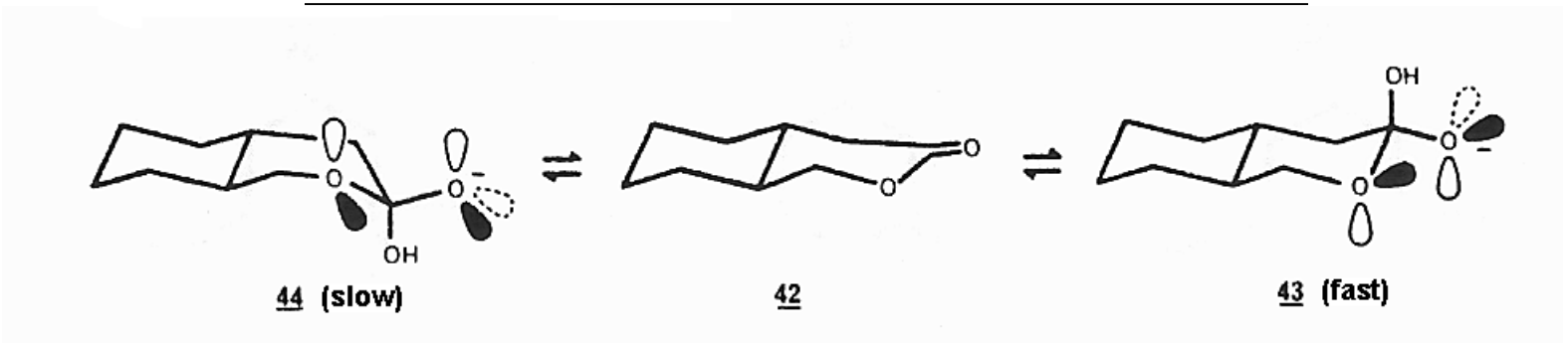
in k_3, cleavage takes place with 2 secondary stereoelectronic effects

in k_2, cleavage takes place with 1 secondary stereoelectronic effects

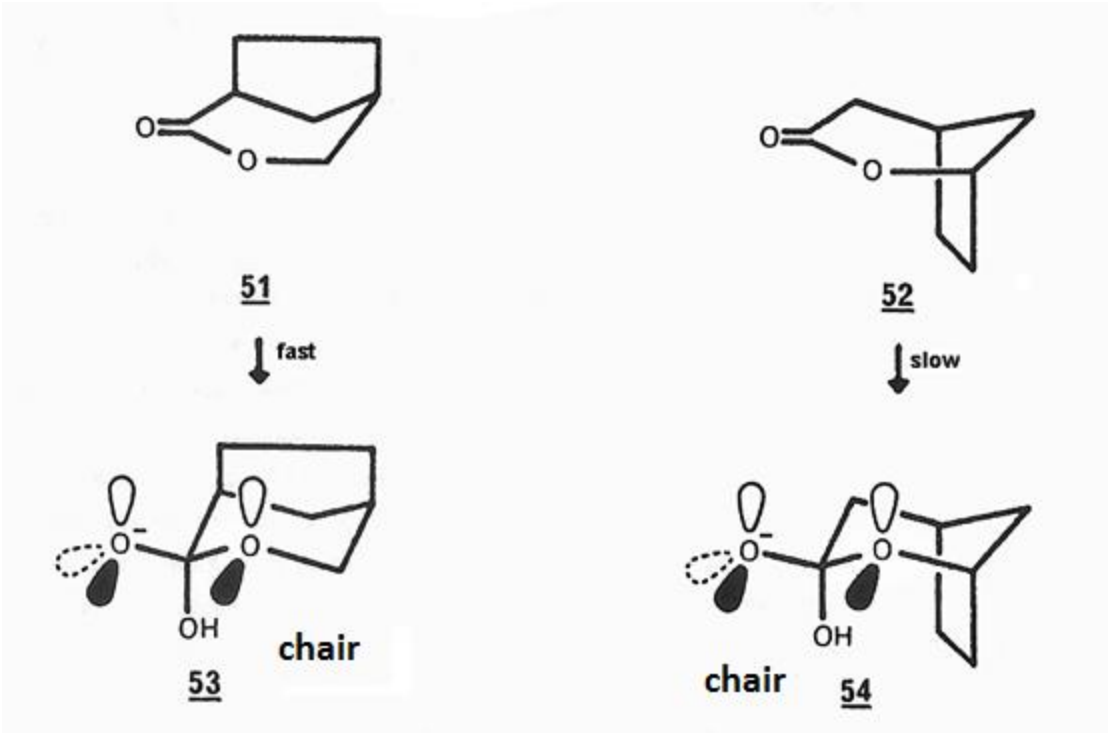
k_3 is thus greater than k_2

consequently no O^{18} exchange even if there is conformational exchange (37 to 38)

Prediction of Hydrolytic Pathway of Lactone

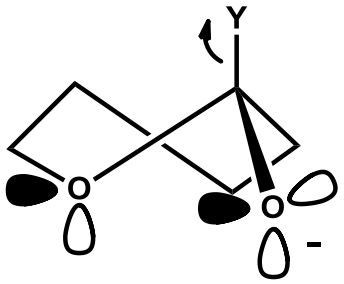


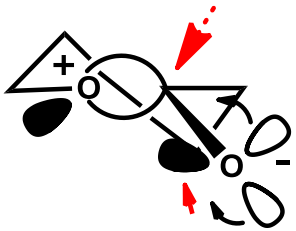
Relative Rate of Hydrolysis of Isomeric Lactones



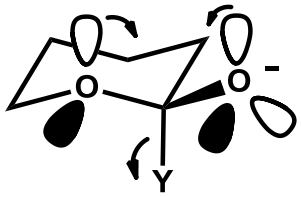
τ Bond and Lactone Tetrahedral Intermediates

twist-boat



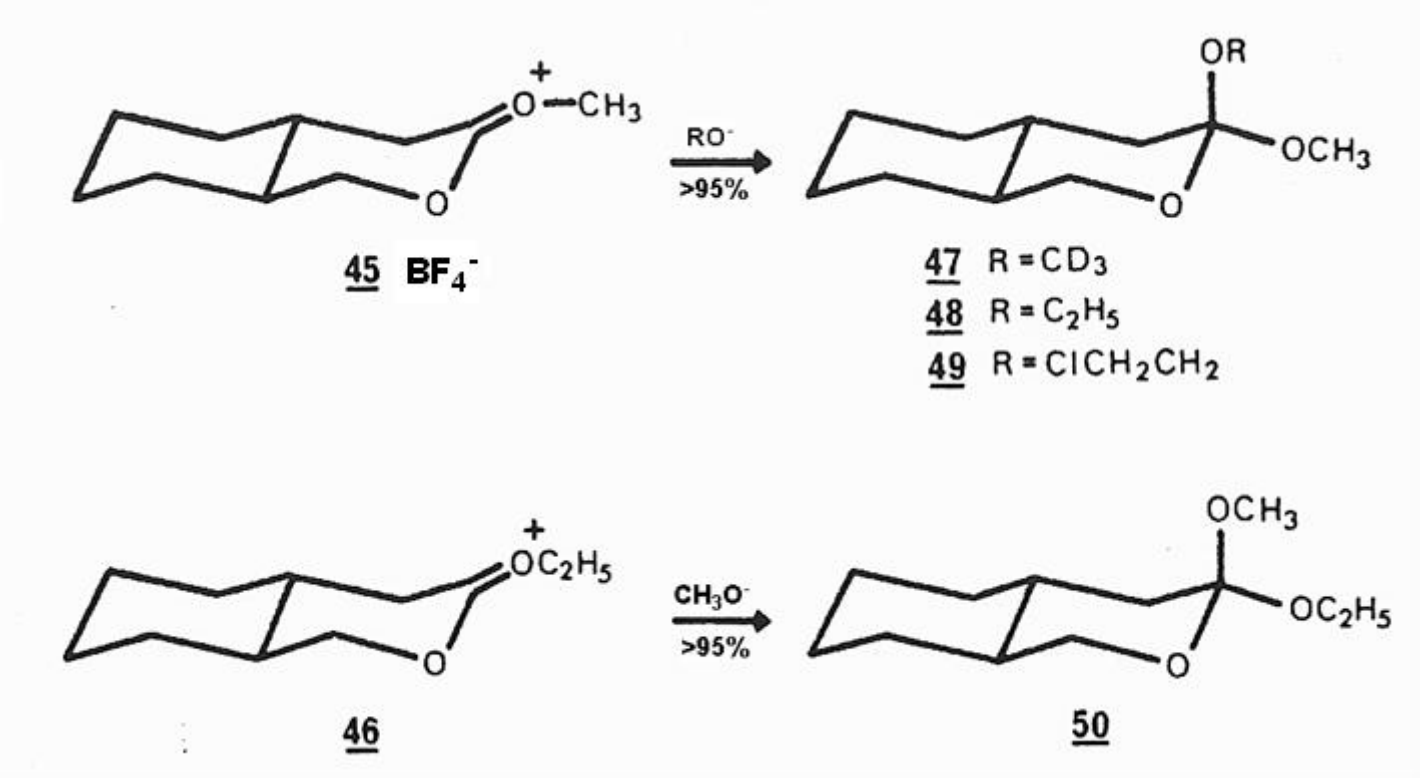


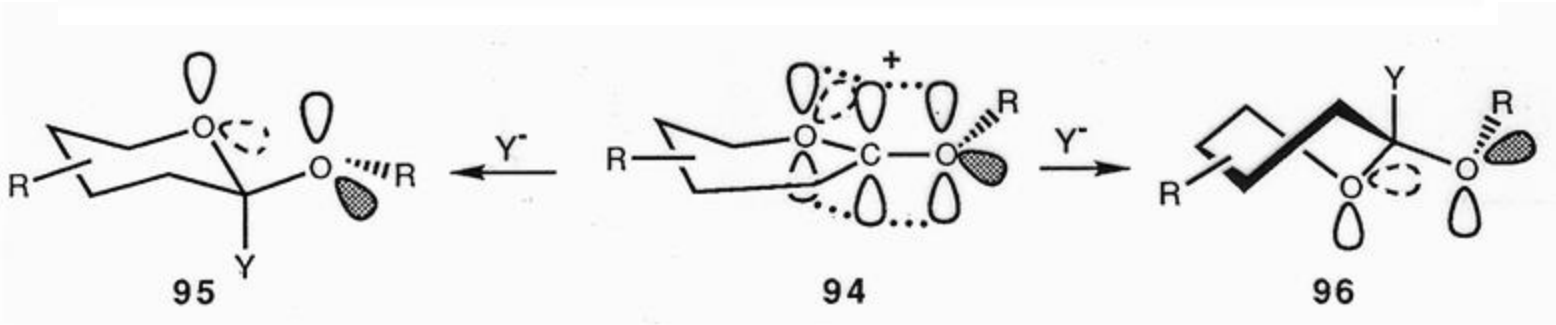
chair
favored



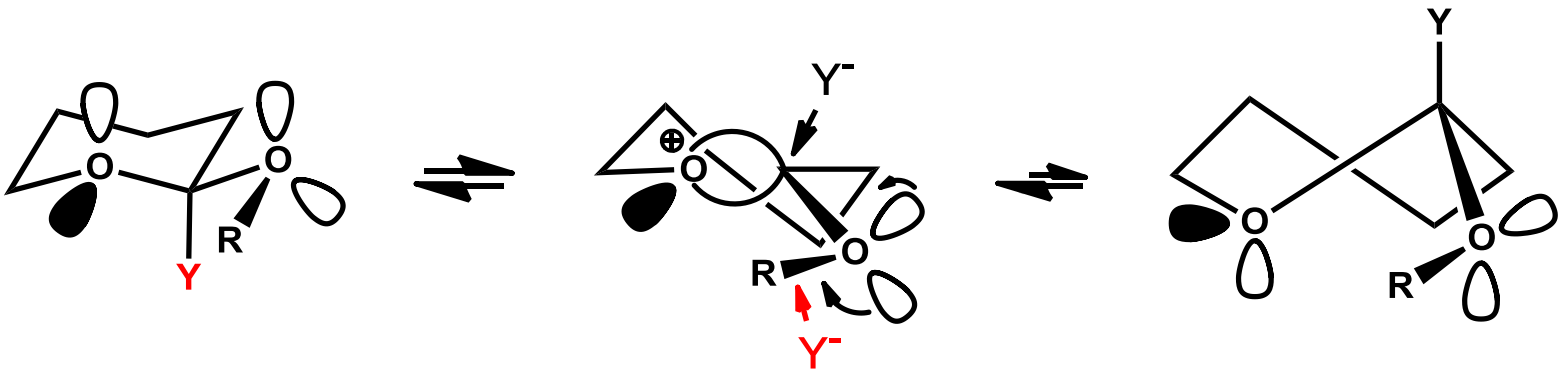
Reaction of Alkoxide on Lactonium Salt

Experimental proof of stereoelectronic control



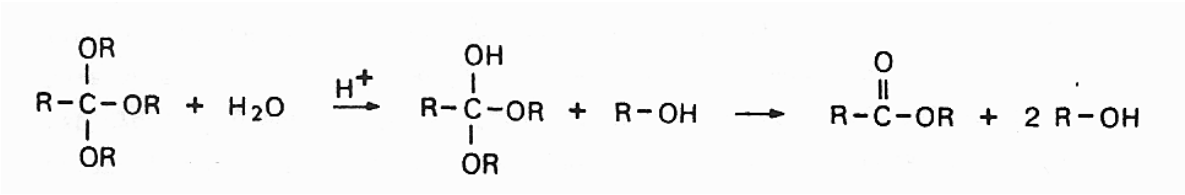


τ Bonds – Alkoxide on Lactonium Salt



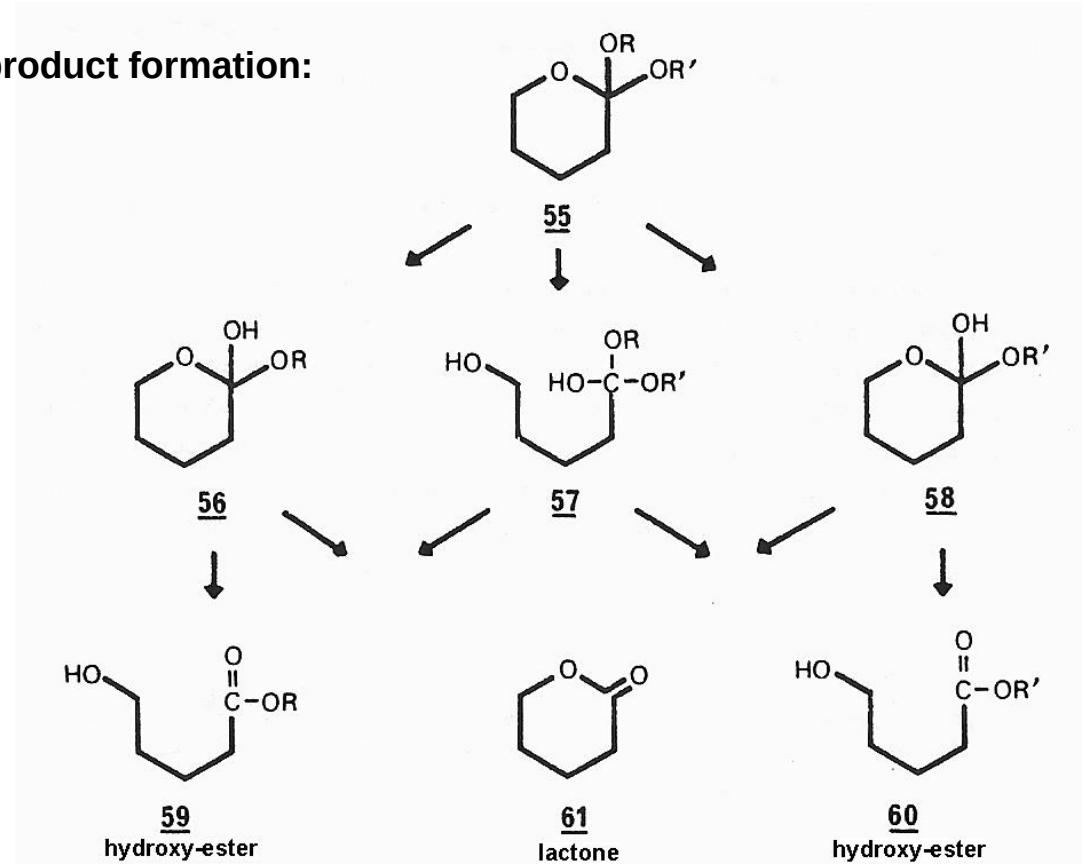
Hydrolysis of Cyclic Orthoesters

The formation of esters from the mild acid hydrolysis of orthoesters proceeds through the formation of a hemi-orthoester tetrahedral intermediate as described by the following equation

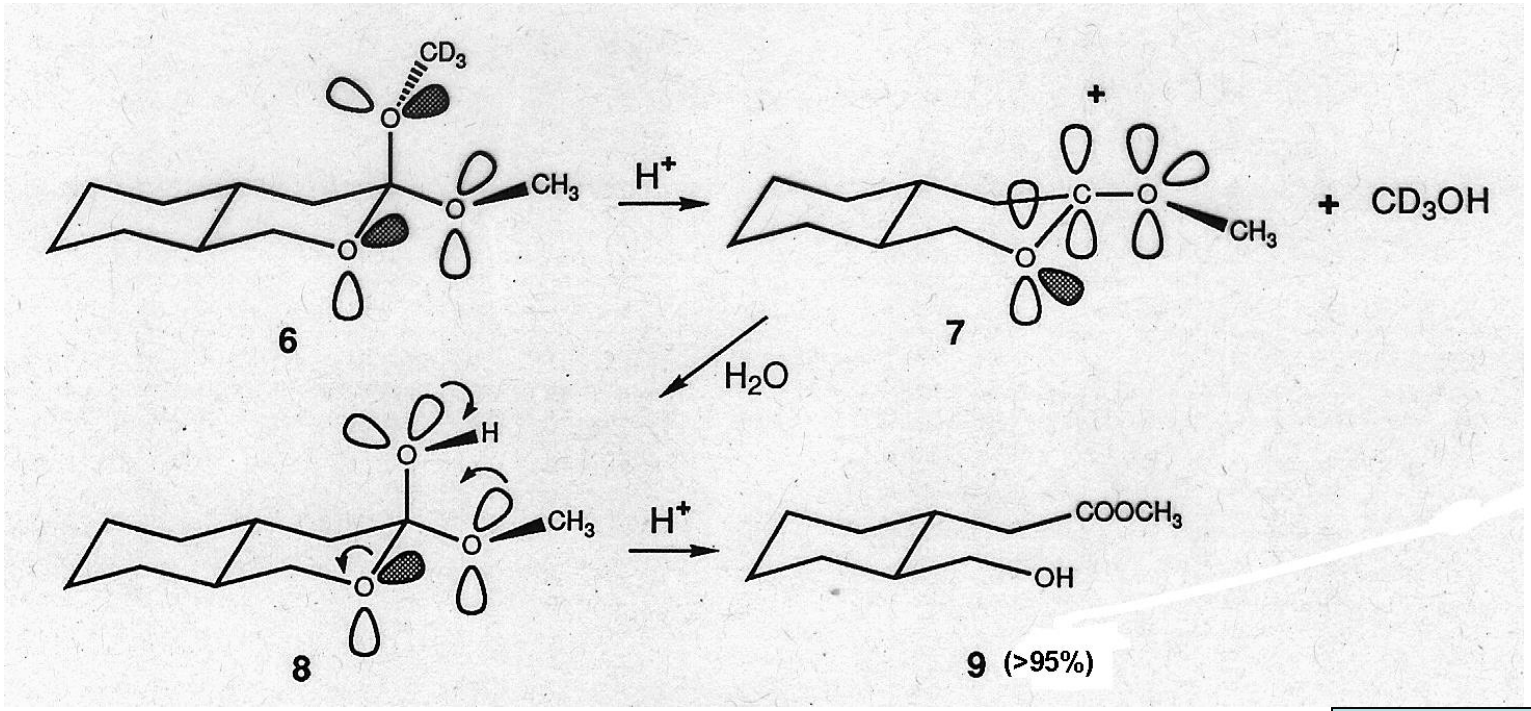


hemi-orthoester

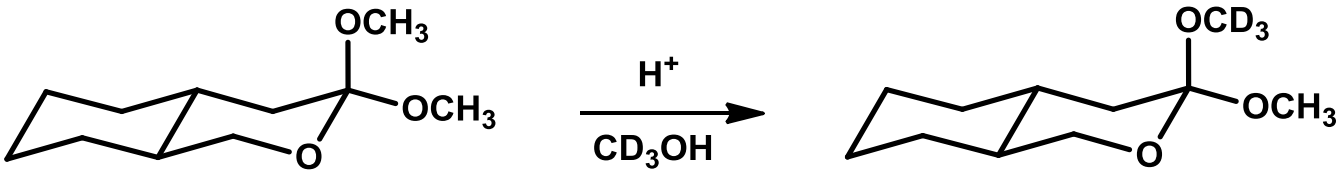
Possible product formation:



Mild Acid Hydrolysis of Bicyclic Orthoester with Two Different Alkoxy Groups



Deslongchamps

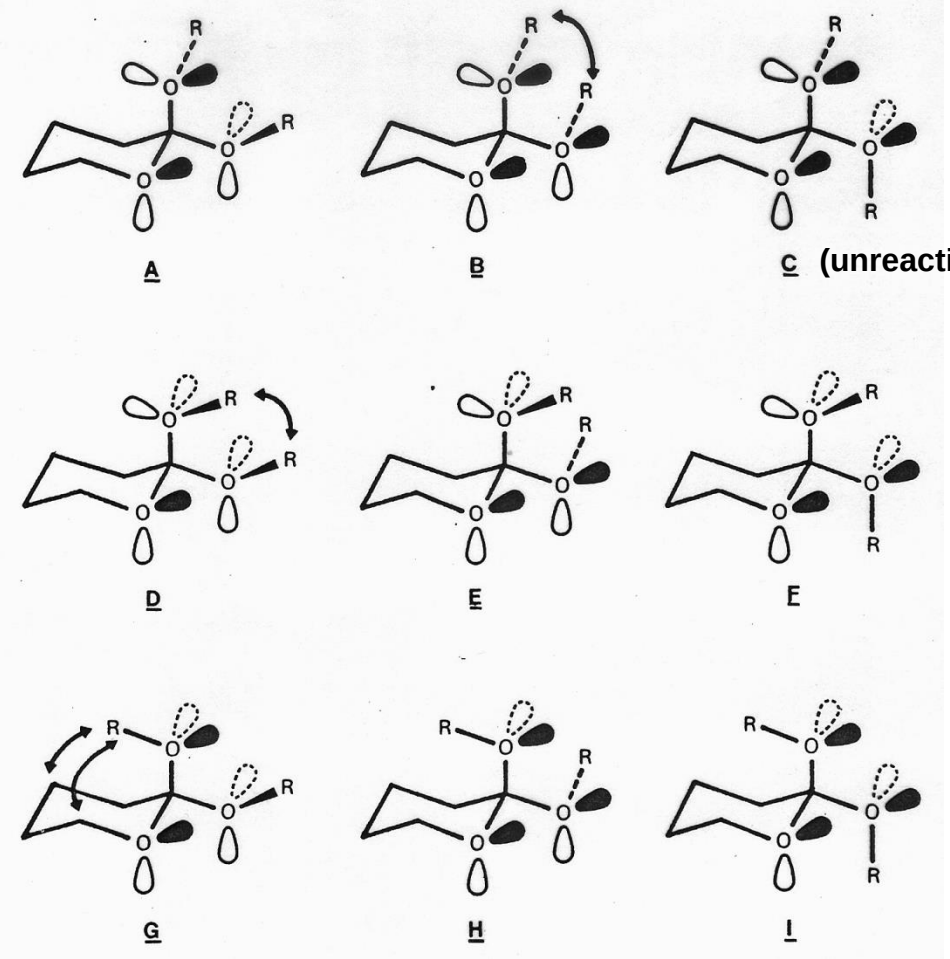


clear preference for the exchange of the axial OCH_3 group (100/1)

Kirby

Tet. Lett. 1982, 4163-4166.

Nine Conformers of Cyclic Orthoester

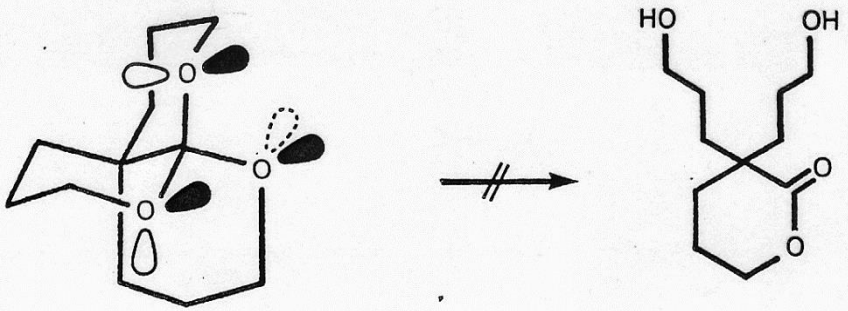


B, D, G, H and I are eliminated because of strong steric effects (>4 kcal).

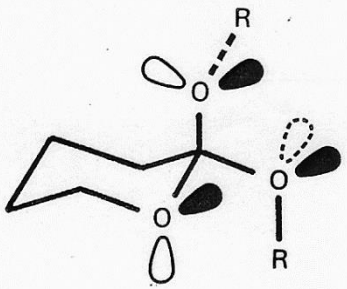
C is unreactive.

A, E and F should be reactive.

C is unreactive in acid



III

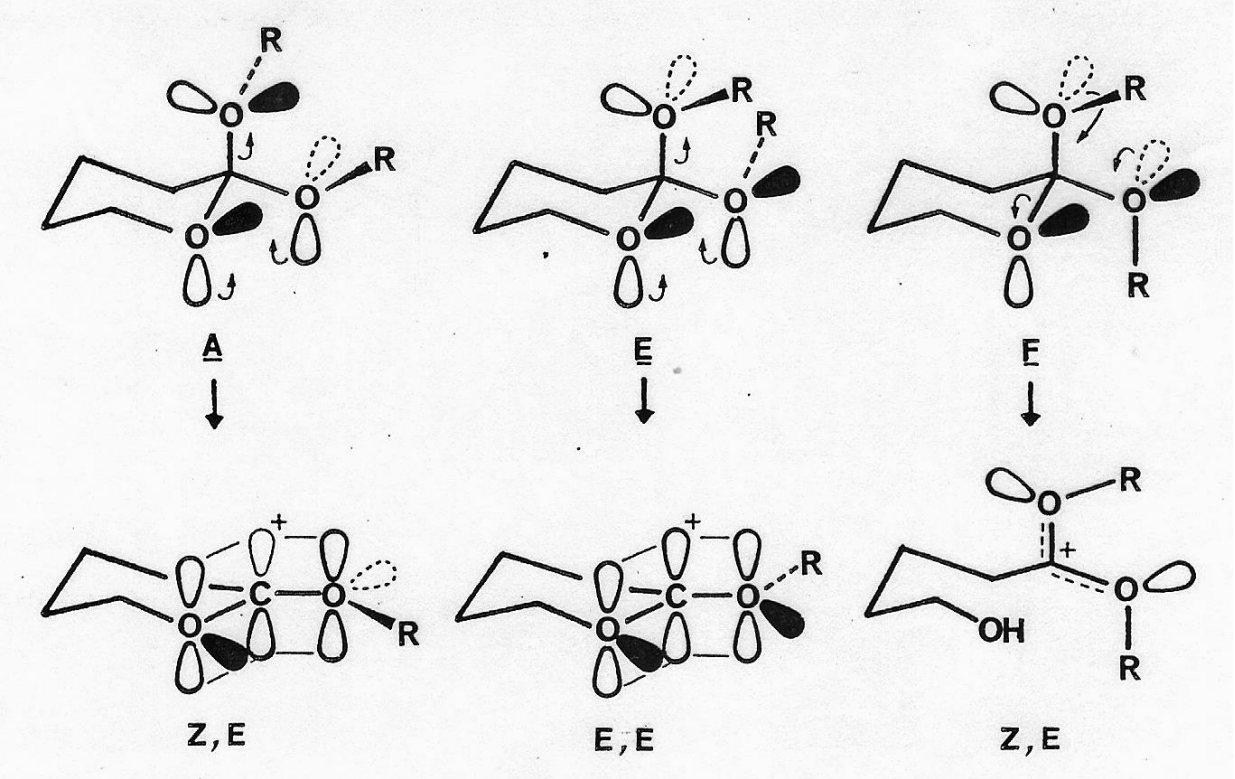


C

P. DESLONGCHAMPS, R. CHÊNEVERT, R.J. TAILLEFER, C. MOREAU, AND J.K. SAUNDERS.

CAN. J. CHEM. 53, 1601 (1975).

The Three Reactive Conformers and their Corresponding Dialkoxy Carbonium Salt



(1) E cleaves with no secondary S.E.

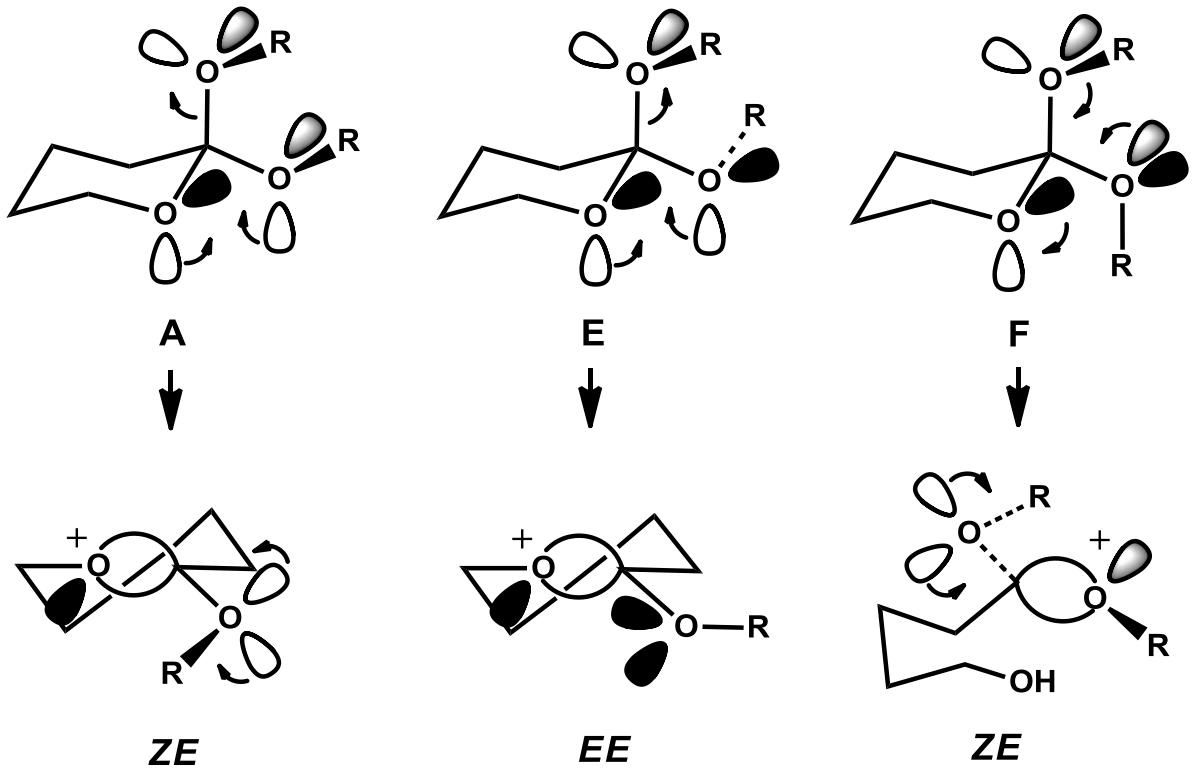
(2) A and F cleave with one secondary S.E.

(3) F yields one molecule (ring is cleaved)

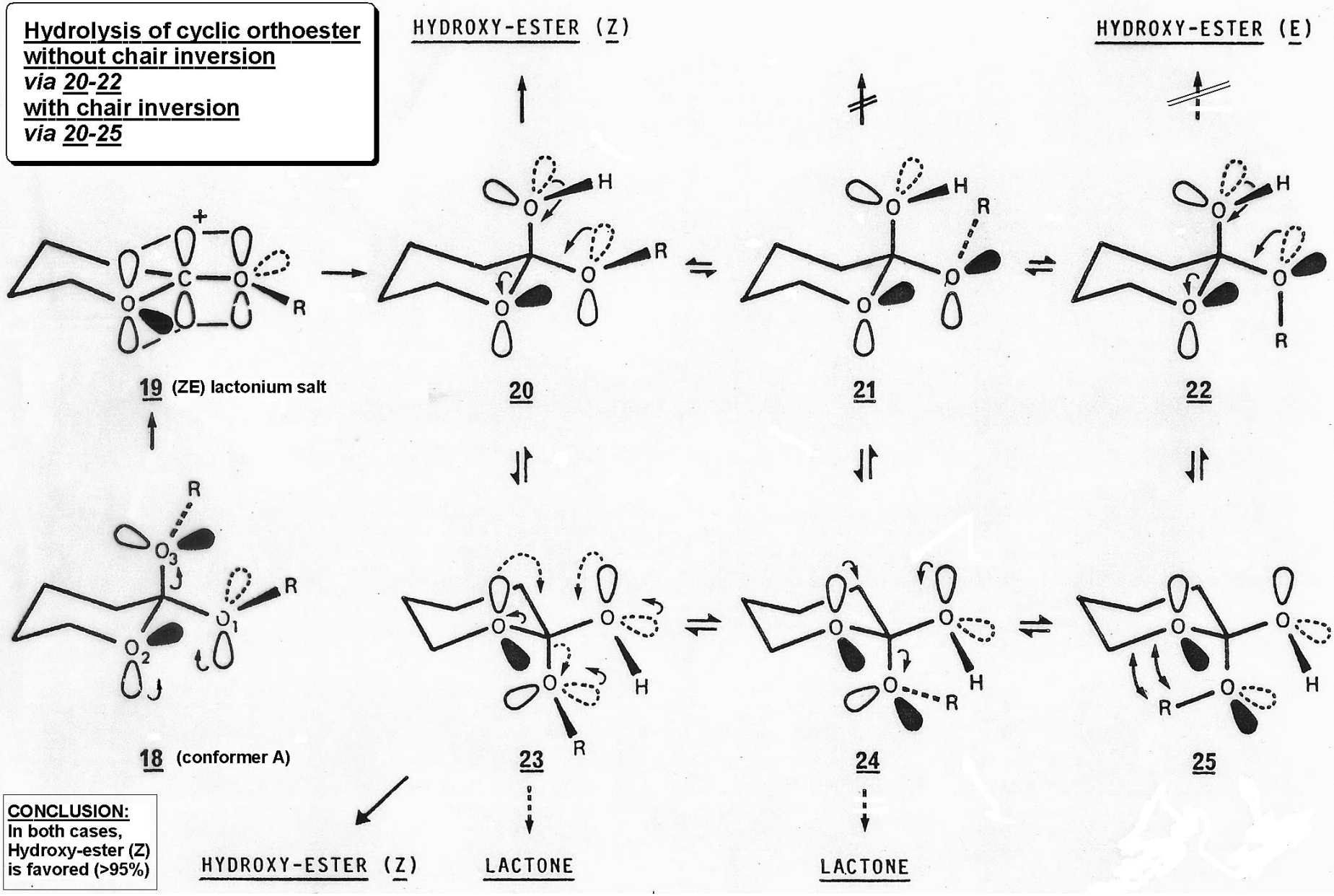
(4) A yield two molecules (favored entropically)

A is thus the favored cleavage

τ Bonds and the Three Reactive Conformers



Hydrolysis of cyclic orthoester
without chair inversion
***via* 20-22**
with chair inversion
***via* 20-25**

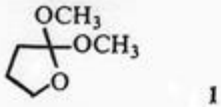
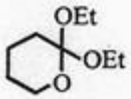
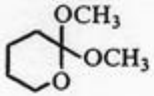
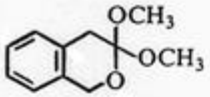
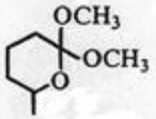
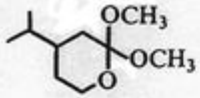
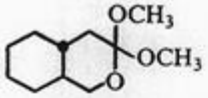


CONCLUSION:
In both cases, Hydroxy-ester (Z) is favored (>95%)

N.B. ~5% lactone in case of no ring inversion is explained by cleavage of the boat form of 20.

>5% lactone in case of ring inversion is explained by cleavage as above and by cleavage of 23 and 24.

Product ratio of lactone (L) and hydroxy-ester (E) from the hydrolysis of cyclic orthoesters as a function of pH*

	pH 0.9	pH 1.9	pH 3	pH 4	pH 4.7
	L%/E%	L%/E%	L%/E%	L%/E%	L%/E%
 1	22:78	21:79	22:78	21:79	15:85
 2	19:81	21:79	26:74	6:94	4:96
 2	33:67	32:68	31:69	16:84	11:89
 6	53:47	55:45	53:47	13:87	7:93
 3	10:90	10:90	9:91	<5:>95	<5:>95
 4	19:81	14:86	13:87	7:93	—
 5	—	6:94	<5:>95	<5:>95	—

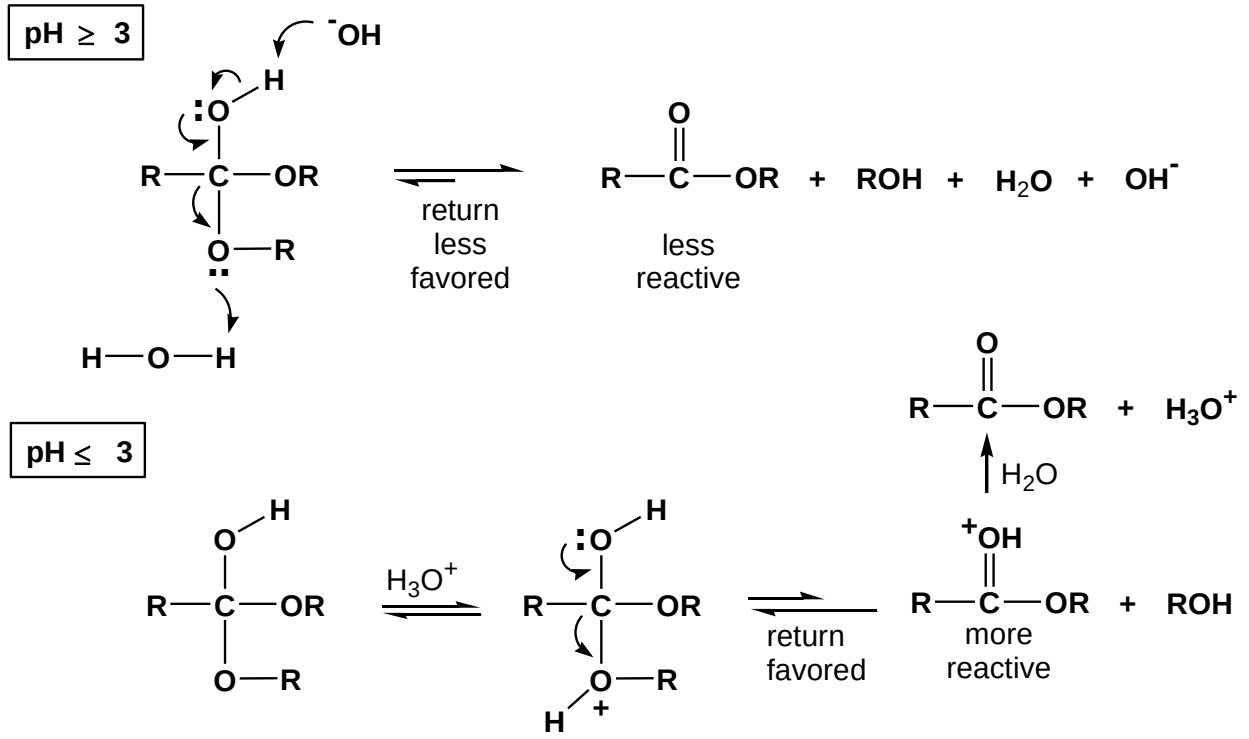
*The pH values refer to the pH of D_2O/DCl solutions before the mixing with the solution of orthoester in hexadeuterated acetone (see Experimental).

RESUME: **With Chair Inversion: pH < 3: more lactone**
pH > 3: < 5% lactone

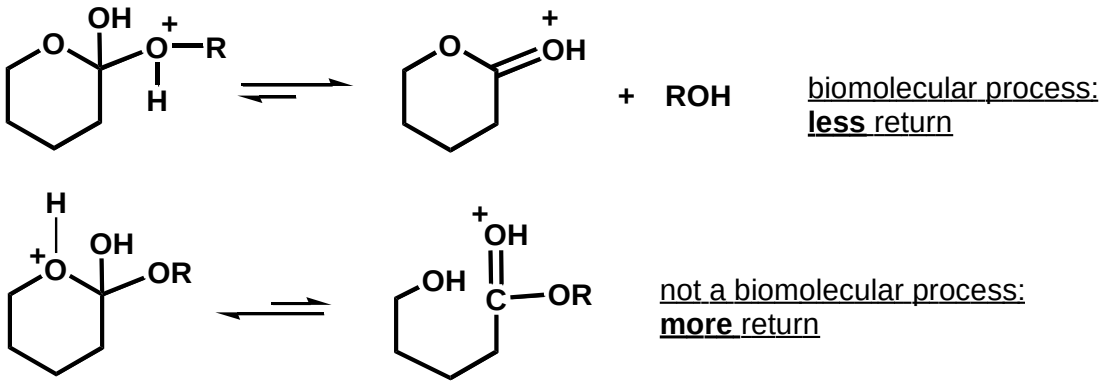
Without Chair Inversion: all pH: > 95% hydroxy-ester

[Can.J.Chem. 1985]

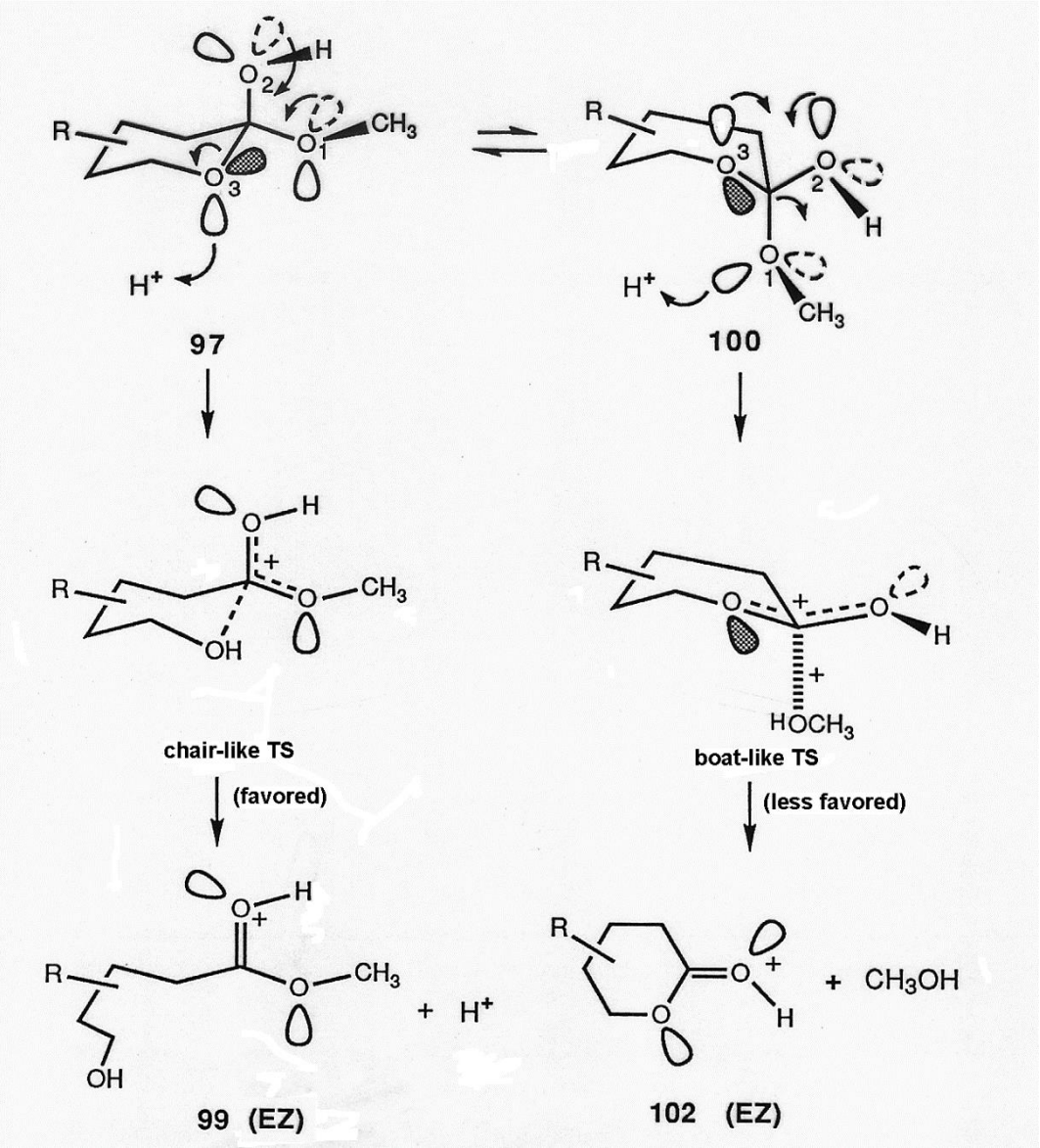
Hemiorthoester Mechanism of Fragmentation as a Function of pH



More Lactone at pH ≤ 3



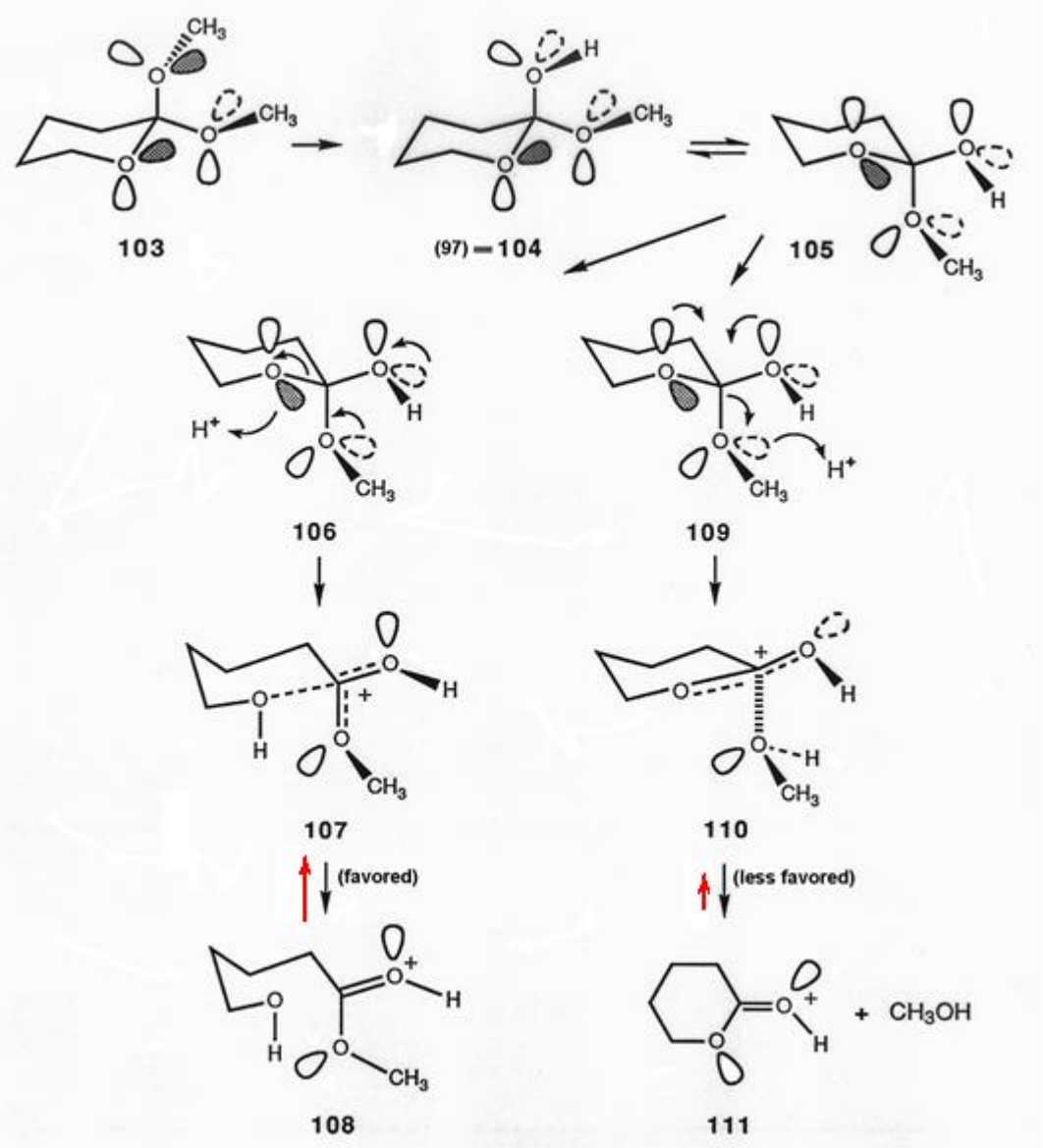
Small % of Lactone Produced in Cyclic Orthoester Hydrolysis



CONCLUSION

~ 5% LACTONE IS PRODUCED VIA 5% COMPETITIVE BOAT-LIKE TS

Cyclic Orthoester with Ring Inversion

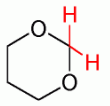
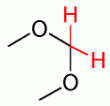
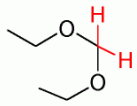
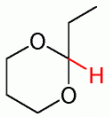
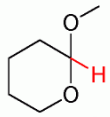
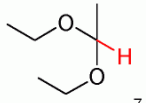
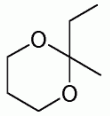
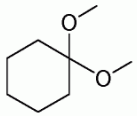
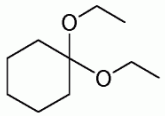
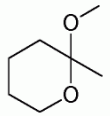
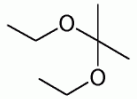
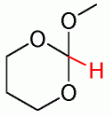
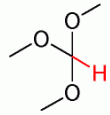
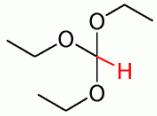
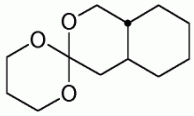
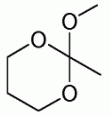
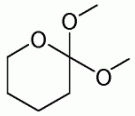
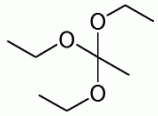
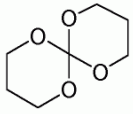
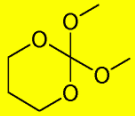
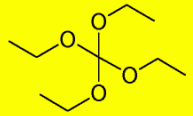


but close back due to internal return

CONCLUSION

MORE LACTONE IS PRODUCED

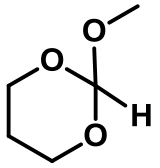
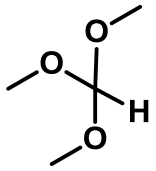
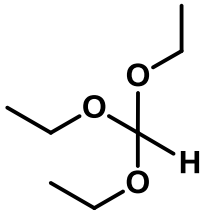
Relative Rates of Hydrolysis

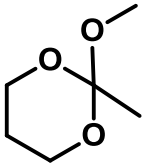
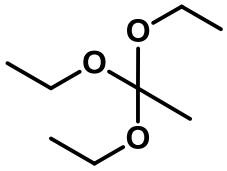
	2 rings	1 ring				acyclic	
		2 O in ring	no O in ring		1 O in ring		
		OMe	OMe	OEt	OMe	OMe	OEt
Acetals		 1				 4.5×10^2	 2.5×10^3
		 1×10^2			 9.3×10^4		 1.5×10^7
Ketals		 3.7×10^6	 2.6×10^8	 2.3×10^9	 2.4×10^9		 4.6×10^{10}
Orthoesters		 6.4×10^8				 2.5×10^9	 1.0×10^{10}
	 4.3×10^8	 8.4×10^9			 4.2×10^{10}		 2.8×10^{11}
Orthocarbonates	 9.6×10^8	 4.2×10^9				 1.7×10^8	 1.0×10^9

S. Li, P. Deslongchamps.
Tetrahedron Lett. *35*, 5641 (1994).
P. Deslongchamps, Y.L. Dory, S. Li.
Tetrahedron *56*, 3533 (2000).

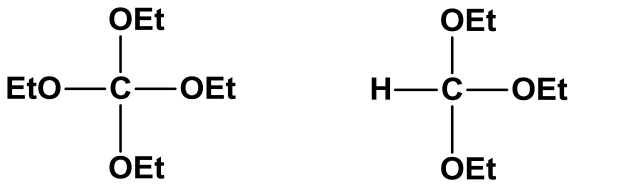
C.A. Bunton, R.H. De Wolfe.
J. Org. Chem. *30*, 1371 (1954).

BIMOLECULAR PROCESS: RELATIVE RATE

Orthoester of formic acid			
Rel. rate:	**6.4×10^8**	**2.5×10^9**	**1.0×10^{10}**
Entropy:	***1 cleavage***	***3 cleavages***	***3 cleavages***
Leaving group:	**CH_3OH**	**CH_3OH**	**C_2H_5OH**

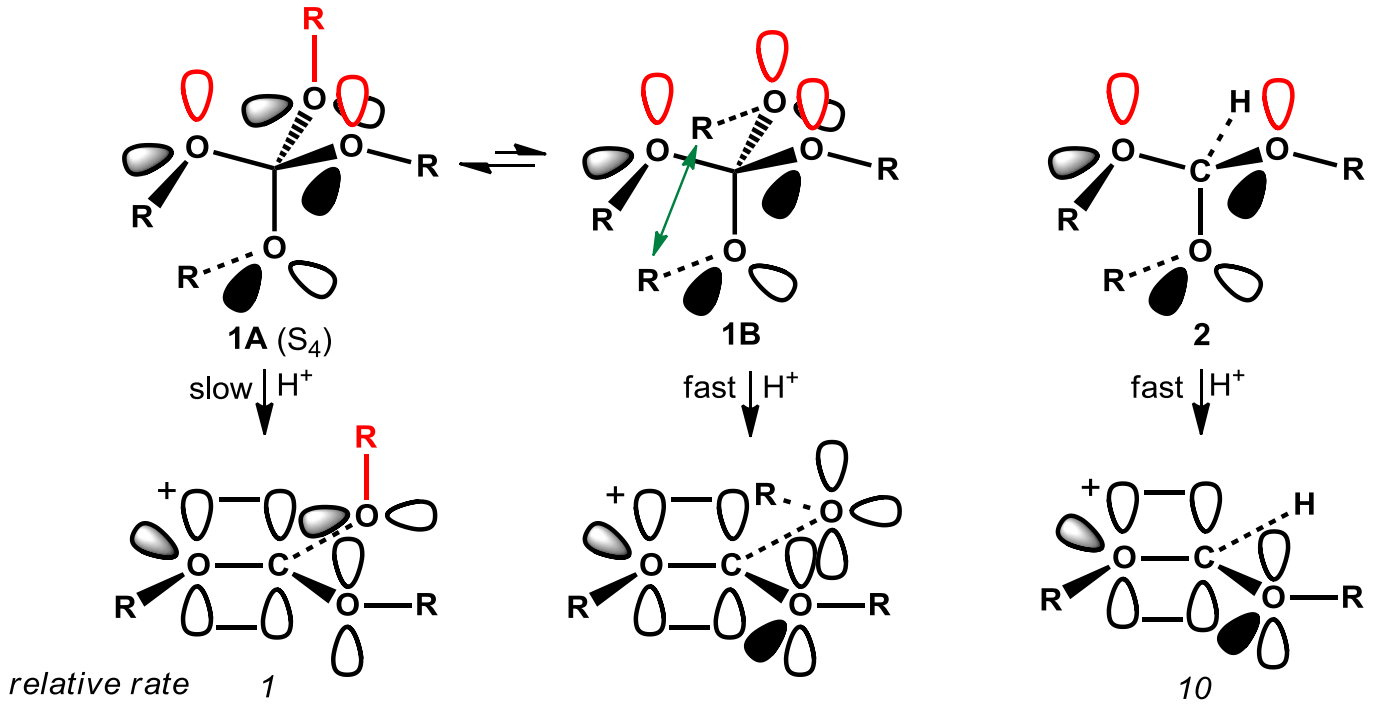
Orthoester of acetic acid		
Rel. rate:	**8.4×10^9**	**2.8×10^{11}**
Entropy:	***1 cleavage***	***3 cleavages***
Leaving group:	**CH_3OH**	**C_2H_5OH**

Sinnott Opposition to « Stereoelectronic » Effect



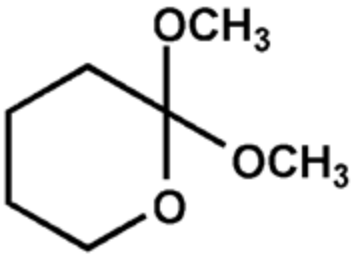
rate of hydrolysis **1** 1.0×10^{9} **2** 1.0×10^{10}

Sinnott[1] concluded that there is evidence that neither a steric nor any transition state "stereoelectronic effect" is responsible for the lower reactivity of the orthocarbonate vs orthoester. This 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 can have only two such lone pairs.



[1] Kandanarachchi, P., Sinnott, M. L. J. Chem. Soc., Chem. Commun. 1992, 777.
[2] Li, S., Deslongchamps, P. Tet. Lett. 1994, *35,* 5641.

RELATIVE RATE OF HYDROLYSIS: ORTHOESTER VS ORTHOCARBONATE



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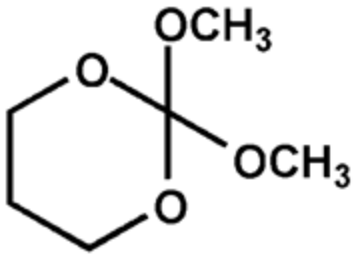

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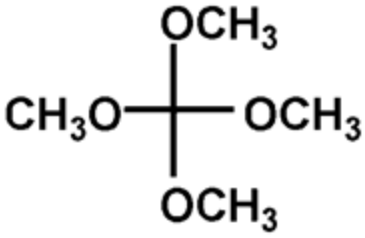

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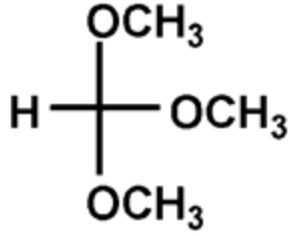

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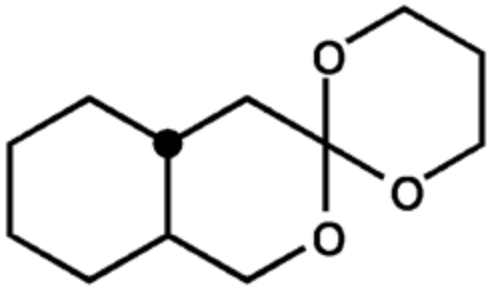

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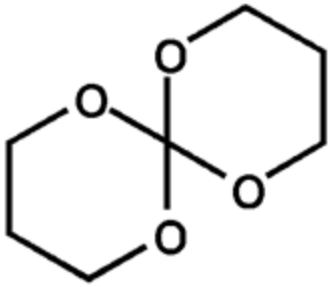
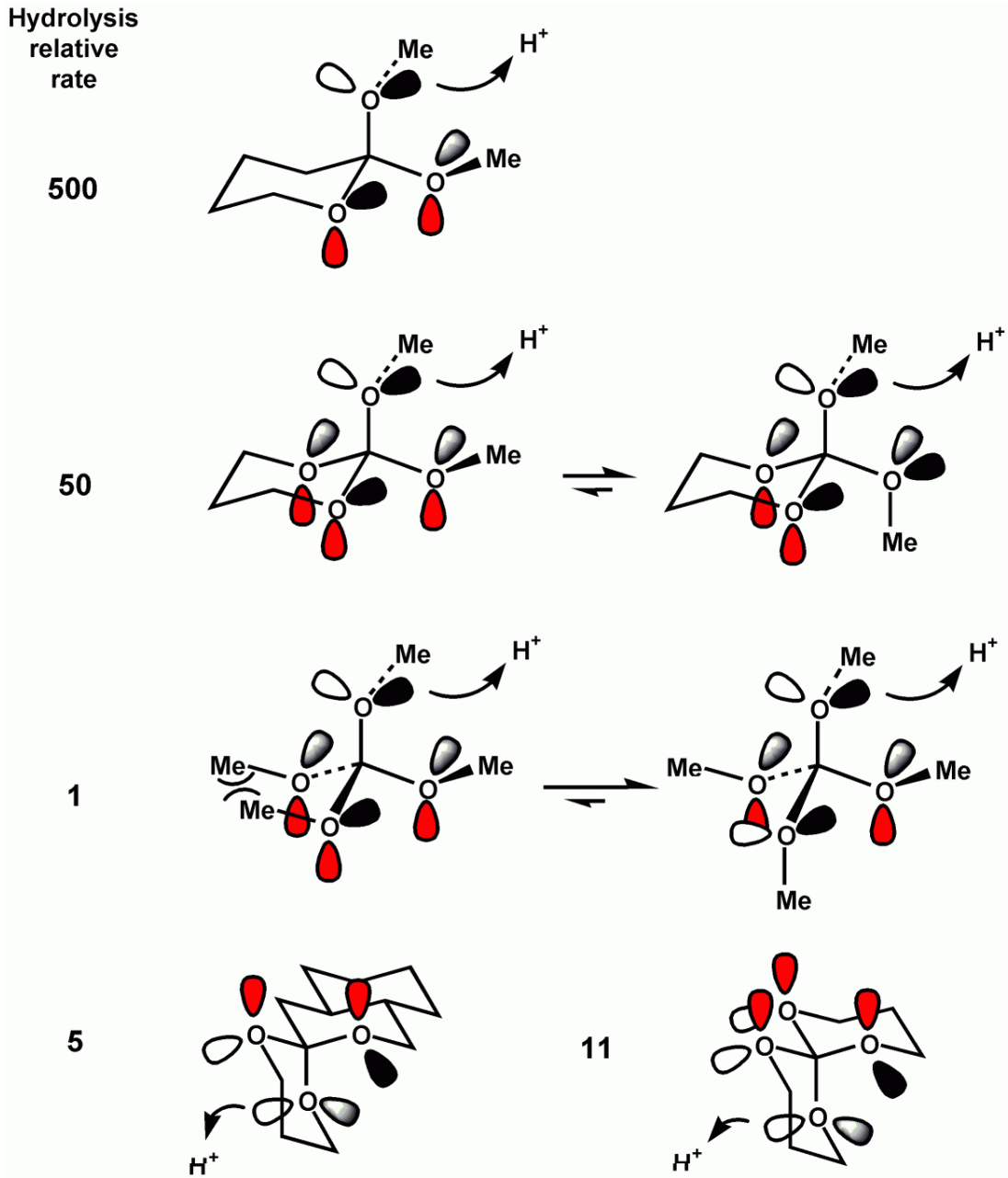


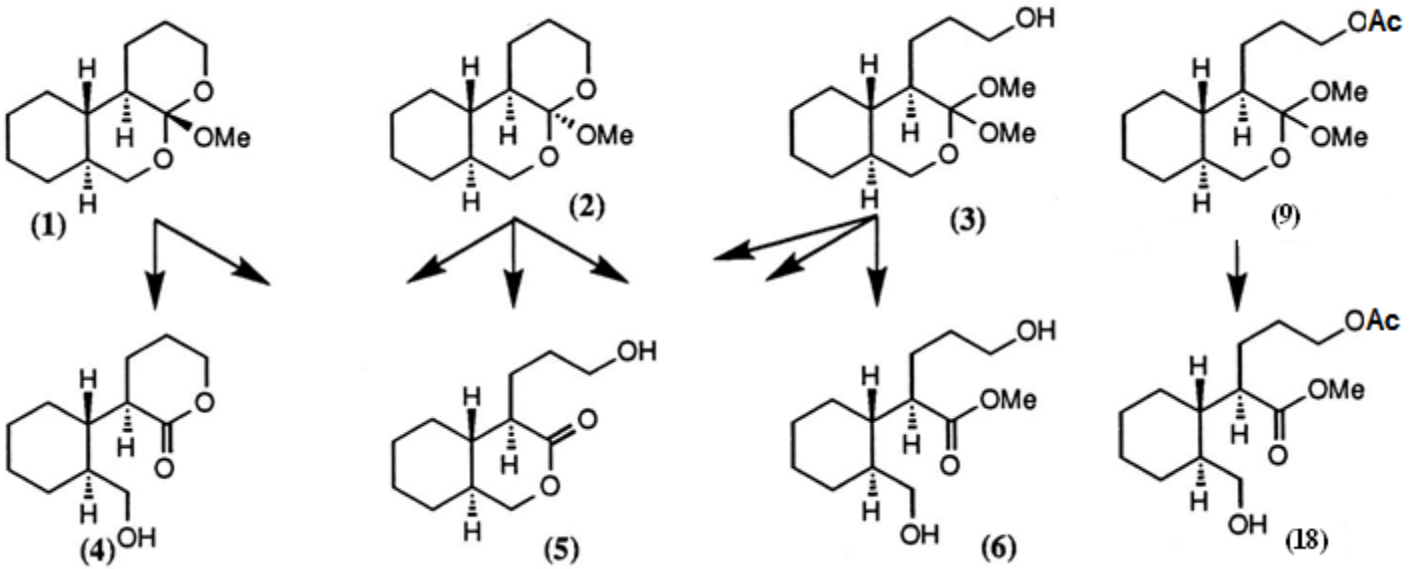
11

ORTHOESTER AND ORTHOCARBONATE:

RELATIVE RATE, CONFORMATIONAL ANALYSIS, AND STEREOELECTRONIC EFFECTS



Acid Hydrolysis of Tricyclic Orthoester



P. Deslongchamps, Y.L. Dory, S. Li.
Heterocycles 1996, *42,* 617.

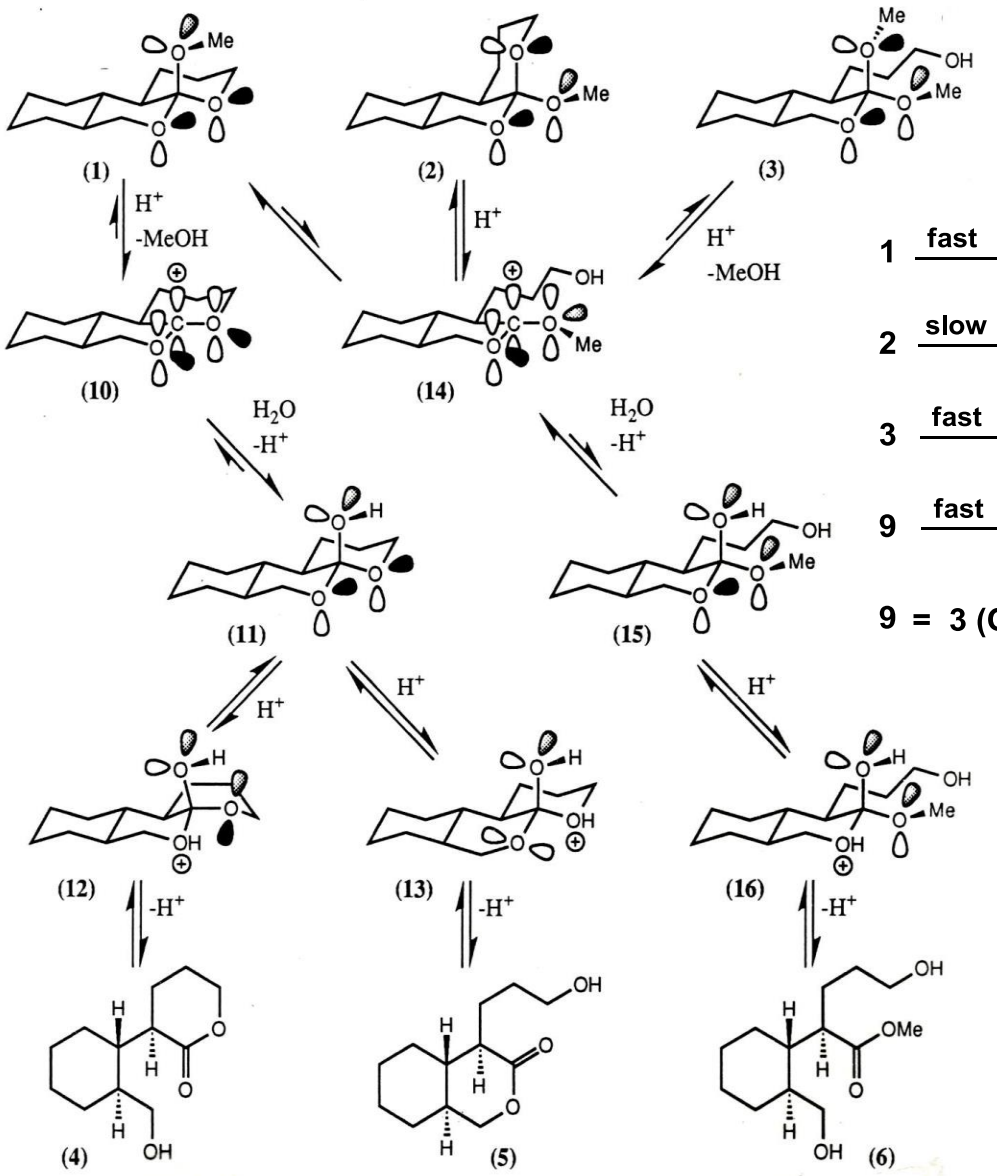
1 —fast→ 4 + 5 (80:20) (5: slow)

2 —slow→ 6 + 4 + 5 (4: slow)

3 —fast→ 6 + 4 + 5 (4: slow)

9 —fast→ 18 (no competing reclosure step)

Reaction Pathways of Hydrolysis of Orthoester



1 $\xrightarrow{\text{fast}}$ 4 + 5 (80:20)
slow

2 $\xrightarrow{\text{slow}}$ 6 + 4 + 5
slow

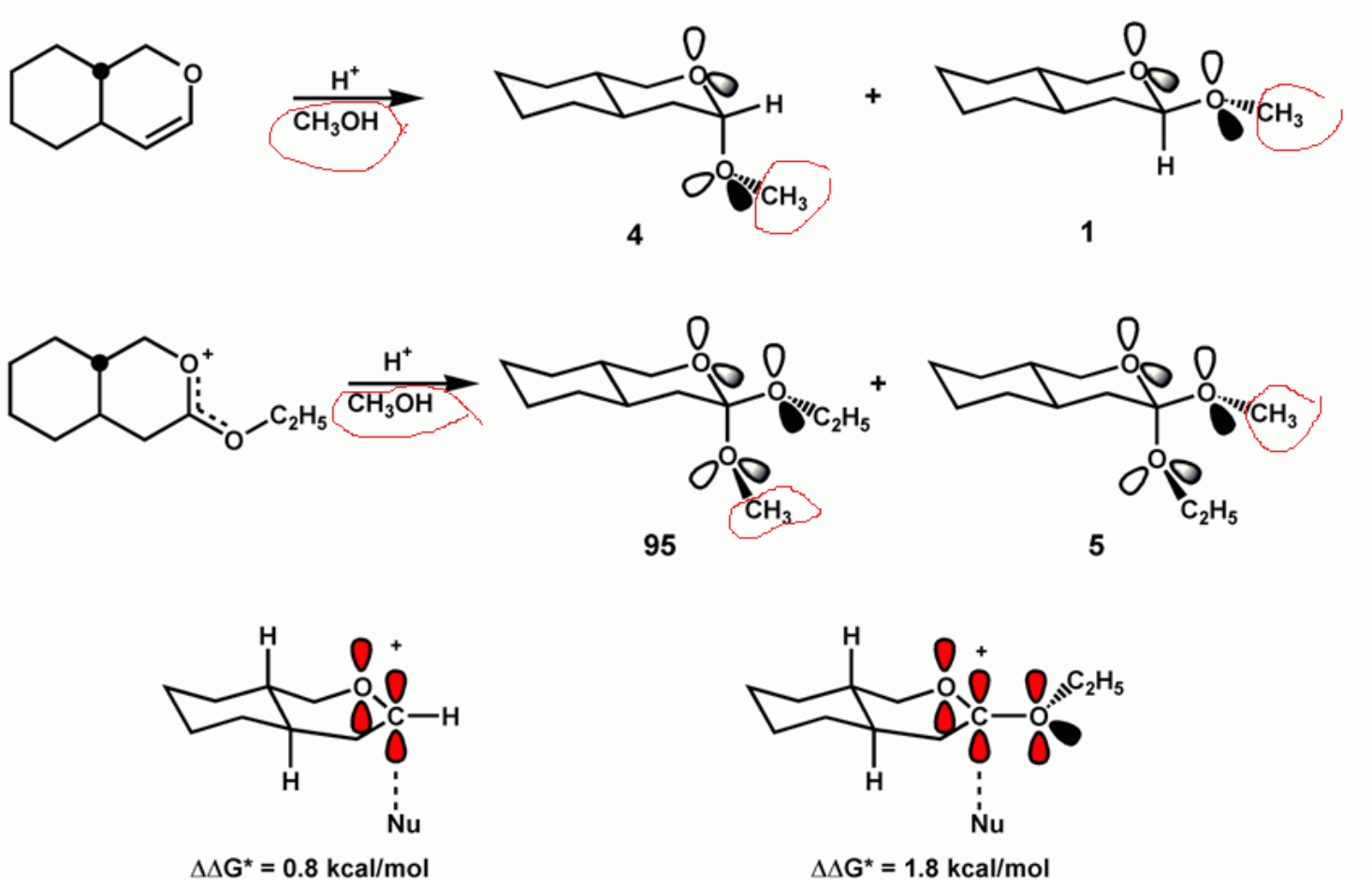
3 $\xrightarrow{\text{fast}}$ 6 + 4 + 5
slow

9 $\xrightarrow{\text{fast}}$ 18 (no competing reclosure step)

9 = 3 (OH = OAc) 18 = 6 ($CH_2CH_2CH_2OH$ = $CH_2CH_2CH_2OAc$)

P. Deslongchamps, Y.L. Dory, S. Li.
Heterocycles 1996, *42,* 617.

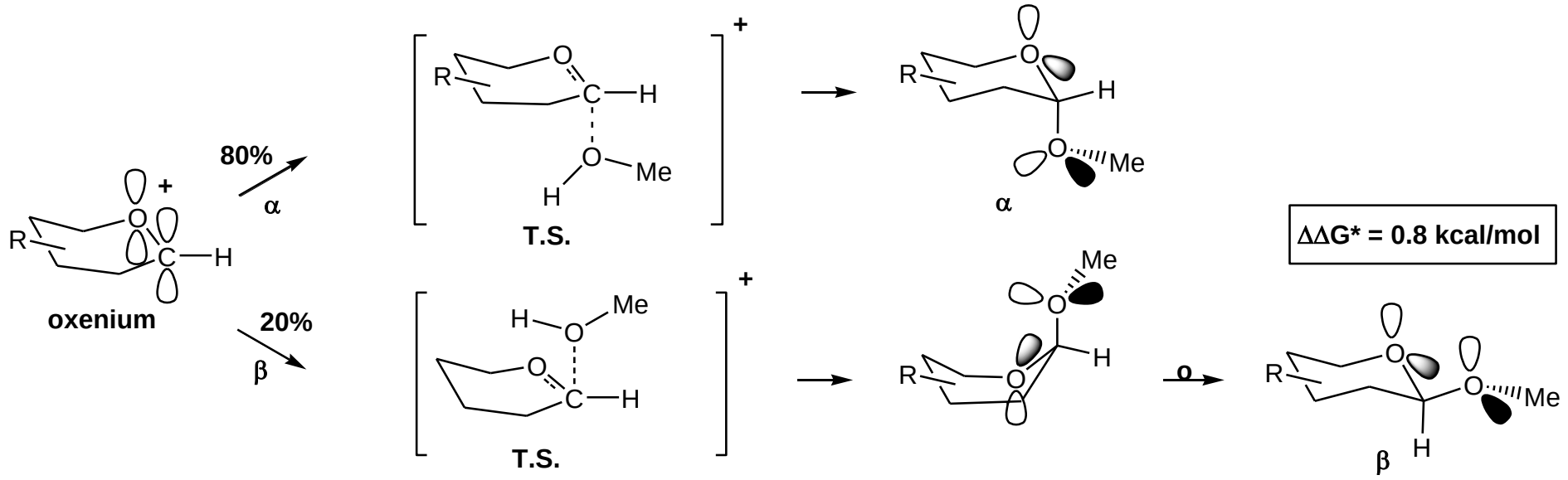
Position of transition state

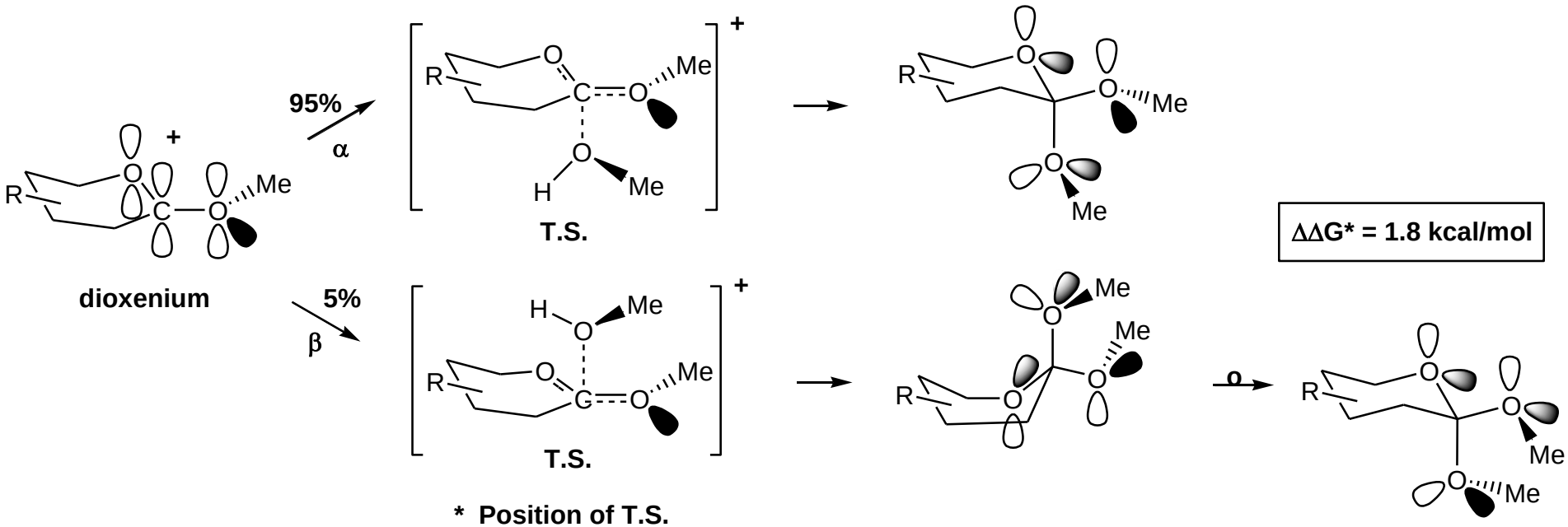


lower than β attack

lower than β attack

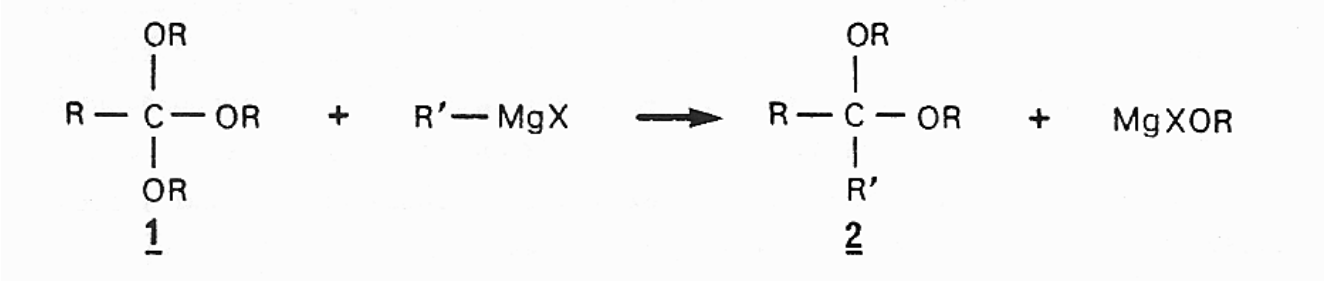
DIFFERENCE OF REACTIVITY BETWEEN OXENIUM AND DIOXENIUM IONS



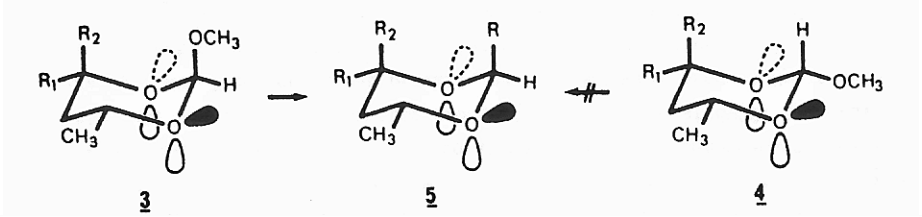


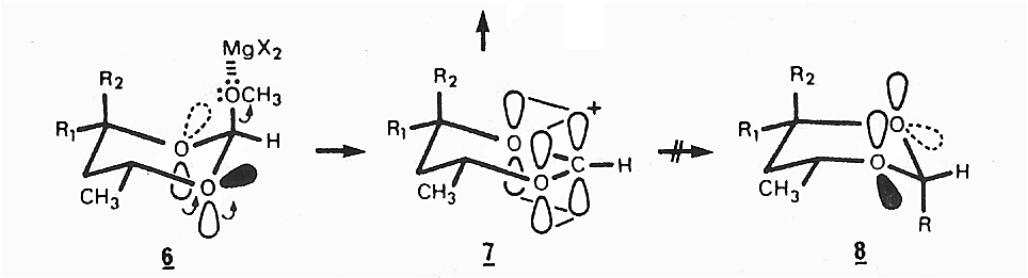
* Position of T.S.

ORTHOESTERS REACT WITH GRIGNARD REAGENTS TO YIELD ACETALS AND KETALS



Orthoester 3 gives 5 with axial R group; 4 is unreactive





3 and 4 ($R_1 = R_2 = H$; $R_1 = R_2 = CH_3$; $R_1 = CH_3$, $R_2 = H$)

Grignard Reagent ($R_1 = CH_3$, C_2H_5, $(CH_3)_2CH$, *p*-RCH_6H_4)

Eliel

N.B. Leaving OCH_3 group and incoming alkyl group prefer axial orientation.