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TETRAHEDRON REPORT

STEREOELECTRONIC CONTROL IN THE CLEAVAGE OF TETRAHEDRAL INTERMEDIATES IN THE HYDROLYSIS OF ESTERS AND AMIDES

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Abstract—A new stereoelectronic theory for the cleavage of the tetrahedral intermediate in the hydrolysis of esters and amides is presented. In this new theory, the precise conformation of the intermediate hemi-orthoester or hemi-orthoamide controls the nature of the hydrolysis products. It is postulated that the breakdown of a conformer of a tetrahedral intermediate depends upon the orientation of the lone pair orbitals of the hetero-atoms. Specific cleavage of a carbon–oxygen or a carbon–nitrogen bond in any conformer is allowed only if the other two hetero-atoms (oxygen or nitrogen) each have an orbital oriented antiperiplanar to the leaving O-alkyl or N-alkyl group. Experimentally, the oxidation of acetals by ozone and the acid hydrolysis of a series of cyclic orthoesters demonstrates clearly that there is indeed a stereoelectronic control in the cleavage of hemiorthoesters. Similarly, a study of the basic hydrolysis of a variety of N,N-dialkylated imidate salts shows that the same stereoelectronic control is operating in the cleavage of hemiorthoamides.

INTRODUCTION

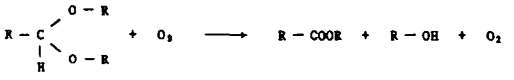
It is generally accepted that the most common mechanism for the hydrolysis of esters and amides proceeds through the formation of a tetrahedral intermediate. The conformation of this tetrahedral intermediate (hemi-orthoester from ester and hemi-orthoamide from amide) has never yet been considered to be an important parameter in order to obtain a better understanding of the hydrolysis reaction.[1] We wish to report a new stereoelectronic theory in which the precise conformation of the tetrahedral intermediate plays a major role.

In this theory, the nature of the products formed from the hydrolysis of an ester or amide depends upon the conformation of the tetrahedral intermediate. It is postulated that the precise conformation of the tetrahedral intermediate is transmitted into the products of the reaction and that the specific decomposition of such an intermediate is controlled by the orientation of the lone pair orbitals of the heteroatoms. Stereoelectronic cleavage of a tetrahedral intermediate is defined in the following way: specific cleavage of a carbon–oxygen or a carbon–nitrogen bond which occurs when two heteroatoms (oxygen or nitrogen) of the tetrahedral intermediate each have an orbital oriented antiperiplanar to the departing O-alkyl or N-alkyl leaving group.

This theory originated in our study of the oxidation of acetals to esters with ozone.[2] We will first describe this reaction and then disclose the principle of stereoelectronic control in the cleavage of hemi-orthoesters[3] which provides an explanation for the formation of products in the ozonolysis of acetals. We will then furnish independent experimental evidence that specific cleavage of hemi-orthoesters does indeed take place, based upon a study of the acid hydrolysis of cyclic mixed orthoesters. Experimental evidence will then be provided to show that the oxidation of acetals with ozone proceed through the formation of a tetrahedral intermediate. Concurrent hydrolysis and isotope oxygen exchange in the hydrolysis of *E* and *Z* esters will also be discussed. Finally, the theory of stereoelectronic control in the cleavage of hemi-orthoamides will be presented.[4] The study presented here on the hydrolysis of imidate salts will confirm that stereoelectronic control occurs in the cleavage of hemi-orthoamides.

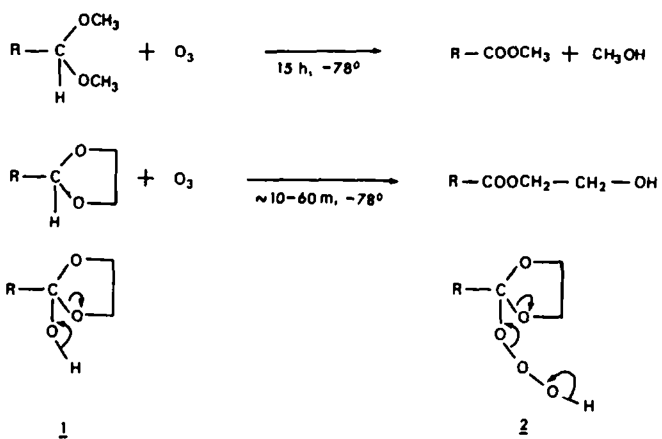
Ozonolysis of acetals

We reported in 1971 that ozone reacts in a completely specific fashion with the acetal function derived from an aldehyde to give the corresponding ester and alcohol. This new reaction is a general one; the nature of the alkyl groups of the acetal function does not influence the final result, and this reaction proceeds in essentially quantitative yield. However, we have found that there is a tremendous difference in the rate of reaction depending on the nature of the acetal function (Scheme 1); cyclic acetals react much faster (few min at −78°) than the acyclic ones (≈15 hr at −78°). The observed large difference in rates of oxidation of cyclic as compared to acyclic acetals was the first indication that there was a direct relationship between the conformation of the acetal function and its reactivity toward ozone. We believe that this reaction involves the insertion of ozone into the C–H bond of the acetal forming an intermediate such as 1 or 2,[5] which can then break down to give the reaction products, the ester and the alcohol.

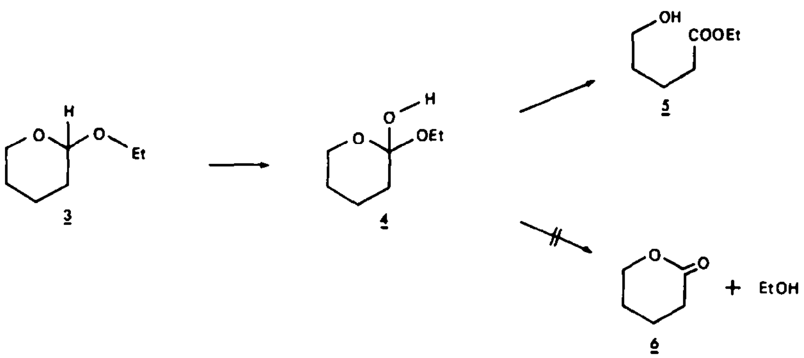


$$R-\underset{H}{C}\begin{smallmatrix}O-R\\O-R\end{smallmatrix} + O_3 \longrightarrow R-COOR + R-OH + O_2$$

We next investigated the oxidation of acetals where the OR groups were not identical. It was of interest to examine such substrates because a tetrahedral intermediate formed during the oxidation of such unsymmetrical acetals, could decompose in two different ways. For instance, a substrate such as 3 (Scheme 2) should lead to an intermediate such as 4. Intermediate 4 could decompose to give the hydroxy-ester 5, or the lactone 6, plus the



Scheme 1.

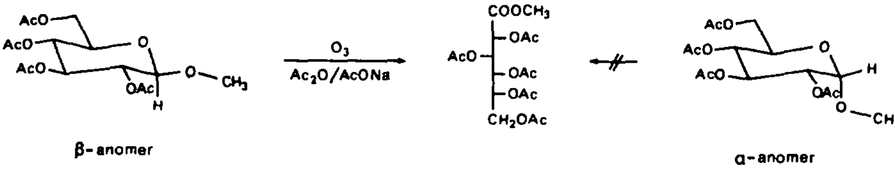


Scheme 2.

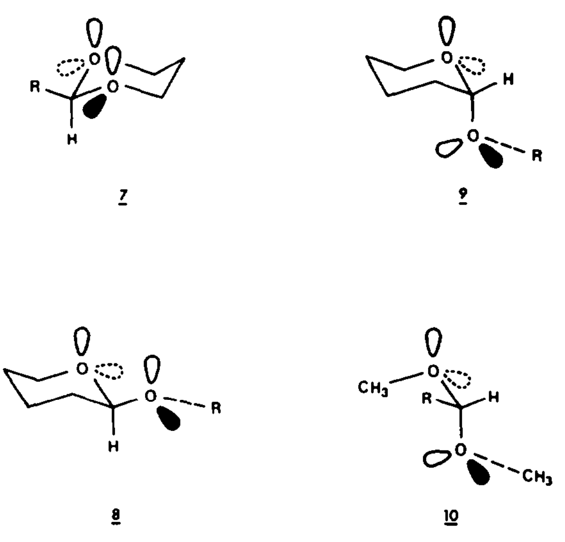
alcohol. We found experimentally that ozone reacts smoothly with tetrahydropyranyl ethers in a completely specific manner, yielding the hydroxy-ester **5** exclusively. No trace of lactone **6** could be detected. Thus, it can be immediately concluded that if the ozonolysis reaction proceeds through the formation of hemiorthoester **4** or its equivalent, this intermediate must decompose in a very specific manner!

After completing our work on the simple tetrahydropyranyl ethers, the logical next step was to study this new reaction on tetrahydropyranyl ethers which possessed a rigid chair conformation. Consequently, the oxidation of a series of conformationally rigid α- and β-methyl glycopyranosides was undertaken. We found a very interesting result: the β-anomers were smoothly oxidized by ozone while the α-anomers were recovered unchanged. For example, methyl 2,3,4,6 - tetra - O - acetyl - β - D - glucopyranoside was converted into methyl 2,3,4,5,6 - penta - O - acetyl - gluconate, while the corresponding α-anomer was shown to be completely unaffected under the same reaction conditions (Scheme 3).

The preceding results can be summarized in the following way: cyclic acetals **7** react readily with ozone, while acyclic acetals **10** react slowly; β-glycosides **8** are reactive, but α-glycosides **9** are inert (Scheme 4). These results suggested that there was a relationship between the conformation of the acetal function and its reactivity toward ozone. After viewing models of the compounds under consideration, we made the following proposal: *any reactive conformer must have on each oxygen atom a lone pair orbital oriented antiperiplanar to the* C–H *bond of the acetal function.*[2]. This requirement was met in the 1,3-dioxane acetals **7** and the most stable rotamer of the β-glycosides **8**.[6] In an α-glycoside, which can be represented as its favored rotamer by structure **9**, the ring oxygen orbitals are not oriented anti-periplanar to the C-H bond; it is the ring carbon–oxygen bond which is antiperiplanar. The lone pair orbitals of the ring oxygen in an α-glycoside (regardless of the rotamer) are never available, indicating that the oxidation does not proceed at detectable rate if only one oxygen has one orbital properly oriented. Furthermore, acyclic dialkoxy acetals are known[7] to exist in one preferred conformation **10** which is identical to the favored rotamer of an α-glycoside **9**. This is quite normal because this conformer is the only one which avoids the anomeric effect.[6] Conformer **10** is inert toward ozone. In order to react with ozone, the



Scheme 3.



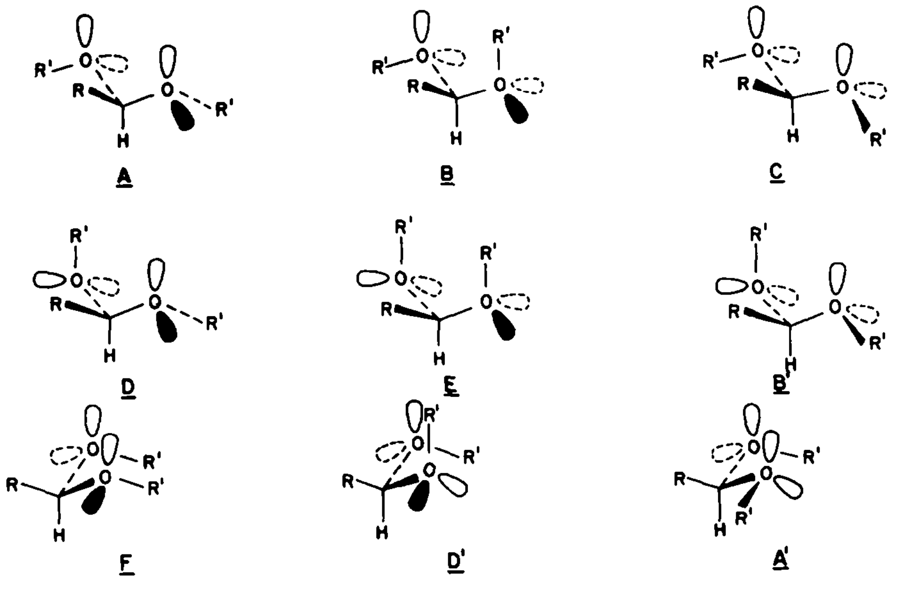
Scheme 4.

dialkoxy-acetals must adopt another conformation which has proper orbital orientation. However, any reactive conformer of the dialkoxy-acetal will be present only in a very small amount at equilibrium because such a conformer has to overcome the anomeric effect which exists when two lone pair orbitals are in a 1,3-*syn*-periplanar arrangement.† Consequently, the reaction rate, which is dependent upon the concentration of the reactive conformer, will be low.

It was clear at this stage of our investigation that the postulate of the orientation of the lone pairs had to be verified in a more rigorous manner. Consequently, we had to consider all the possible gauche conformers that an acetal function can assume, make rigid chemical models for each of them if possible and compare their respective reactivity toward ozone.

Scheme 5 shows the nine gauche conformers that are theoretically possible for an acetal function. Conformers A, B and D have no plane of symmetry. In fact, conformers A′, B′ and D′ are their respective mirror images, and therefore chemically equivalent. The remaining conformers C, E and F possess a plane of symmetry. Consequently, there are only six conformers for an acetal function (A, B, C, D, E and F) which are chemically different. Of these, only conformers A, C and F possess a lone pair orbital on each oxygen oriented antiperiplanar to the C–H bond. Conformers B and D have only one oxygen with a lone pair properly oriented, and conformer E has none. Consequently, if the above postulate is valid, conformers B, D and E should be inert and conformers A, C and F should be reactive.

Scheme 6 describes the conformers of Scheme 5 in which a 6-membered ring has been incorporated. One can observe that the first three conformers A, B and C represent the three rotamers of a conformationally rigid β-glycoside. Conformers D, E and B′ correspond to the three conformers of a rigid α-glycoside. We have found that α-glycosides are inert toward ozone, conformers D, E and B′ are therefore not reactive. Conformer B′ is chemically equivalent to conformer B; they are mirror images in Scheme 5, and B is therefore not reactive. These conformers were further eliminated by observing that *cis* - 1,8 - dioxaoctahydronaphthalene **11** does not react with ozone (Scheme 7). Being a *cis* decalin, this compound **11** is conformationally mobile and exists in the two conformations **12** and **13** which are in perfect equilibrium since they are mirror images; they also correspond to conformers B and B′ respectively and constitute ideal chemical models for these two conformers. *trans* - 1,8 - Dioxaoctahydronaphthalene **14** is an excellent rigid model for conformer C and it was readily oxidized by ozone to hydroxylactone **15** in quantitative yield within 1·5 hr at −78°. 6,8 - Dioxabicyclo[3.2.1]octane **16** is a rigid model for conformer E and it was found to be unreactive toward ozone. This result has to be taken with some reserve; this compound is not the most appropriate rigid model for E since the hydrogen of the acetal function is incorporated in a bridgehead. Conformer D is the most stable rotamer of an α-glycoside, since α-glycosides are inert to ozone, D



Scheme 5.

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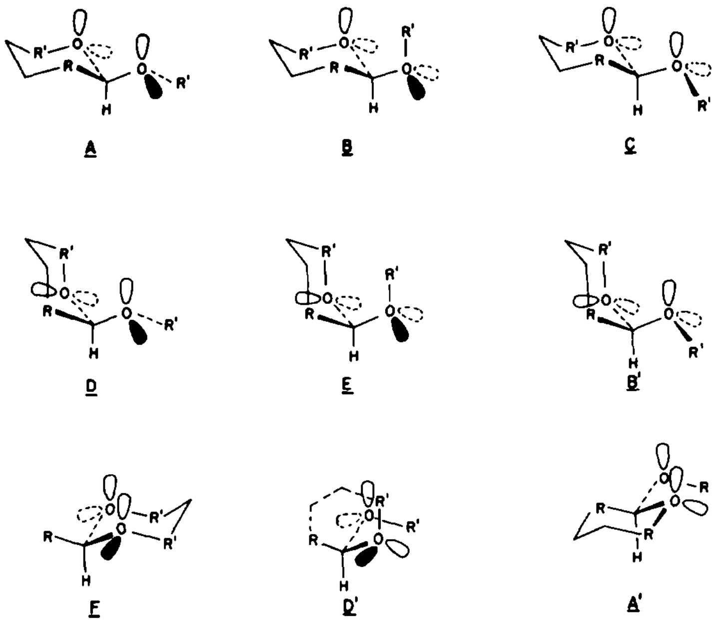
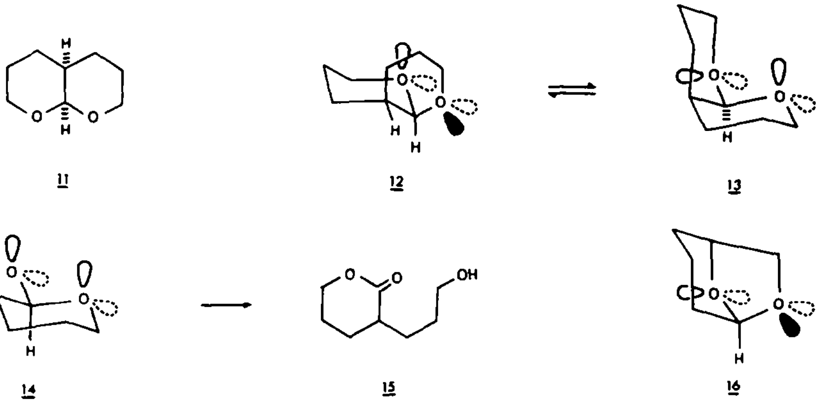
†A 1,3-*syn*-periplanar arrangement is equivalent to a 1,3-diaxial arrangement in a six-membered ring.



Scheme 6.



Scheme 7.

is eliminated as a reactive conformer and there is no need to look for a more rigid chemical model for this one. Conformer A or its mirror image A′ represents the most stable rotamer for a β-glycoside, and it is very likely that A is a reactive conformer. The best chemical model that we have studied for conformer A is the β-glycoside. It is very difficult to construct a rigid bicyclic model of the preferred rotamer of a β-glycoside; the direction that the O–R′ bond is taking makes it difficult to reattach this side chain to the ring in a rigid manner. Finally, 1,3-dioxane acetals represent an ideal model for conformer F and such acetals have been shown to be reactive with ozone. The relationship between the conformation of the acetal function and its reactivity toward ozone was further confirmed by a study of the ozonolysis of some conformationally labile glycopyranosides as well as some glycofuranosides.

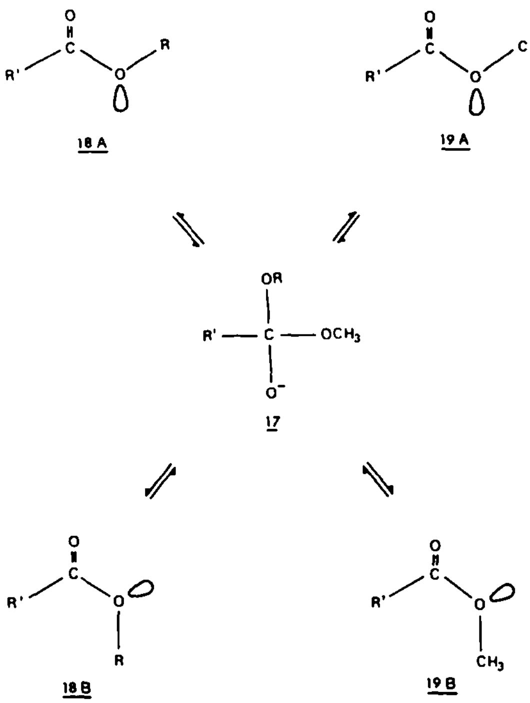
The preceding experimental results establish fairly rigorously that of the six possible gauche conformers for an acetal function, three (**A**, **C** and **F**) are reactive and three (**B**, **D** and **E**) are inert toward ozone. Consequently, we consider that the postulate that each reactive gauche conformer of an acetal function needs to have a lone pair orbital on each oxygen oriented antiperiplanar to the C–H bond, has been verified.

We have also postulated that the oxidation of acetals proceeds via the formation of a hemi-orthoester as an intermediate. The formation of such intermediate explains very well the products of the reaction. Also, if this postulate is correct, it means that a tetrahedral intermediate such as **4** (Scheme 2) decomposes in a completely specific manner, yielding the hydroxy-ester **5**, none of the lactone **6** being observed. Thus, the question arises whether the orientation of the lone pair orbitals also plays an important role in the cleavage of hemi-orthoesters.

Indeed, we have been able to develop a theory of stereoelectronic control which can predict the cleavage of hemi-orthoester. In this new approach, the precise conformation of the tetrahedral intermediate and the orientation of the lone pair orbitals are the two important factors.

Stereoelectronic control in the cleavage of hemi-orthoesters

A hemi-orthoester intermediate such as **17** (Scheme 8) can be cleaved to yield two different esters, **18** and **19**,



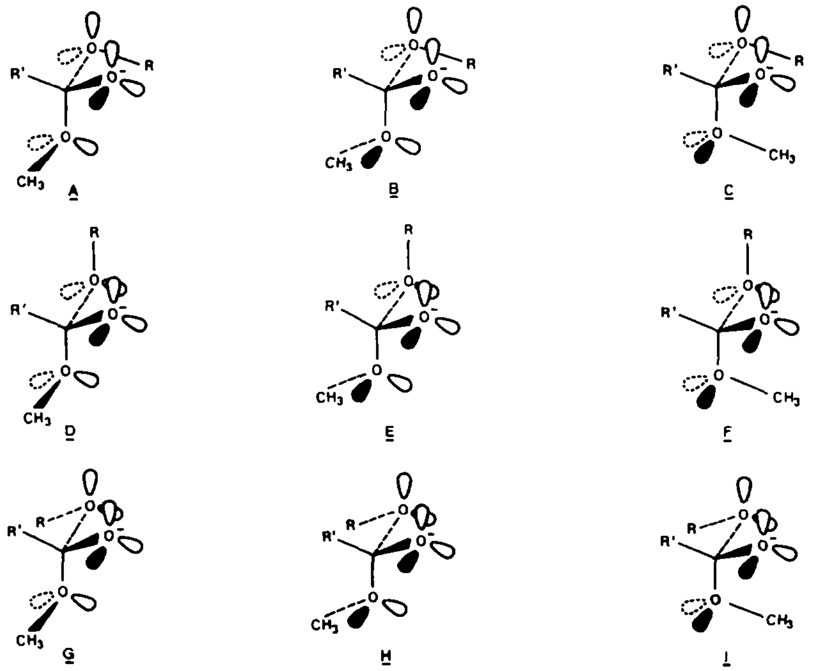
Scheme 8.

each of which can have a *trans* (*E*) or a *cis* (*Z*) conformation.[8,9] Thus, 17 can lead, in principle, to four products: **18A**, **18B**, **19A** or **19B**. Theoretically, there are nine different gauche conformers for a tetrahedral intermediate such as 17 (Scheme 9). The stereoelectronic theory which predicts the manner by which each tetrahedral conformer can cleave, is very simple: The precise conformation of the tetrahedral intermediate is transposed into the product of the reaction and a cleavage of a C–O alkyl bond is allowed only if the other two oxygens of this intermediate each have an orbital oriented antiperiplanar to the C–O alkyl bond to be broken. We will examine in detail the stereoelectronically controlled cleavage of conformers **A**, **B** and **C** as examples.

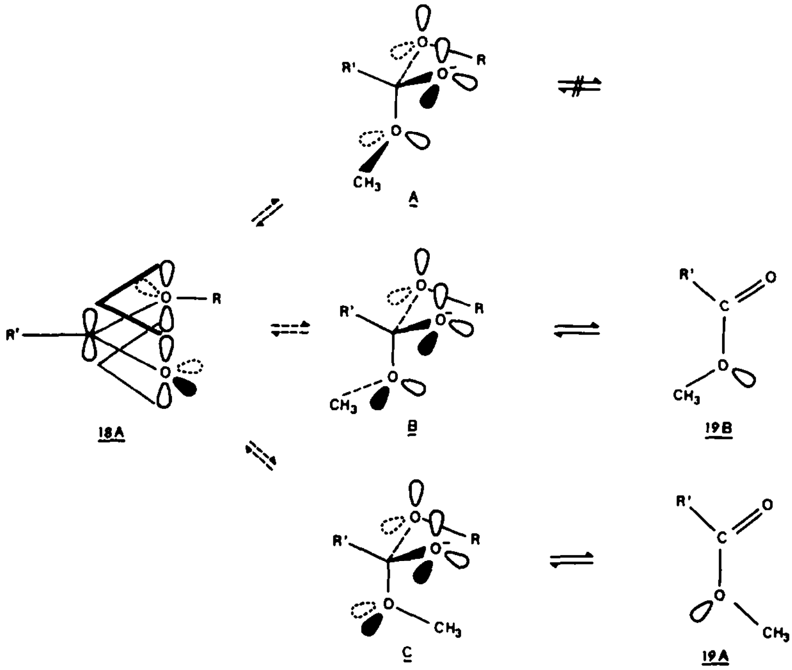
Conformer **A** (Scheme 10) is allowed to break down in only one direction yielding the *E*-ester **18A** by ejecting the OCH_3 group. The C–OCH_3 bond can be easily cleaved because the negative oxygen and the OR oxygen each have an orbital oriented antiperiplanar to this bond. The R'–C bond in conformer **A** is antiperiplanar to the O–R bond, and this spatial arrangement will be transposed in the resulting ester. Thus, stereoelectronically controlled cleavage of **A** furnishes the **E** ester **18A**. The negative oxygen has one orbital oriented antiperiplanar to the C–OR bond, but the oxygen of the OCH_3 group does not: it is the CH_3–O bond which is antiperiplanar to the C–OR bond. Consequently, the cleavage of the C–OR bond in conformer **A** should be a higher energy process than the cleavage of the C–OCH_3 bond because the ejection of the OR group cannot be achieved with the assistance of a lone pair orbital properly aligned on each of the two remaining oxygens. This process should therefore not be observed.

Conformer **B**, like conformer **A**, possesses proper orbital orientation and has a correct conformation to give the *E*-ester **18A**. In addition, it can be cleaved in a stereoelectronically controlled manner to give the *Z*-ester **19B**, because conformer **B** has one orbital on the negative oxygen and one on the oxygen of the OCH_3 group properly aligned to permit the ejection of the OR group. The R' group in **B** is in a gauche orientation with respect to the CH_3 group, so, the *Z*-ester **19B** should be obtained. Thus, conformer **B** has proper orbital orientation and conformation to give either the *E*-ester **18A** or the *Z*-ester **19B**.

Conformer C, like conformers **A** and **B**, also has proper conformation and orbital orientation to give the *E*-ester **18A**. It can also give the *E*-ester **19A**, since the negative oxygen and the oxygen of the OCH_3 group each have an orbital antiperiplanar to C–OR bond, and the conforma-



Scheme 9.



Scheme 10.

tion of **C** is such that the R′–C bond is antiperiplanar to the O–CH_3 bond. Thus, **C** can either give *E* esters **18A** or **19A** via stereoelectronic control. Table 1 describes the stereoelectronic cleavages that are theoretically possible for the nine different gauche conformers of hemi-orthoester **17**.

According to the principle of microscopic reversibility, the generation of a hemi-orthoester via alkoxide ion attack on an ester should also occur with stereoelectronic control. Thus, when methoxide ion reacts with **18A** for example, it can either give conformer **A**, **B** or **C**. These conformers are the result of methoxide ion attack perpendicular to the plane of the ester **18A**. The *E*-conformation of the starting ester **18A** is thus transposed into the intermediate and, since methoxide ion can present itself in three different orientations, the three hemi-orthoester conformers **A**, **B** and **C** are theoretically possible.

Table 1

Ester 18		Conformer		Ester 19
E	$\rightleftharpoons$	A	$\not\rightleftharpoons$	
E	$\rightleftharpoons$	B	$\rightleftharpoons$	Z
E	$\rightleftharpoons$	C	$\rightleftharpoons$	E
	$\not\rightleftharpoons$	D[a]	$\not\rightleftharpoons$	
	$\not\rightleftharpoons$	E	$\rightleftharpoons$	Z
	$\not\rightleftharpoons$	F	$\rightleftharpoons$	E
Z	$\rightleftharpoons$	G	$\not\rightleftharpoons$	
Z	$\rightleftharpoons$	H	$\rightleftharpoons$	Z
Z	$\rightleftharpoons$	I	$\rightleftharpoons$	E

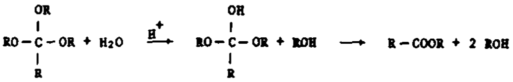
[a] If a rigid conformer such as **D** is produced, it should cleave but the transition state will be of higher energy. Ozonolysis of *trans*-1,8-dioxaocta-hydronaphthalene gives an intermediate equivalent to **D**[2].

The products formed in the ozonolysis reaction can now be easily explained. A tetrahydropyranyl ether reacts with ozone (Scheme 11) through its most stable rotamer **8**, giving specifically the tetrahedral intermediate **20**. This intermediate has proper orbital orientation to break the ring oxygen–carbon bond, thus forming the hydroxy-ester **5**. Loss of the OR group to generate the δ-lactone **6** is not possible through an orbital assisted mechanism simply because the lone pair orbitals of the ring oxygen are not properly aligned. It is the C_6–O bond of the ring oxygen which is antiperiplanar to the OR group. The intermediate **20** is an example of conformer **A** in Scheme 10.†

This explanation is of course valid only if the ozonolysis reaction really occurs through the formation of a hemi-orthoester intermediate. It is however experimentally difficult to demonstrate that a hemi-orthoester is formed in the course of this reaction. Thus, the results obtained from the ozonolysis reaction could be utilized to propose the stereoelectronic theory but not to verify it. Consequently, it was necessary to find another method to generate hemi-orthoesters in order to confirm that specific cleavage does indeed take place.

Hydrolysis of cyclic mixed orthoesters

The formation of esters from the mild acid hydrolysis of ortho-esters doubtless proceeds through the formation of a hemi-orthoester intermediate as described in the following equation.[10]



$$RO-\overset{OR}{\underset{R}{C}}-OR + H_2O \xrightarrow{\overset{+}{H}} RO-\overset{OH}{\underset{R}{C}}-OR + ROH \longrightarrow R-COOR + 2\,ROH$$

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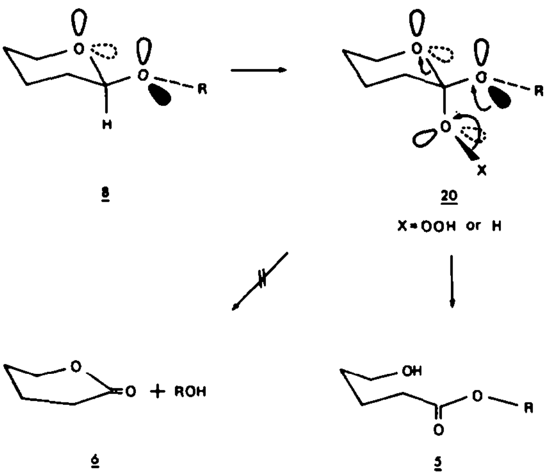
†The theory also implies that when a tetrahedral intermediate can break down in a stereoelectronically controlled fashion, the energy barrier for its cleavage is much lower than that for rotation to give other conformers. Consequently, the lifetime of **20** will be very short and there is no need to consider conformers other than **20**.

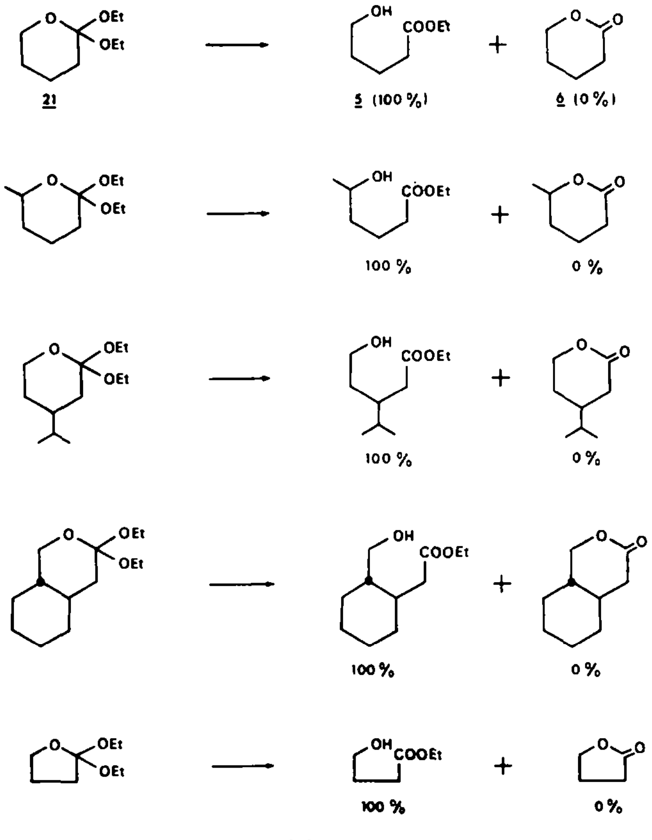


Scheme 11.

Accordingly, the preparation and the hydrolysis of the cyclic orthoesters shown in Scheme 12 was undertaken. The formation of products from the mild acid hydrolysis of these orthoesters was followed by 13C-NMR spectroscopy. After 10 min at room temperature, the hydrolysis of the orthoesters was completed and the corresponding hydroxy-esters were formed exclusively. No lactone products were detected. These results constitute rigorous experimental evidence that hemiorthoesters do indeed break down in a specific manner.†

In order to see if the stereoelectronic theory can explain the exclusive formation of hydroxy-ester from the mild acid hydrolysis of orthoesters, we must consider the stereoelectronically controlled cleavage of precise conformations of hemi-orthoesters. Consequently, all the possible conformations that an orthoester can assume must first be considered. The simple 6-membered cyclic orthoester **21** is a good example to use because it is preferable to discuss precise conformation in a 6-membered rather than in a 5-membered ring.

There are nine gauche conformers which are theoretically possible for the cyclic orthoester **21**. They are described in Scheme 13. The next task is to define which conformers of **21** should be taken into consideration. It is logical to assume that the hydrolysis of **21** will proceed through the most energetically favored conformers which have at the same time, proper orbital orientation to permit the cleavage of a carbon–oxygen bond. A detailed examination of each conformer shows that six of them (**B**, **C**, **D**, **G**, **H** and **I**) are readily eliminated. There is a severe 1,3-*syn*-periplanar interaction between the two ethyl groups in conformers **B** and **D**, thus the population of these conformers at equilibrium will be very small. Conformers **G**, **H** and **I** can also be ruled out by using a similar argument; the ethyl group of the axial ethoxy group in each conformer is in a 1,3-*syn*-periplanar arrangement with two methylenes (C_3 and C_5) of the ring; thus, there is two severe 1,3-*syn*-periplanar steric interactions in **G**, **H** and **I**. The population of these conformers



Scheme 12.

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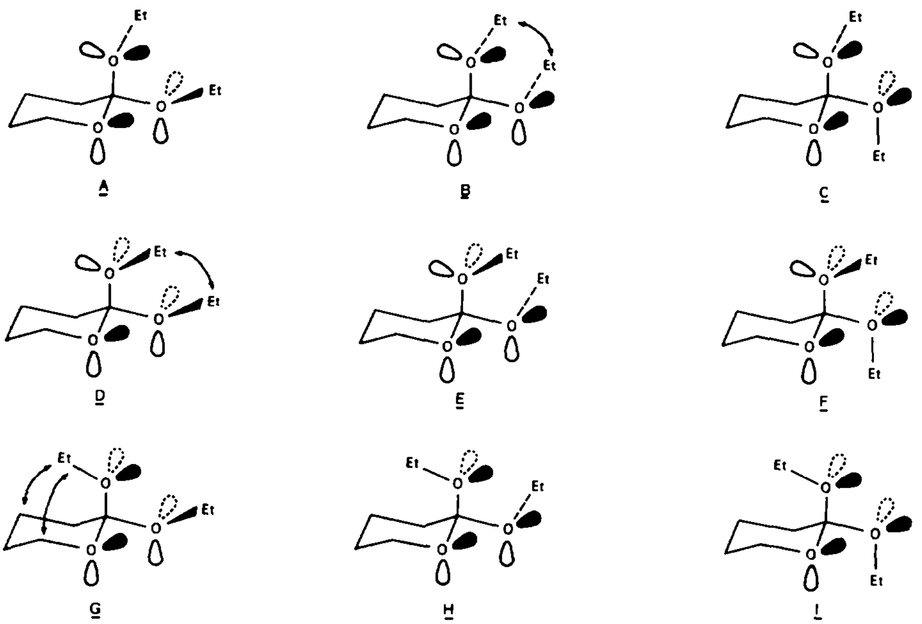
†The hydrolysis of **21** was also carried out with ^{18}O-labeled water. The resulting hydroxy-ester **5** was then acetylated to give the acetoxy-ester **5** (H = CH_3CO). Mass spectral analysis showed that the labeled oxygen was incorporated exclusively in the $COOC_2H_5$ group. This result confirms that the hydrolysis of **21** occurs via the formation of an hemi-orthoester as intermediate.

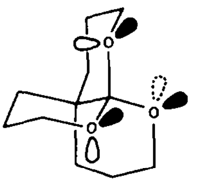


Scheme 13.

will be very small at equilibrium, they can therefore be neglected.

The remaining four conformers **A**, **C**, **E** and **F** do not suffer substantial internal strong steric interactions. The magnitude of the anomeric effect,[6] which occurs whenever two lone pair orbitals are in a 1,3-*syn*-periplanar arrangement, is approximately the same in each conformer. Two of such orbital arrangements are present in conformers **A**, **E** and **F**. Conformer **C** has three. Thus, these four must represent the most important conformers of **21**.

Conformer **C** must be eliminated as a reactive conformer simply because it does not have proper orbital orientation on two oxygen atoms to permit the cleavage of the C–O bond of the third oxygen atom. We have prepared the tricyclic orthoester **22**[11] which is a perfect rigid model for conformer **C**. When compound **22**, which is soluble in water, was submitted to the mild acidic conditions used for the hydrolysis of the preceding orthoesters, it was found to be completely stable after 24 hr at room temperature. Consequently, we have obtained strong experimental support that conformer **C** is not reactive. Indeed, it is a remarkably unreactive conformer and can therefore be eliminated.



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The remaining conformers **A**, **E** and **F** each have two oxygens with proper orbital orientation to cleave the C–O bond of the third oxygen atom. They will therefore be considered separately.

The cleavage of conformer **A** (Scheme 14) can only give the dioxolenium ion **23** because of the orbital orientation. This ion **23** will then be attacked by water on the β face to form specifically the hemi-orthoester **24** in which the ring oxygen and the OEt oxygen each have an orbital antiperiplanar to the C–OH bond which has just been formed. Attack of water with stereoelectronic control, on the α face of ion **23** would result in a hemi-orthoester with a ring in a boat form. The hemi-orthoester **24** can break down in the direction of the hydroxy-ester **5** only; the OH and the OEt groups each have an orbital oriented antiperiplanar to the ring oxygen–C_1 bond. The conversion of **24** into δ-valerolactone **6** is a higher energy process because the ring oxygen atom does not have proper orbital orientation to assist the cleavage of the C–OEt bond.

Conformer **F** (Scheme 14) should also yield the hydroxy-ester **5** exclusively, since orbital orientation permits only the cleavage of the ring oxygen–carbon bond, yielding the dioxolenium ion **25**. Hydration of this ion **25** can be done in two ways giving the hemi-orthoesters **26** and **27**. Nevertheless each hemi-orthoester **26** and **27** can then break down to give only the hydroxy-ester **5**.

Conformer **E** (Scheme 15) has proper orbital orientation to permit the cleavage of the axial ethoxy group; the ion **28** will thus be formed and hydration will then give the hemi-orthoester **29**. The hemi-orthoester **29** does not have proper orbital orientation to permit the cleavage of a carbon–oxygen bond. In order to break down, **29** will have to rotate one of its C–O bonds to obtain a reactive conformer.† For example, a rotation of the C–OEt bond will give **24** which will break down to give the hydroxy-ester **5**. A chair inversion of **29** to **30** is also possible in a conformationally labile system; this new

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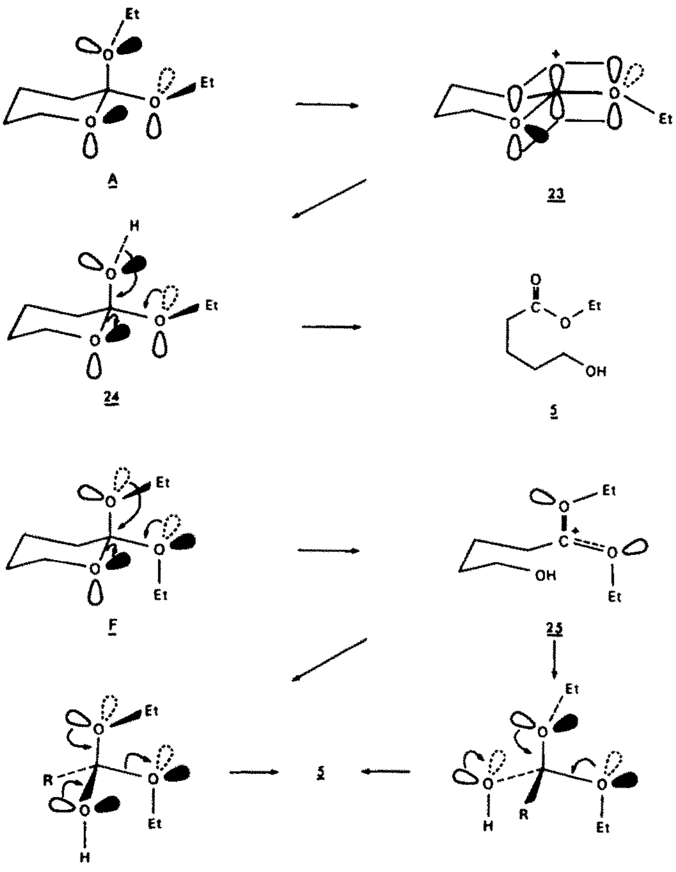
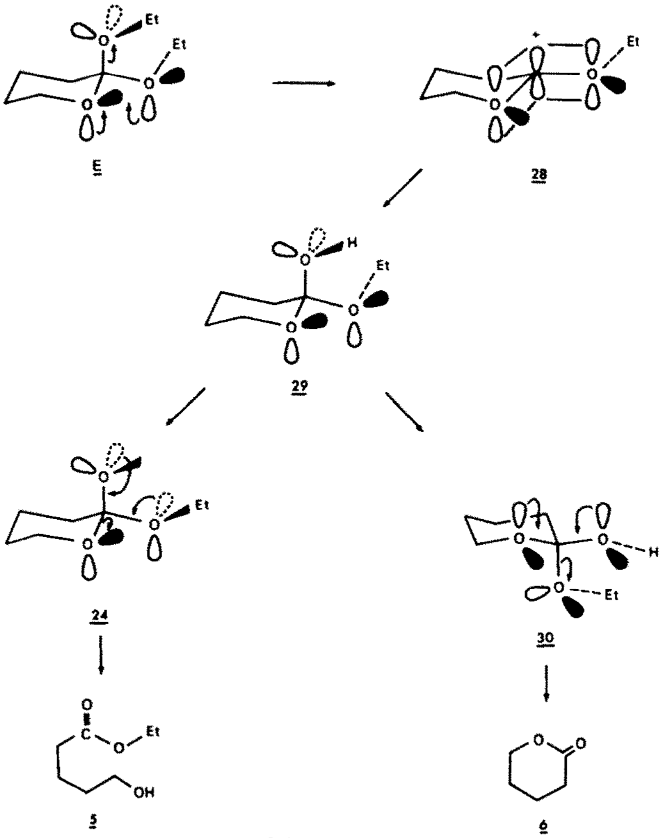
†The theory implies that when a tetrahedral intermediate cannot break down with stereoelectronic control, the energy barrier for its cleavage becomes larger than that for rotation to give other conformers. Consequently, we postulate that a tetrahedral intermediate which cannot break down with stereoelectronic control will prefer to undergo rotational changes to give new tetrahedral intermediates which can be cleaved by an orbital-assisted mechanism.



Scheme 14.



Scheme 15.

intermediate **30** should give δ-valerolactone **6**. Thus, lactone formation could have been observed to some extent via conformer **E** if the chair conformation of the orthoester is labile.

The preceding discussion on the manner by which conformers **A**, **E** and **F** should break down indicates that each of them is, in principle, a reactive conformer. If the relative stability of the dioxolenium ions is taken into consideration, we believe conformer **E** can be eliminated. Conformers **A**, **E** and **F** are going to form the dioxolenium ions **23**, **28** and **25** respectively (Scheme 16). The ions **23** and **25** are *trans* and the ion **28** is *cis*. It is known that *trans* dioxolenium ions are more stable than *cis* dioxolenium ions,[12] just as *trans* esters are more stable than *cis* esters.[8] If this difference in stability between **23**, **25** and **28** is also operative in the transition states from which these dioxolenium ions are formed, the cleavage of conformer **E** should be a higher energy process. Conformer **E** can thus be eliminated on that basis.

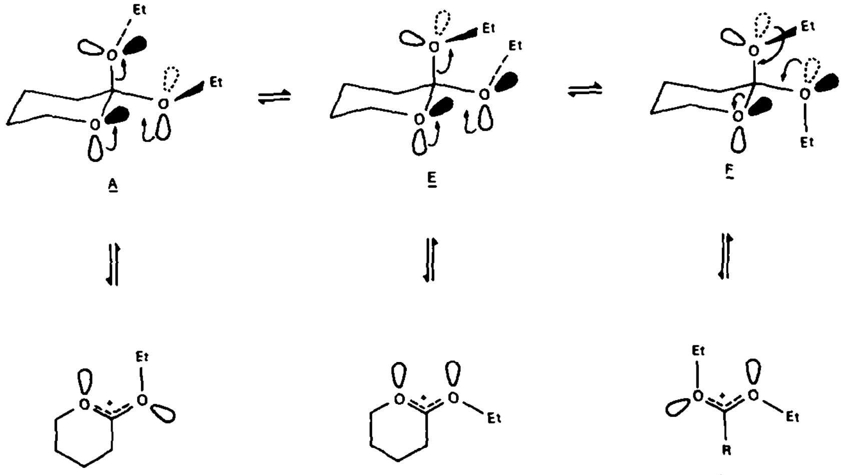
It is more difficult to find arguments to differentiate between conformer **A** and conformer **F**; however, the formation of the ion **23** from **A** should be an easier operation than formation of **25** from **F**. In principle, the formation of a cyclic dioxolenium ion **23** should be favored over an acyclic dioxolenium ion **25** when the starting orthoester is cyclic. Furthermore, cleavage of conformer **A** gives two molecules, the cyclic ion **23** and ethanol while conformer **F** gives only one molecule, the ion **25**. This entropy factor should favor conformer **A** over conformer **F** as the reactive species. Conformer **A** is in rapid equilibrium with conformer **F** (also with conformers **C** and **E**) by bond rotation. If the barrier to give **23** from **A** is more than $2{\cdot}5\ \text{kcal mol}^{-1}$ lower than the barrier to give **25** from **F** (or the barrier to give **28** from **E**), the orthoester **21** will be hydrolysed preferentially via conformer **A** only.

It is possible in principle to devise a simple experiment to find out it conformer **E** is reactive when compared to conformer **A**. If the stereoelectronic theory is applied, it is interesting to note that conformer **A** will give the hydroxy-ester **5** by the loss of its axial ethoxy group. Conformer **F** is predicted to form **5** by ejecting its equatorial ethoxy group. Scheme 14 describes these operations; with regards to **F**, both intermediates **26** and **27** will hydrolyse by ejecting the same ethoxy group, which was the equatorial one in conformer **F**. Thus, if the preparation of rigid cyclic orthoesters having two different alkoxy groups can be realized, it should be easy to differentiate between these two pathways.

We had already developed a method for the synthesis of such conformationally rigid cyclic orthoesters. For instance, lactone **31** was converted into the salt **32** which gave the cyclic orthoester **33** (Scheme 17). This successful synthesis of a rigid cyclic orthoester by sequential introduction of the alkoxy groups was ideal for the synthesis of mixed orthoesters, if the last step is stereospecific. If the stereoelectronic theory is valid, the addition of alkoxide ion to a rigid lactonium salt like **32** should indeed be completely stereospecific.

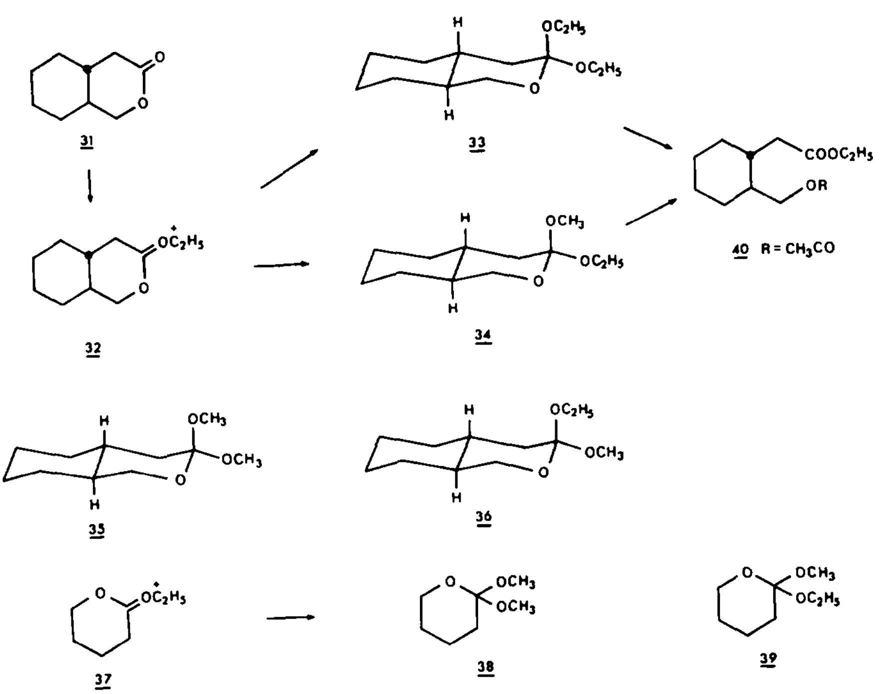
When the salt **32** was treated with sodium methoxide in a mixture of methanol and i-propanol, the mixed orthoester **34** was obtained with a small quantity (≈3%) of the dimethoxy orthoester **35**. None of the other possible mixed orthoester **36** was present. The addition of sodium methoxide to **32** is thus completely stereospecific. The stereoelectronic rule permits the formation of **36** from **32**, but the attack of methoxide ion at the α face of the salt **32** would give **36** in a high energy conformation; the orthoester ring of **36** would be in a boat form. The α attack is therefore much less favored than the β attack which yields **34** directly in its more stable conformation. The small quantity of **35** must be formed by a secondary process. When the salt **32** was reacted with sodium methoxide in pure methanol, this secondary process became more important, since **35** was formed in 60% and **34** in 40% yield.[†]

The methyl lactonium salt **41** was prepared by reaction of lactone **31** with trimethyloxonium tetrafluoroborate (Scheme 18). An authentic sample of the dimethoxy ester **35** was prepared by reacting **41** with sodium methoxide in methanol. The methyl lactonium salt **41** was also reacted with sodium ethoxide in ethanol and a mixture of the



Scheme 16.

[†] Under certain conditions, this unexpected reaction can become the major process! When the simple ethyl lactonium salt **37** was treated with sodium methoxide in methanol, none of the mixed orthoester **39** was isolated, the dimethoxy orthoester **38** was the only orthoester isolated. We have also shown that the diethoxy orthoester **21** is completely stable in presence of sodium methoxide in methanol. We think that this reaction occurs via the intermediate ketene acetal which can be formed by reaction of sodium methoxide with the lactonium salt. We are presently studying this new reaction.



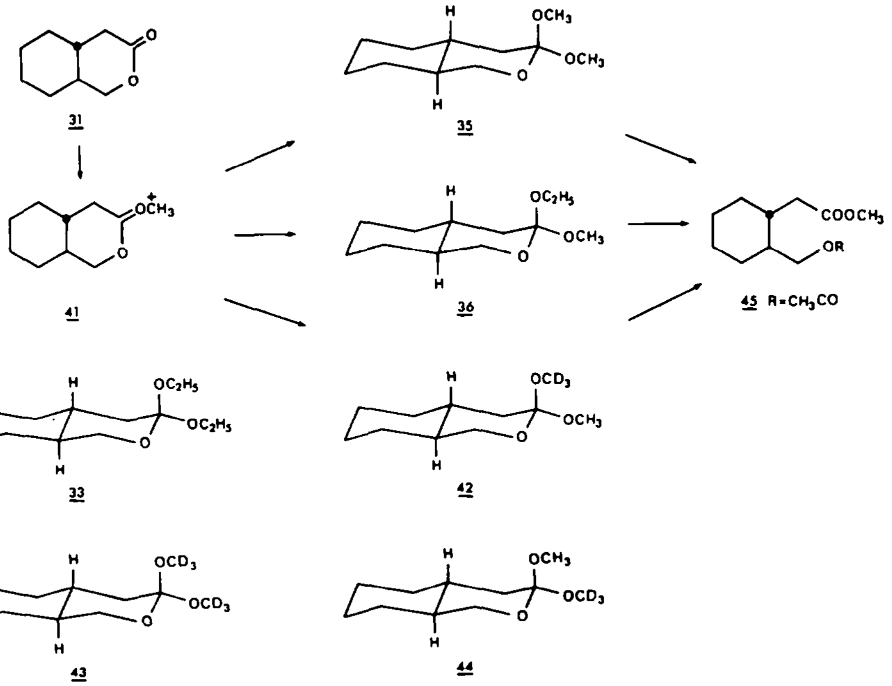
Scheme 17.

mixed orthoester **36** (95%) and the diethoxy-orthoester **33** (5%) was isolated. The lactonium salt **41** was also reacted with deuterated sodium methoxide and the mixed cyclic orthoester **42** was obtained with a small amount (10%) of the completely deuterated orthoester **43**; none of the isomeric orthoester **44** was formed.

The orthoesters **34**, **36** and **42** were hydrolysed with water containing *p*-toluenesulfonic acid. The mixture was then treated with pyridine and acetic anhydride and the resulting acetoxy-esters were isolated. Compound **34** (containing ≃3% of **35**) gave the acetoxy ethyl ester **40** containing a small quantity of **45** (≃3%). Compound **36** (containing ≃5% of **33**) gave the acetoxy methyl ester **45** containing a small quantity of **40** (≃5%). Finally, the hydrolysis of **42** (containing 10% of **43**) gave the acetoxy methyl ester **45** containing a small quantity of **45** ($CH_3 = CD_3$, 10%).

The above results show that the hydrolysis of cyclic orthoesters proceed by the lost of the axial alkoxy group. Conformer F can be eliminated as a reactive conformer; consequently, the hydrolysis of cyclic dialkoxy orthoester takes place through the reaction of conformer A.

We would like to point out that the successful stereospecific synthesis of mixed cyclic orthoesters



Scheme 18.

constitutes rigorous evidence for the direction of attack of the alkoxide on the cyclic dioxolenium ions. Also, the stereospecificity observed in the hydrolysis of these mixed cyclic orthoesters demonstrates that this reaction proceeds according to the same principle in the opposite direction.

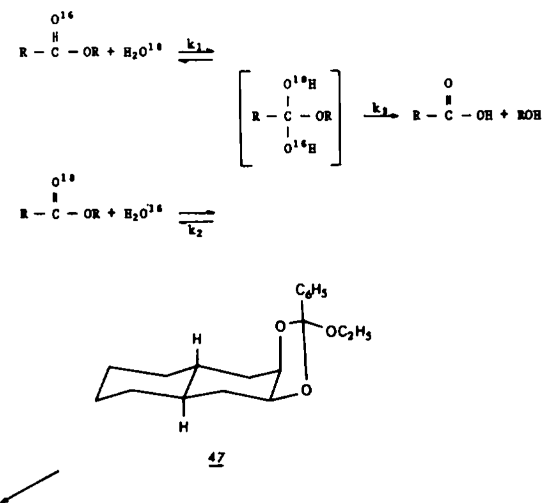
King and Allbutt[13] have described the stereoselective hydrolysis of dioxolenium ions and orthoesters fused to anchored 6-membered rings. Mild acid hydrolysis of the dioxolenium salt **46** or the orthoester **47** afforded the axial ester-equatorial alcohol **49** with a very small amount of the isomer **50** (Scheme 19). They further established by equilibrium studies that the more stable isomer is the expected equatorial benzoate **50**, thus indicating that the formation of the isomer **49** is the result of a kinetically controlled hydrolysis of **46** and **47**. The hydrolysis of **46** and **47** proceeds through the formation of the hemi-orthoester tetrahedral intermediate **48**. The intermediate **48** can assume two different conformations **51** and **52** which can give respectively the axial ester **49** and the equatorial ester **50** through an orbital assisted mechanism. However, conformer **51** is sterically favored over conformer **52**, and the axial ester **49** is selectively formed.

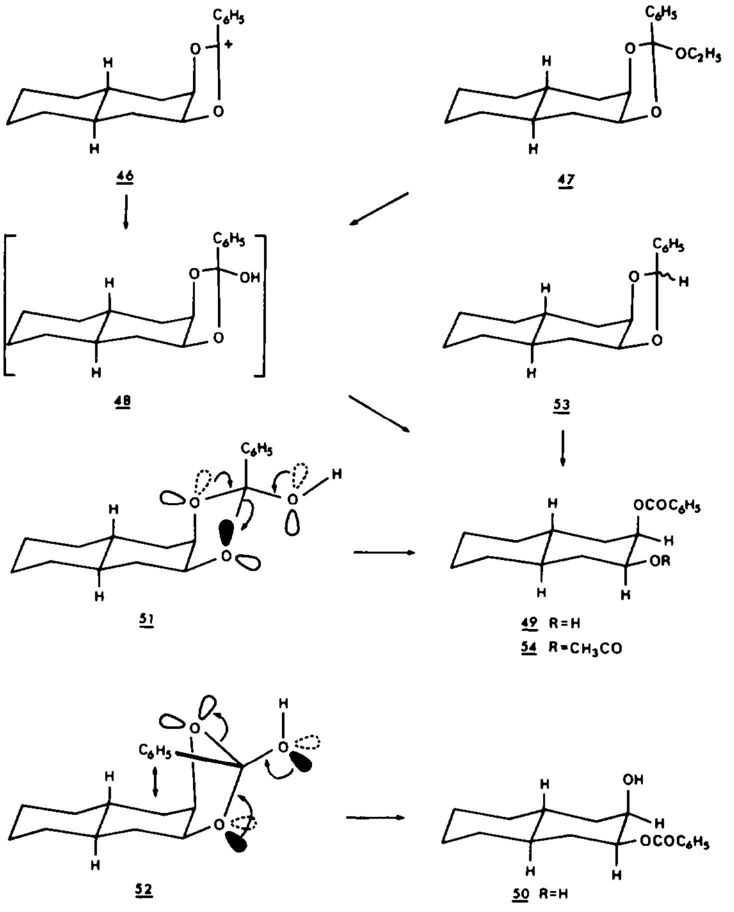
We have studied the ozonolysis of the benzylidene derivative **53** of 9β,10α-decalin 2β,3β-diol in acetic anhydride containing sodium acetate. This solvent system is known to be useful for transformation *in situ* an alcohol function into an acetate function,[2] thus eliminating the possibility of a *trans*-esterification of hydroxy-benzoate **49** into hydroxy-benzoate **50** during the reaction or the work-up procedure. As expected, oxidation of **53** gave only one product, the axial benzoate-equatorial acetate derivative **54**. Similar results have been obtained by oxidation of the benzylidene derivative of 5α-cholestane 2β,3β-diol.

Thus, the ozonolysis of benzylidene acetal **53** shows the same stereoselectivity as observed in the kinetic decomposition of hemi-orthoester **48**. Therefore, it is logical to conclude that this oxidation reaction involves the formation of an intermediate which is either equivalent or identical to a hemi-orthoester. Consequently, we think that all the results obtained from the ozonolysis of acetals can be used to support the idea of stereoelectronic control in the cleavage of hemi-orthoesters.

Concurrent isotope oxygen exchange and hydrolysis of esters

Concurrent carbonyl–oxygen exchange and hydrolysis have been demonstrated to occur in the hydrolysis of esters. The oxygen exchange has been taken as experi-





Scheme 19.

mental evidence for the formation of a tetrahedral intermediate in ester hydrolysis.[1,14] Evidence has also been obtained that the intermediate necessary for carbonyloxygen exchange lies on the reaction path of ester hydrolysis.[15]

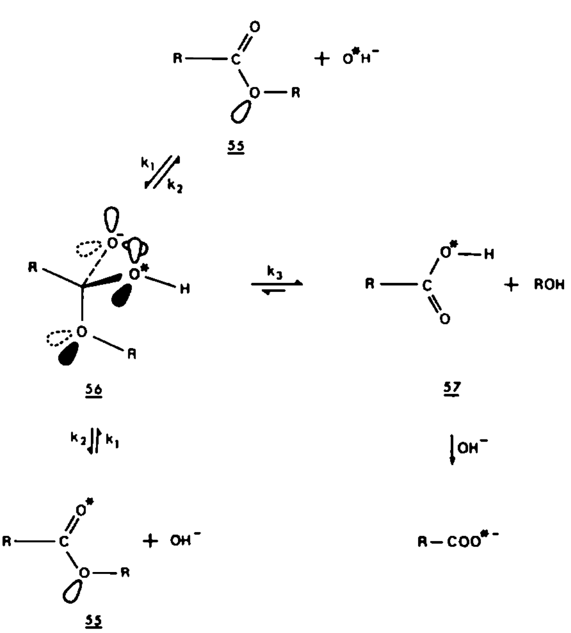
Most substrates which have been studied show concurrent oxygen exchange but there are exceptions. It has been postulated that reactions in which oxygen exchange is not detected still conform to the general mechanism; in those cases, no exchange is taking place because the ratio of k_3/k_2 is greater than 100.[1,16,17] Although this explanation is certainly valid in some cases, we believe that a more complete explanation can be obtained on the basis of the stereoelectronic theory.

According to this theory, the reaction of hydroxide ion on the *trans* *E*-ester **55** should give the tetrahedral conformer **56** specifically (Scheme 20). In **56**, the precise conformation of **55** has been transposed, the R–C bond is again antiperiplanar to the O–R bond. Also, there is a lone pair orbital on the negatively charged oxygen and on the OR group which are antiperiplanar to the new C–O*H bond. We assumed that proton transfer to the tetrahedral intermediate **56** is a very fast process;[18] consequently, a O–H bond is considered equivalent to a lone pair orbital. It is easy to recognize a plane of symmetry in **56** if the O–H bond is replaced by a lone pair. Intermediate **56** can eject either hydroxyl group equally well (→**55**); the oxygen of the OR group has a lone pair orbital properly oriented to eject either hydroxyl group with the aid of the remaining hydroxyl group (which has also a lone pair orbital properly oriented). Intermediate **56** can also expel the OR group to yield **57** since each oxygen of the OH groups has again proper orbital orientation. Also, we have already postulated that whenever a tetrahedral intermediate has proper orbital orientation, its lifetime is very short; it breaks down to products immediately. Thus, no tetrahedral conformer other than **56** should be taken into consideration in the hydrolysis of an *E*-ester.

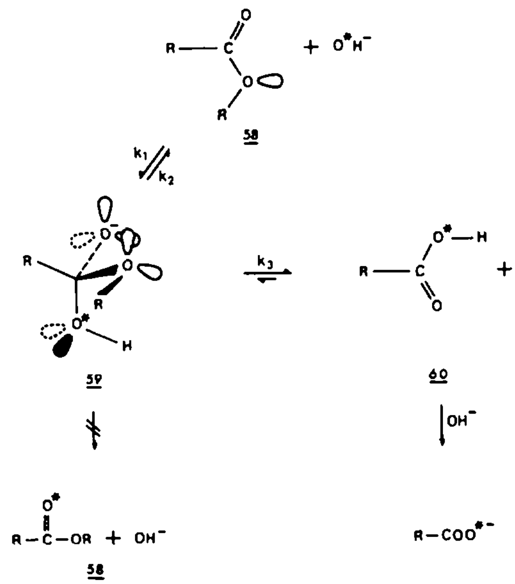
Consequently, the hydrolysis of *E*-esters should always occur simultaneously with carbonyl–oxygen exchange with the solvent. The extent of carbonyl exchange can vary depending on the relative value of k_3 and k_2. When k_3/k_2 is greater than 100, there will be a very low exchange which will be difficult to detect. This is in agreement with experimental results obtained with *E*-esters.[1]

In the hydrolysis of *cis* *Z*-ester **58**, the stereoelectronic theory predicts the formation of the tetrahedral conformer **59** (Scheme 21). Again, the conformation of **58** is transposed into **59**. The R–C and R–O bond which were *syn* in **58** are now in a gauche arrangement in **59** and there is a lone pair orbital on the negatively charged oxygen and on the OR group which are anti-periplanar to the newly formed C–O*H bond. Thus, the intermediate **59** is not symmetrical and it has proper orbital orientation to break down in only two directions. It can eject either the OR group to yield **60** or the labelled hydroxyl group (O*–H) to give back starting material **58**. The other hydroxyl group in **59** cannot be ejected because the OR group does not have a lone pair orbital properly oriented. The hydroxyl group which cannot be removed comes from the carbonyl oxygen of the ester and the hydroxyl group which can be removed comes from the hydroxide ion (O*–H$^-$). Thus, even if k_2 is of the same order of magnitude as k_3, it is impossible to incorporate labelled oxygen in **58**. Again, only conformer **59** can be taken into consideration with an *Z* ester. Consequently, the above stereoelectronic theory predicts that carbonyl–oxygen exchange should never occur in the hydrolysis of lactones (*Z*-ester). This prediction is in accord with experimental results: γ-butyrolactone does not show carbonyl–oxygen exchange in its hydrolysis;[16,19] similarly, no exchange has been observed with D-glucono-δ-lactone.[20]

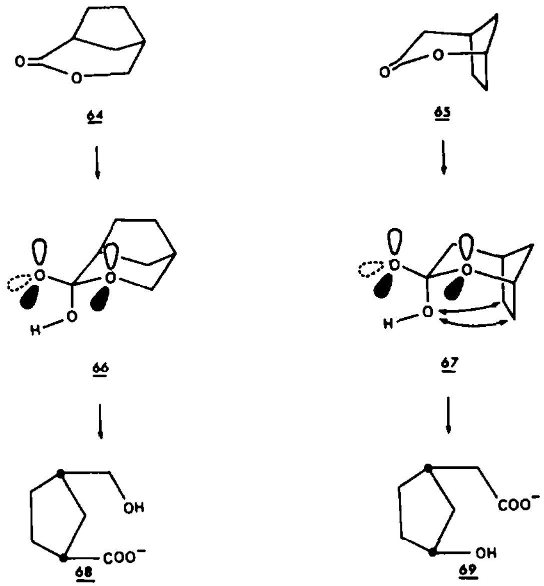
A consequence of stereoelectronic control is that it is possible to predict the direction of attack of a hydroxyl ion on a conformationally rigid lactone. For instance, with a rigid lactone having a conformation such as **61**, attack on the β face (→**62**) should be an easier operation than the attack on the α face (→**63**) (Scheme 22). In both cases, a requirement of the stereoelectronic theory is that the two oxygens of the lactone function must develop a lone pair orbital antiperiplanar to the new C–OH bond in the orthoacid. Thus, a β attack leads to the chair form **62** and



Scheme 20.



Scheme 21.



Scheme 23.

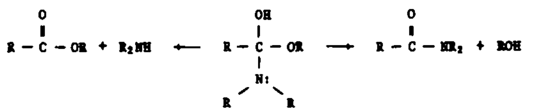
an α attack to the boat form **63**. The energy difference between **62** and **63** is certainly more than 3 kcal mol^{-1} and since these two modes of attack are competing, the reaction leading to **63** can be eliminated. The specific formation of the mixed cyclic orthoesters **34**, **36** and **42** from the lactonium salts **32** and **41** provides strong experimental support for a preferential attack.

Thus, stereoelectronic control provides not only an explanation for the non-incorporation of labelled oxygen during the hydrolysis of lactones, it also predicts which face of a lactone function reacts with hydroxide ion. Consequently, a more precise knowledge of the reaction mechanism can be obtained.

It is also interesting to compare the relative rate of hydrolysis of isomeric lactones such as **64** and **65** which are obtained by Baeyer-Villiger oxidation of norbornanone[21,22] (Scheme 23). Attack by hydroxide ion should give the ortho-acids **66** and **67** respectively. The orthoacid **67** has two 1,3-diaxial steric interactions between the axial OH group and the methylene groups of the bridge. Such steric interactions do not exist in orthoacid **66**. The hydrolysis of a mixture of **64** and **65** was carried out with sodium hydroxide and indeed lactone **64** was found to hydrolyse at a much faster rate. This difference in the rate of hydrolysis can be used to separate isomeric lactones which are obtained as a mixture in the Baeyer-Villiger oxidation of ketones.[23,24]

Stereoelectronic control in the cleavage of hemi-orthoamides

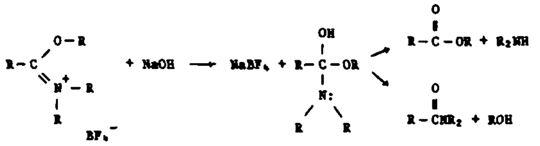
We have described so far, experiments which support the idea of stereoelectronic control in the cleavage of hemi-orthoesters. If this principle is indeed valid, it should also be equally important in the cleavage of an hemi-orthoamide. An hemi-orthoamide such as **68** can break down to give either the amide-alcohol or the esteramine products.



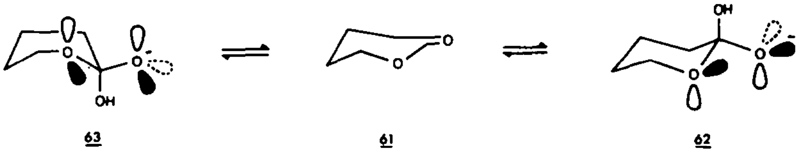
$$\mathrm{R-\overset{\overset{\Large O}{\|}}{C}-OR + R_2NH} \longleftarrow \mathrm{R-\underset{\underset{\large R\diagup\ \diagdown R}{\overset{|}{N:}}}{\overset{\overset{\large OH}{|}}{C}}-OR} \longrightarrow \mathrm{R-\overset{\overset{\Large O}{\|}}{C}-NR_2 + ROH}$$

In order to verify if the principle of stereoelectronic control can be applied in the cleavage of an hemiorthoamide, a method must be found to produce such an intermediate in an irreversible manner. This method should also provide some knowledge about the conformation of **68** in order to find out if there is a correlation between that conformation, the orientation of the lone pair orbitals of the heteroatoms (O or N) and the products formed from the cleavage of the tetrahedral intermediate.

It is not possible to produce such a hemi-orthoamide in an irreversible fashion by treating an amide with an alkoxide (hydroxide) ion. Similarly, it cannot be obtained by treating an ester with an amide anion. It was therefore desirable to find an alternative precursor to the hemiorthoamide. An ideal precursor appeared to be an N,N-dialkylated imidate salt, which can be considered to be an activated amide. Indeed, it is known that imidate salts are rapidly hydrolysed under basic conditions, at room temperature, to give ester and amine or amide and alcohol as products.[25]



$$\mathrm{R-C\begin{matrix}\diagup O-R\\ \diagdown\!\!\!\diagdown \underset{\underset{\large R}{|}}{N^+}-R\end{matrix}\ \ BF_4^- + NaOH \longrightarrow NaBF_4 + R-\underset{\underset{\large R\diagup\ \diagdown R}{\overset{|}{N:}}}{\overset{\overset{\large OH}{|}}{C}}-OR}\ \begin{matrix}\nearrow \mathrm{R-\overset{\overset{O}{\|}}{C}-OR + R_2NH}\\ \searrow \mathrm{R-\overset{\overset{O}{\|}}{C}NR_2 + ROH}\end{matrix}$$



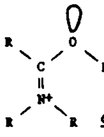
63 61 62

Scheme 22.

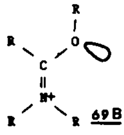
When a imidate fluoroborate such as **69** reacts with sodium hydroxide, it forms sodium fluoroborate and the intermediate **68** which rapidly breaks down to the products of the reaction. The amide and alcohol products will always completely predominate over the ester and amine products under equilibrating conditions. The amide and alcohol products are therefore the thermodynamic products resulting from the cleavage of the intermediate **68**. If ester and amine are obtained as products, it is clear that it is the result of kinetically controlled cleavage of **68** and will indicate that the transition state leading to those products is of lower energy than the one leading to the more stable amide and alcohol products. However, it is possible that in some cases, the amide and alcohol are also the kinetic products of the cleavage of the intermediate **68**. In such a circumstance, it is in principle possible to use the result as evidence for the stereoelectronic theory, if it can be clearly established that the reaction is kinetically controlled. If the corresponding ester and amine are not converted into the thermodynamic products under the experimental conditions, it demonstrates that the formation of amide and alcohol is the result of a kinetically controlled cleavage of the intermediate **68**.

It is experimentally very difficult to know the precise conformation of a hemi-orthoamide such as **68**. However, the conformation of **68** can be obtained indirectly by the utilization of the stereoelectronic theory and the knowledge of the precise conformation of the starting imidate salt **69**. If a good correlation between the proposed conformation of **68** and its cleavage is obtained, it constitutes experimental evidence in favor of the stereoelectronic theory. Thus, the conformation of the imidate salts must first be taken into consideration.

We believe that imidate salts are planar and thus can exist in two different conformations, the *anti* (**69A**) or the *syn* (**69B**) form. In the *anti* conformation **69A**, the O–R bond is antiperiplanar to the C–R bond. In the *syn* conformation **69B**, the O–R bond is *cis* to the C–R bond. Application of the stereoelectronic theory on each type of imidate salt leads to the following predictions concerning the precise conformation of the intermediate **68** and to the manner by which each conformer of **68** should then break down.



69A



69B

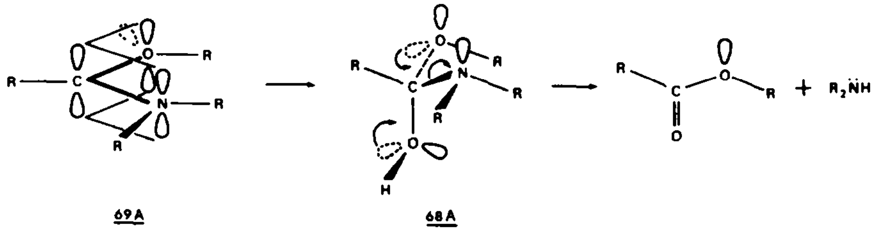
According to this theory, the reaction of hydroxide ion with the *anti* form **69A** of an imidate salt should give the tetrahedral conformer **68A** specifically (Scheme 24). Conformer **68A** is the result of hydroxide ion attack perpendicular to the plane of the salt **69A**. The conformation of the starting imidate salt **69A** is thus transposed to the intermediate **68A**; the R–C bond in **68A** is antiperiplanar to the O–R bond and to one of the N–R bonds as in the *anti* imidate **69A**.† As a consequence of the stereoelectronic theory, one of the lone pair orbitals of the oxygen of the OR group and the lone pair orbital of the nitrogen must be oriented antiperiplanar to the new C–O bond. Thus, the reverse reaction, the ejection of the hydroxyl group can be achieved by an orbital-assisted mechanism because there are two hetero-atoms each having a lone pair orbital properly oriented antiperiplanar to the leaving group. The principle of microscopic reversibility is thus adhered to.

One more assumption has to be made to render the preceding theory valid. Whenever a tetrahedral intermediate possesses proper orbital orientation, its half-life is very short and it breaks down to products immediately. This implies that the energy barrier for conformational changes by rotation of C–N and C–O bonds in **68A** is higher than the energy barrier for its breakdown. With such a condition, no tetrahedral conformer other than **68A** need to be taken into consideration.

Examination of the orientation of the lone pair orbitals in **68A** indicates that this conformer should break down to yield the ester and the amine only. The nitrogen orbital is not properly oriented to assist in expelling the OR group. At the same time, both oxygens have a lone pair orbital oriented antiperiplanar to the C–N bond to permit a facile ejection of the amino group. Consequently, it is predicted that the basic hydrolysis of the *anti* form **69A** of an imidate salt should lead to the exclusive formation of ester and amine as a result of the cleavage of conformer **68A**.

If the preceding stereoelectronic theory is valid, the reaction of hydroxide ion on the *syn* form **69B** will give specifically the conformer **68B** (Scheme 25). Again, **68B** is the result of an attack perpendicular to the plane of the salt **69B** by hydroxide ion. The conformation of **69B** has also been retained in the intermediate **68B**. There are lone pair orbitals on the nitrogen and on the oxygen of the OR group which are each oriented antiperiplanar to the C–OH bond.

It is interesting to note that conformer **68B** cannot break down to products by an orbital assisted mechanism; the nitrogen non-bonded orbital is not antiperiplanar to the C–OR bond. Similarly, the oxygen atom of the OR group does not have a non-bonded orbital properly oriented antiperiplanar to the C–N bond. In this case, we postulate that rotation of C–N and C–O bonds in conformer **68B** becomes more facile than its breakdown to products and new conformers must be considered. If these new



Scheme 24.

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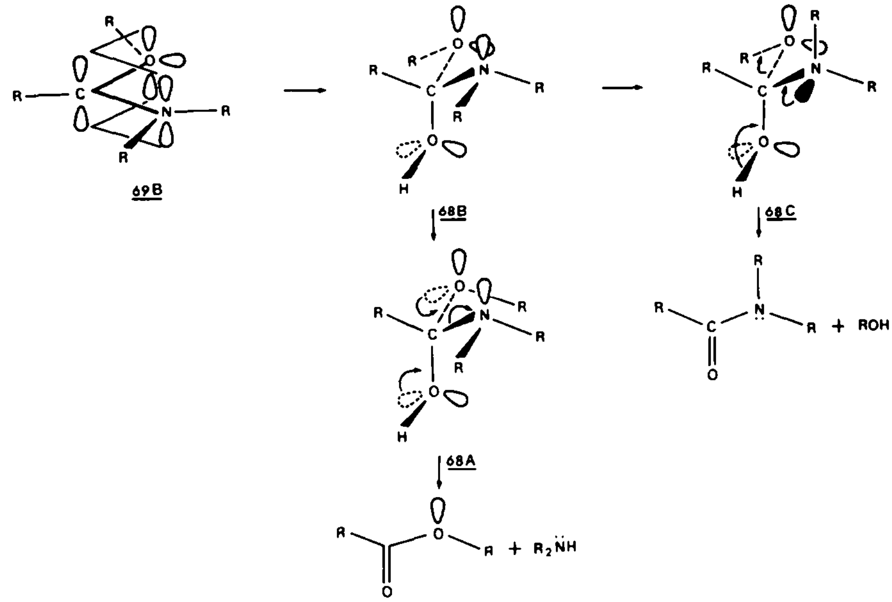
†In principle, hydroxide ion attack on the imidate can either lead to conformer **68A** or two other conformers which differ in the orientation of the O–H bond. These three conformers can be interconverted by proton transfer. This interconversion occurs at a diffusion controlled rate.[18] Since we assume that the breakdown of the tetrahedral intermediate is a slower process than proton transfer, the three conformers are therefore equivalent as far as the theory is concerned.



Scheme 25.

conformers have their orbitals properly oriented, they will break down immediately to give products. The energy barrier for C–N rotation should be of the same order of magnitude as the one for carbon–oxygen rotation. Both types of rotation must therefore be taken into consideration.

For example, by rotation of the C–N bond, conformer **68B** can give a new conformer such as **68C**. In conformer **68C**, the hydroxyl oxygen and the nitrogen each have a lone pair orbital oriented antiperiplanar to the C–OR bond. Intermediate **68C** should thus immediately produce the amide and alcohol products. By rotation of the C–OR bond in **68B**, a new conformer such as **68A** can also be obtained. We have already described that **68A** should give the ester and amine products. Other conformers can be obtained by other rotations in **68B**. The relative proportions of ester and amine products versus amide and alcohol products will thus depend on the new conformers that will be formed by bond rotation in conformer **68B**. Consequently, it is predicted that the basic hydrolysis of the *syn* form **69B** of an imidate salt will give mixtures of products, in principle.

Hydrolysis of N,N-*dialkylated imidate salts*

We will first describe the results obtained from the basic hydrolysis of imidate salts haveing an *anti* conformation. The first substrate selected was the 5-membered ring imidate salt **70** in which the *anti* conformation is assured by the cyclic structure (Scheme 26). Hydrolysis of **70** with three equivalents of sodium carbonate in a mixture of acetonitrile and water gave the benzoate-amine **71** exclusively. If the reaction mixture was left at room temperature for a period of 24 hr, the aminobenzoate **71** was completely converted into the more stable benzamide–alcohol **72**.

These experimental results can be easily explained by the stereoelectronic theory. The salt **70** forms the hemi-orthoamide intermediate **73** in which the energy barrier for fragmentation is lowered by the alignment of the orbitals on both oxygen atoms and under kinetically controlled conditions, the ester-amine product **71** is the only product. It is possible that the experimental conditions used favor the re-formation of tetrahedral intermediates by an attack of the amino group on the ester function of **71**. Compound **71** can either re-form **73** or form a new intermediate such as **74** which has its orbitals properly aligned to yield the more stable product, the amide-alcohol **72**. Consequently, the final result will be the exclusive formation of the thermodynamic product under those equilibrating conditions. These conditions were obtained after a period of 24 hr with sodium carbonate; they were immediately obtained when sodium hydroxide was used.†

The hydrolysis of imidate salt **76** was also carried out with sodium carbonate (Scheme 27). After 10 min, it gave mainly the acetate–amine **77** which was then slowly converted into the actamide–alcohol **78** after standing for 1·5 hr at room temperature.

The basic hydrolysis of a 6-membered ring imidate salt was also performed. After 15 min at room temperature, the hydrolysis of **79** with sodium carbonate gave the benzoate–amine **80** exclusively. The presence of benzamide–alcohol **81** was not detected in the mixture even after a period of 5 hr. The hydrolysis of **79** was also carried out with sodium hydroxide. The imidate salt was completely hydrolysed after a few minutes and it yielded mainly the benzoate-amine **80** (≃95%) with a small quantity of the benzamide–alcohol **81** (≃5%). After standing for a period of 30 min at room temperature, the reaction mixture consisted of the benzamide–alcohol **81** only. This result indicates again that the ester **80** is first

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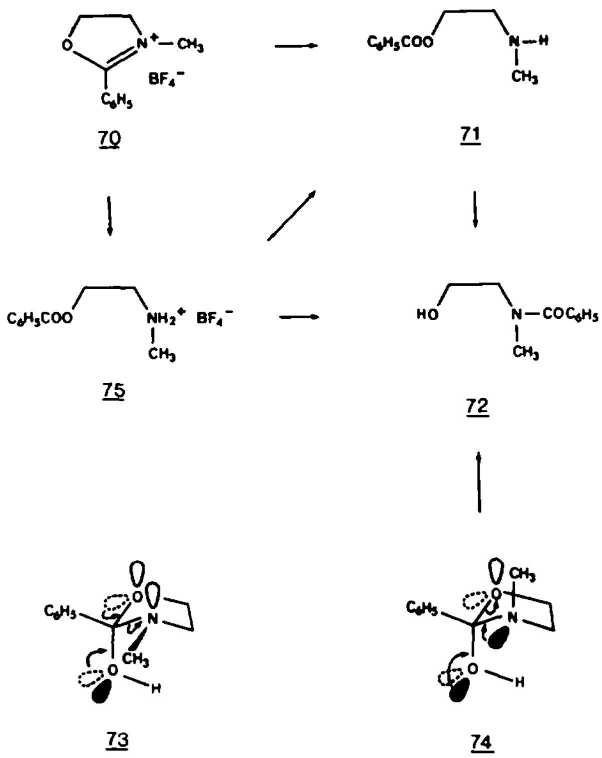
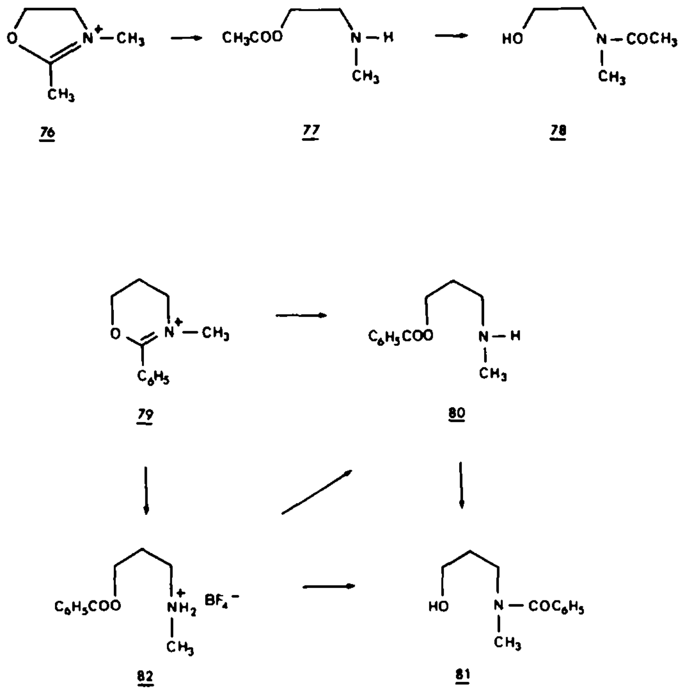
†The basic hydrolysis of **70** was also carried out with sodium hydroxide. Under these conditions, the imidate salt **70** gave directly the benzamide-alcohol **72**, while the benzoate–amine **71** was not detected. This unexpected result can be explained if the transformation of the benzoate–amine **71** into the more stable benzamide-alcohol **72** is very rapid in the presence of sodium hydroxide. This assertion was shown to be true in the following way. The benzoate–ammonium salt **75** was prepared by the hydrolysis of **70** in neutral water. When the ammonium salt **75** was treated with sodium hydroxide under the conditions described for the hydrolysis of **70**, it gave directly the benzamide–alcohol **72**. Treatment of **75** with sodium carbonate gave the benzoate–amine **71**.



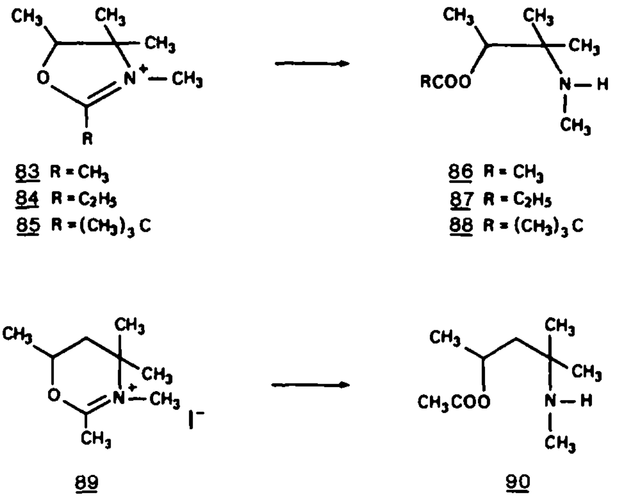
Scheme 26.



Scheme 27.

formed and then converted into the more stable amide product **81**. This assumption was further verified by treating the ammonium salt **82** under identical basic conditions. Like the imidate **79**, **82** gave also the benzoate–amine **80** first, which was then completely converted into the benzamide–alcohol **81** within a period of 30 min. The ammonium salt **82** was obtained by the hydrolysis of **79** in neutral water.

The basic hydrolysis of the imidate salts **83**, **84** and **85** has been previously reported by Allen and Ginos[26] (Scheme 28). These salts gave the corresponding ester-amine products **86**, **87** and **88** in basic conditions. We have also carried out the basic hydrolysis of imidate salt **89**[27] and it gave the ester-amine **90**. There are two factors which help the cleavage of the C–N bond in the hydrolysis of **83**, **84**, **85** and **89**. According to the theory, **83**, **84** and **85**

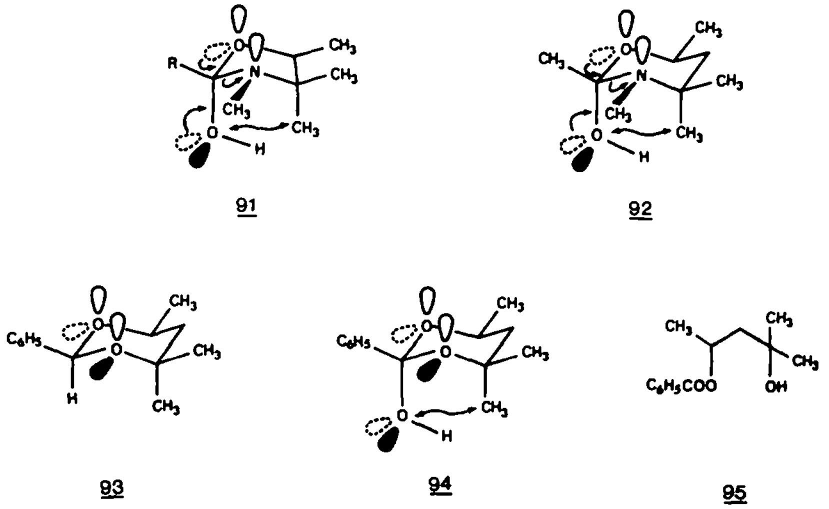


Scheme 28.

should form the intermediate **91** which has proper orbital alignment to yield the corresponding ester-amine products (Scheme 29). In **91**, there is also a pseudo 1,3-diaxial type of interaction between the OH group and one of the methyl groups which promotes the cleavage of the C–N bond. Compound **89** should give the intermediate **92** in which there is again a similar steric compression factor. This, combined with the orbital orientation factor, favors the C–N bond cleavage.

It was of interest to find out if this steric compression factor was important enough to direct the cleavage of the intermediate exclusively in one direction. We have verified experimentally that this factor is indeed important by carrying out the ozonolysis of the acetal **93**. Oxidation of **93** by ozone gave the ester **95** exclusively. During this reaction, it is postulated that the intermediate **94** is formed. In **94** the orientation of the non-bonded orbitals favors the opening in both directions equally well. Consequently, the experimental results demonstrate that the interaction between the OH group and the axial methyl group in **94** is strong enough to allow via steric decompression, a specific cleavage in one direction. This result is in agreement with the minimum value of 2·4 kcal mol^{-1} which has been estimated for 1,3-diaxial interaction between a hydroxyl and a methyl group.†

Having a good estimate for the importance the steric decompression factor, it is in principle possible to obtain some idea about the magnitude of the orbital orientation effect by opposing these two factors in the same system. The salt **96** was therefore prepared for that purpose (Scheme 30). Its reaction with hydroxide ion should give the intermediate **97**, in which the orbital orientation promotes the cleavage of the C–N bond, while the 1,3-diaxial methyl-hydroxyl steric interaction favors the cleavage of the C–O bond. Hydrolysis of **96** with sodium carbonate gave exclusively the ester-amine product **98**. Additionally, salt **99** was also prepared. Its hydrolysis yielded first the ester-amine **100** which was rapidly transformed under the experimental conditions into the benzamide–alcohol **101**. In the above examples, the reaction was still specific toward the formation of the ester-amine product despite a steric factor (estimated to be $\geqslant 2 \cdot 4$ kcal mol^{-1}) which favors the formation of the



Scheme 29.

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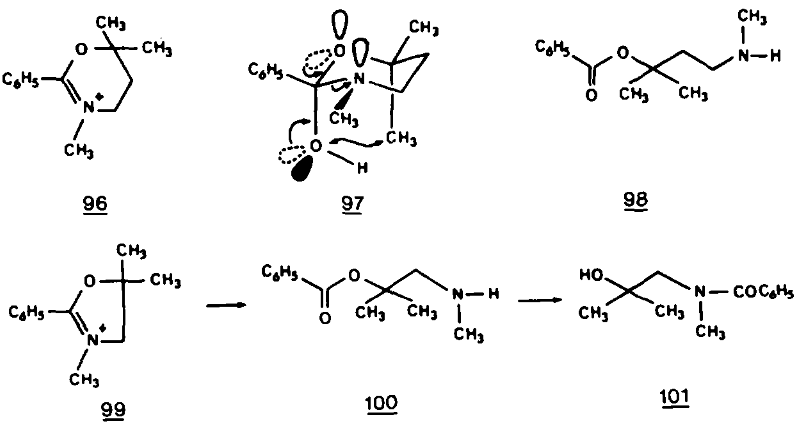
†The energy difference between the two conformers of *cis* - 3 - methyl - cyclohexanol can be estimated at about 3·8 kcal mol^{-1} and an experimental value of 2·4 kcal mol^{-1} [28] is taken as the basis for the 1,3-diaxial methyl-hydroxyl interaction.[29]



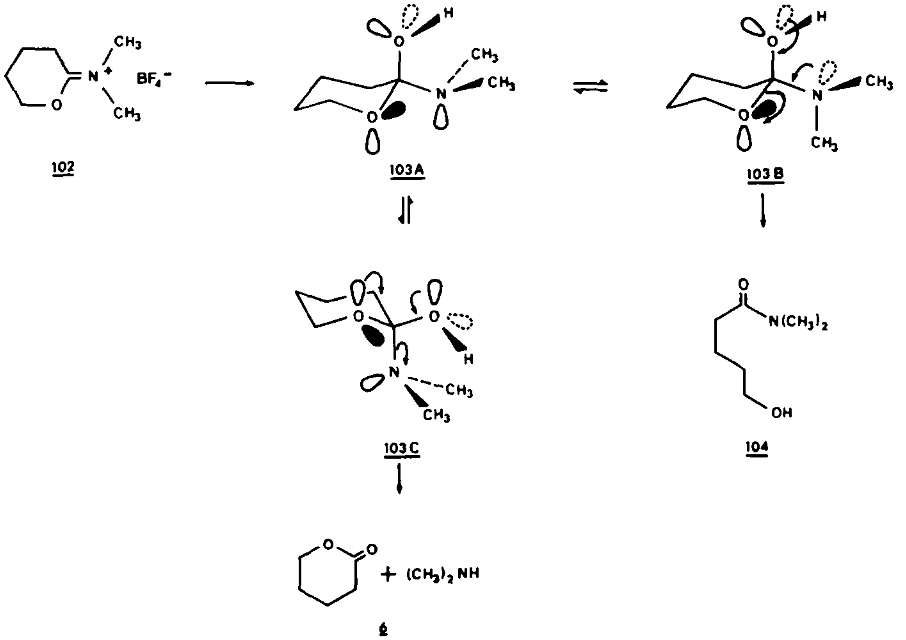
Scheme 30.

amide–alcohol product. It is considered that a reaction path is specific when it is favored by at least 2·5 kcal mol^{-1}. The minimum value for the orbital orientation effect can therefore be estimated to be at least 5 kcal mol^{-1}.

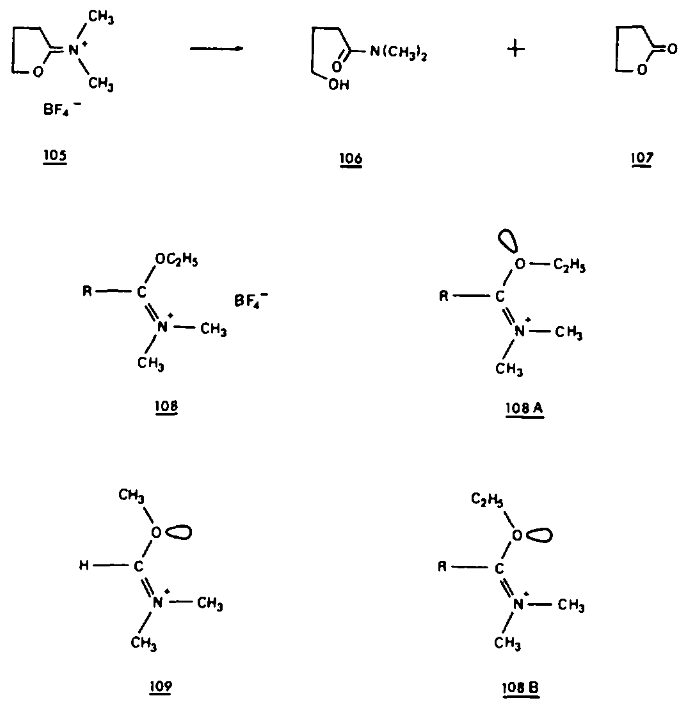
So far, we have described the hydrolysis of rigid *anti* imidate salts. These compounds were predicted to give the ester-amine products exclusively. The preceding experimental results clearly demonstrate that indeed, the ester-amine products are the only products observed under kinetically controlled conditions.

We have also undertaken the basic hydrolysis of the imidate salts **102** and **105** which have a *syn* conformation due to their cyclic structure. The hydrolysis of **102** (Scheme 31) should give the intermediate **103A** which is equivalent to **68B**. Thus, **103A** cannot break down easily if the stereoelectronic theory is valid. However intermediate **103A** can undergo conformational changes to yield either **103B** by carbon–nitrogen rotation or **103C** by chair inversion. Conformer **103B** has its orbitals properly oriented to give the hydroxy-amide **104** while conformer **103C** should yield the lactone **6** and dimethylamine. Thus, the stereoelectronic theory predicts a mixture of products **6** and **104** from the basic hydrolysis of **102**. The hydrolysis of **102** was carried out with sodium hydroxide in aqueous acetonitrile. Indeed, the imidate salt **102** gave a mixture of hydroxy-amide **104** (66%) and δ-valerolactone (**6**, 33%) and dimethylamine (33%). Likewise, the hydrolysis of the imidate salt **105** (Scheme 32) gave a one to one mixture of the corresponding hydroxy-amide **106** and γ-butyrolactone (**107**).

We have also studied the basic hydrolysis of a series of imidate salts **108**, in which the group R was varied (R = hydrogen, methyl, isopropyl, cyclohexyl, t-butyl and phenyl). Such salts can exist in principle in *anti* (**108A**) or *syn* (**108B**) forms. The extent of the electronic interaction which stabilizes or destabilizes either of these two forms is as yet unknown. There is however a steric repulsion between the group R and the ethyl group in the *syn* form **B**. There is also a 1,3 - *syn* - periplanar interaction between the ethyl and the methyl groups in the *anti* form **A**. When R is a small group, one can postulate that the *syn* form **B** might be favored since it avoids the rather strong interaction which exists in the *anti* form **A**. However,



Scheme 31.



Scheme 32.

Table 2. Basic hydrolysis of imidate salts **108**[a,b]

R	% Ester	% Amide
H	50	50
CH_3	81	19
C_6H_{11}[c]	50	50
$(CH_3)_3C$	100	0
C_6H_5	100	0

[a] Hydrolysis was carried out with NaOH (1 – 2*N*) in a mixture (~1 : D) CD_3CN-H_2O in an NMR tube.

[b] Yields were estimated by NMR spectroscopy analysis.

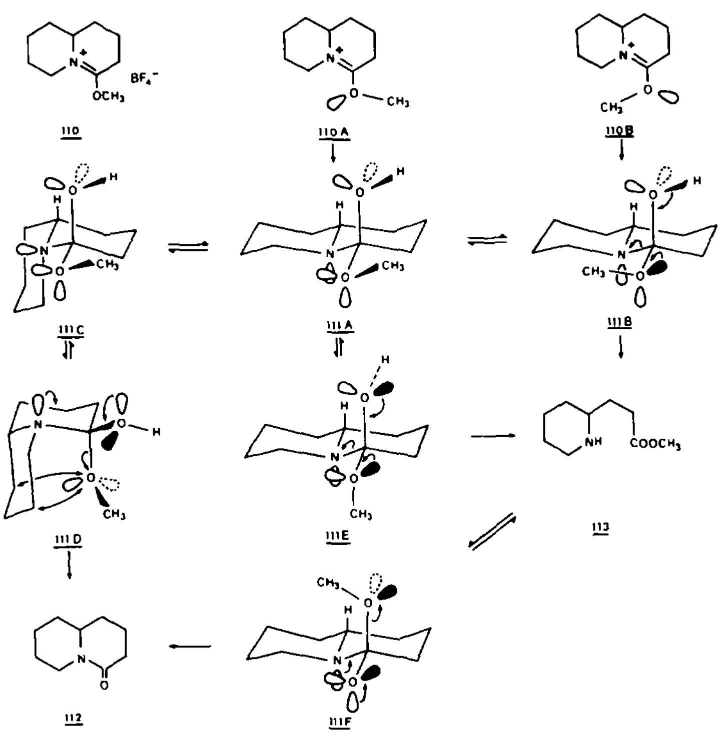
[c] Yields were estimated by VPC analysis.

when R is a large group such as the t-butyl or the planar phenyl group, the *anti* form A might predominate so that the rather severe interaction between the ethyl group and the large group R is now avoided. If this assumption is valid, it would indicate that (**108**; R = H) exists mainly as the *syn* form. A nuclear Overhauser effect study on the salt **109** indicates clearly that it exists mainly in the *syn* conformation. When R is a methyl, an isopropyl or a cyclohexyl group, **108** would exist either as the pure *syn* form or as an equilibrium mixture of the *syn* and the *anti* forms. Finally, when R is a t-butyl or a phenyl group, **108** would exist in the pure *anti* form.

The above reasoning, in conjunction with stereoelectronic theory predicts that mixtures of ester-amine and amide–alcohol products should be observed in the hydrolysis of **108** when R is a hydrogen, a methyl, an isopropyl and a cyclohexyl group. It also predicts that the basic hydrolysis of **108** when R is a t-butyl or a phenyl group should give the ester and amine products exclusively. The result of the hydrolysis of those salts (carried out with sodium hydroxide) is described in Table 2. These data are in striking accord with the preceding discussion.

We have also studied the bicyclic imidate salt **110** (Scheme 33), which can exist either in the *syn* (**110A**) or the *anti* (**110B**) form. Steric interactions in **110** are similar to those of salt **108** (R = Me). Consequently, we assume that the *syn* conformation **110A** must be predominant. Application of the stereoelectronic theory to this system leads to the following conclusions. Reaction of **110A** with hydroxide ion should yield the conformer **111A** specifically. Since conformer **111A** cannot break down by an orbital-assisted mechanism, conformational changes should take place. Nitrogen inversion is possible in **111A** to give the new conformer **111C**. However, this new conformer, like **111A**, does not have proper orbital orientation to break down. Since, **111C** is equivalent to a *cis* decalin system, it can undergo a chair inversion to give conformer **111D**. Conformer **111D** should break down to give the lactam product **112** in a stereoelectronically controlled fashion. However, in conformer **111D**, there are two severe 1,3-diaxial steric interactions between two methylene groups of ring A and the oxygen of the Me group. The energy barrier for the conversion of **111A** into **111D** will be increased accordingly. Thus, if **111A** can undergo other conformational changes having a lower energy barrier and leading to a new conformer which can break down via stereoelectronic control, the pathway through **111D** can be eliminated from consideration. Conformer **111A** can also change its conformation by rotation of the O–Me bond. In this fashion, it can give either **111B** or **111E**. These two conformers have proper orbital orientation to break down to yield the esteramine product **113**. Formation of **113** via **111B** and **111E** is an easier process than formation of the lactam **112** via the sterically unfavored **111D**. The kinetic product of the hydrolysis reaction of **110** must therefore be the ester-amine **113**.

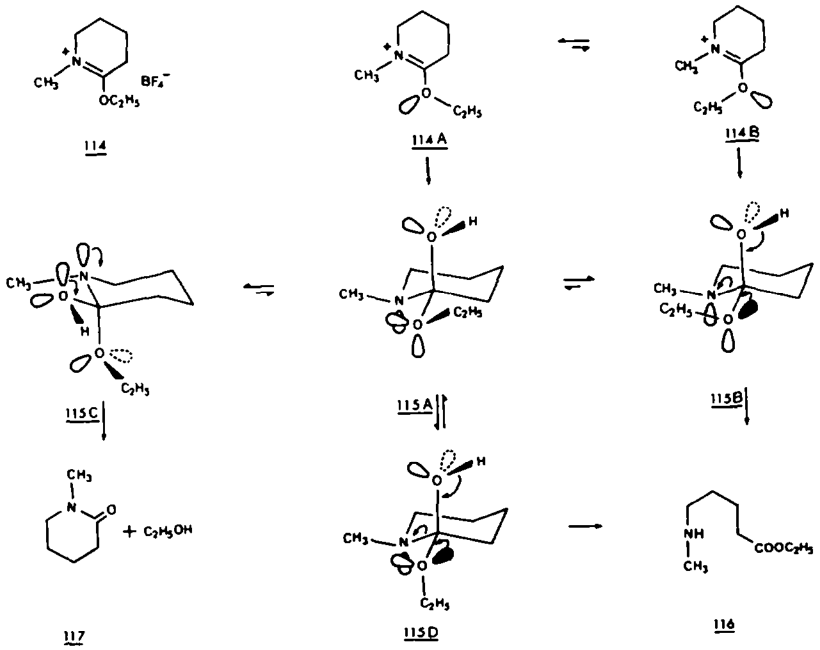
In the experiment, the imidate salt **110** was hydrolysed with sodium carbonate and gave the ester-amine **113**



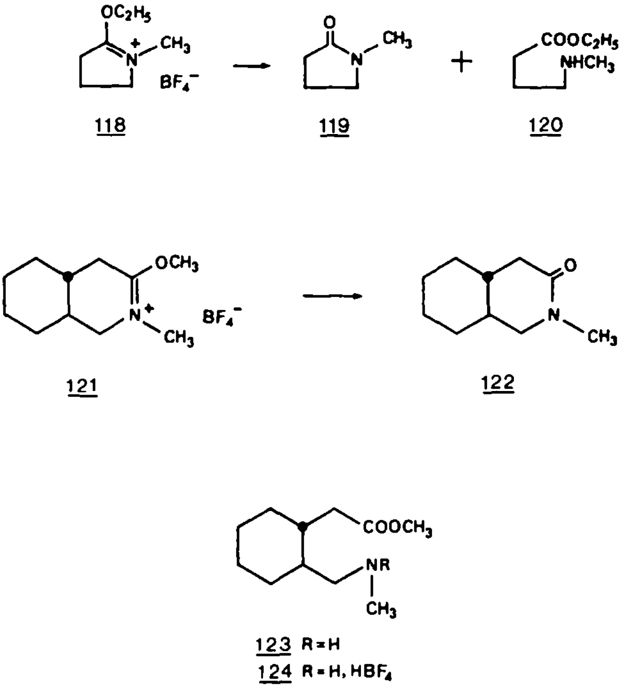
Scheme 33.

exclusively after 15 min of reaction. The ester-amine **113** was then slowly converted into the lactam **112** in the reaction mixture (66% of conversion after 76 hr). The formation of lactam **112** via stereoelectronic control must occur by the new tetrahedral conformer **111F** which can only be formed from the ester-amine **113**.

The hydrolysis of the imidate salt **114** was also carried out (Scheme 34) and it gave a mixture of ester-amine **116** (83%) and lactam **117** (17%). The salt **114** can be considered as the monocyclic version of the bicyclic salt **110** which gives tetrahedral intermediates (**111**) which cannot undergo a proper nitrogen inversion without creating severe steric interactions. The salt **114** can form tetrahedral intermediates (**115A**, **B**, **C** and **D**) in which proper nitrogen inversion can occur as well as rotation of the C–OCH$_3$ bond. Thus, we should expect some lactam product from **114**. This prediction is in agreement with the experimental result. A similar result was obtained from the hydrolysis of the salt **118** (Scheme 35) which gave also a mixture of ester-amine **120** (65%) and lactam **119** (35%).



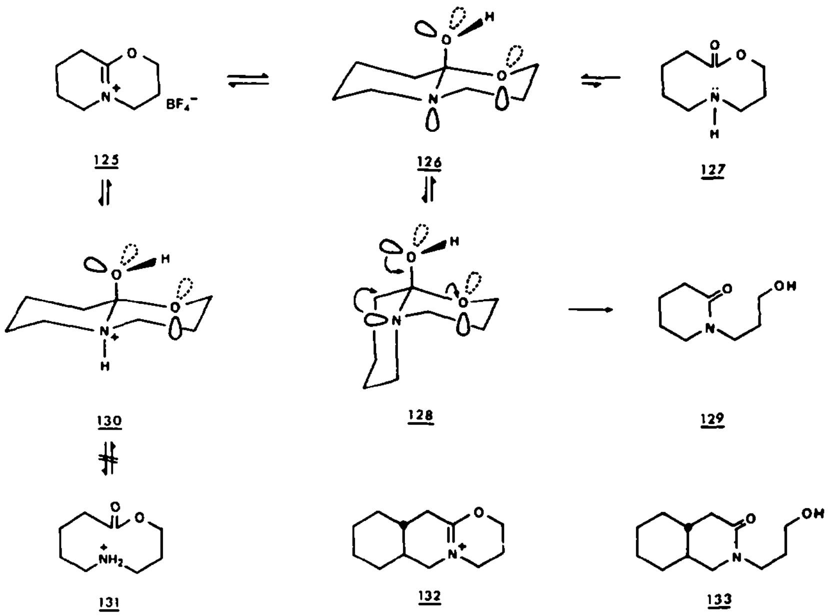
Scheme 34.



Scheme 35.

The hydrolysis of the bicyclic imidate salt **121** was also investigated. Its hydrolysis with aqueous sodium carbonate gave directly the lactam **122**, while none of the expected amine–ester **123** was detected. However, hydrolysis of **121** in aqueous acid gave the ester–ammonium salt **124**. On treatment of **124** with aqueous sodium carbonate only the lactam **122** was obtained. The amine–ester **123** was not observed. Consequently, the above result cannot be used against the stereoelectronic theory, because the basic hydrolysis of **121** gives directly the thermodynamic product **122** under conditions where the kinetic product **123** cannot survive long.

The hydrolysis of the *anti* bicyclic imidate salt **125** was also examined (Scheme 36). If the stereoelectronic rule is followed, the salt **125** should give the intermediate **126** which has its orbitals properly aligned to yield the aminolactone **127**. The presence of the large ring in **127** keeps the nitrogen in close proximity to the carbonyl of the ester function. It is therefore logical to expect that the re-formation of intermediate **126** from **127** should be especially facile. If **126** has a sufficient lifetime because it is in mobile equilibrium with **127**, it can undergo a conformational change to **128** by nitrogen inversion. Stereoelectronically controlled cleavage of **128** yields the hydroxy-lactam **129** which is the thermodynamic product of the reaction. So, even if the conversion of **126** into **128**



Scheme 36.

is a much slower process than its breakdown into **127**, once **128** is obtained, it represents a means by which the reaction can become thermodynamically controlled. Consequently, kinetically controlled conditions should be difficult to obtain in this case. Accordingly, the basic hydrolysis of salt **125** was carried out and it led to the exclusive formation of hydroxy-lactam **129**.

On the other hand, the reaction of **125** in acidic medium should give the intermediate **130** which can break down into the lactonium-ammonium salt **131** by an orbital assisted mechanism. The intermediate **130** cannot undergo a conformational change to give the protonated form of **128**; the nitrogen in **130** cannot be inverted because its lone pair orbital is now protonated. The formation of hydroxy-lactam **129** should therefore not be observed in acidic medium. The hydrolysis of **125** was attempted in aqueous hydrochloric acid (0·1*N*), and this compound was found to be completely stable under those conditions for a period of eight months! Thus, not only the hydroxy-lactam product **129** was not formed, but the ammonium salt **131** was not even produced. The stability of **125** in aqueous acid can be explained in two ways: (*a*) the salt does not react with water to form a tetrahedral intermediate and it is therefore stable; (*b*) it does react with water to form the intermediate **130** but it prefers to give back the starting salt **125**, for the reason that **125** is more stable than the ammonium salt **131**. We think that the first explanation is not valid. It is difficult to find one good reason to explain the resistance of **125** to form a tetrahedral intermediate in acidic medium. All other imidate salts that we have reported in this article do form an intermediate since they are all hydrolysed in aqueous acid. We have prepared the tricyclic imidate salt **132** which has a structure similar to **125** and we should thus expect the same kind of reactivity. In aqueous base, **132** gave the expected hydroxy-lactam **133**, in aqueous acid, it was found to be completely stable.

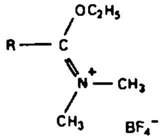
The preceding results clearly demonstrate that a mixture of ester-amide and amide-alcohol products are formed in the basic hydrolysis of *syn* imidate. Consequently, they can be used to support the principle of stereoelectronic control.

STEREOELECTRONIC CONTROL AND PH OF THE REACTION MEDIUM

In our preceding study on the basic hydrolysis of imidate salts, we have not taken account of the pH of the reaction medium, except that we have tried to use the most basic conditions which allow a kinetically controlled reaction. So, whenever possible, sodium hydroxide was used. In other cases, the less suitable sodium carbonate was used. However, when sodium carbonate was used, the reaction medium was always maintained at a pH higher than 11. Consequently, it is very likely that the protonation of the basic nitrogen of the tetrahedral intermediate was completely suppressed under those conditions.

We had also to use a mixed aqueous–organic solvent so that the products of the reaction could be directly analyzed by NMR spectroscopy. In was important to follow the reaction directly in the reaction mixture in order to ensure that the observed results were produced by a kinetically controlled reaction. In order to complete this investigation, we have undertaken a study of the products formed in the hydrolysis of some N,N-dialkylated imidate salts in aqueous solvent over a range of pH. We will now describe this work and discuss the stereoelectronic theory with respect to the generally accepted mechanism for the hydrolysis of imidate salts in acidic and basic media.

The imidate salts **134**, **135**, **136** and **137** (**108**) were selected for this study (Scheme 37). The results of their hydrolysis as a function of pH are shown in Fig. 1. At pH 8·5 or lower, the four imidate salts yield the ester-amine products exclusively. The imidate salts **136** and **137** yield the ester-amine products over the entire range of pH values. At pH greater than 8·5, imidate salts **134** and **135** start to produce the amide–alcohol products which reach a maximum yield at pH 11 (20% for **134** and 25% for **135**) and that value remains unchanged at higher pH.



<u>134</u> R = CH_3
<u>135</u> R = C_6H_{11} (cyclohexyl)
<u>136</u> R = C_6H_5
<u>137</u> R = $(CH_3)_3C$

Scheme 37.

Several previous studies on the hydrolysis of imidate salts have resulted in the following proposed mechanism.[25] Hydroxide ion reacts with an imidate salt such as **69** (Scheme 38) to give the tetrahedral intermediate T°. It is assumed that proton transfer on the tetrahedral intermediate is faster than its breakdown, thus, T° is kinetically equivalent to $T^{\pm}$. Consequently, T° will also exist as $T^{\pm}$ at the pH corresponding to the pK_a of the tetrahedral intermediate (pH ≃ 10). At low pH, T° will exist as T^{+} and at high pH as T^{-}. The variation in product formation with pH was thus explained by the various charged forms of T°.† It was proposed that T^{+} and $T^{\pm}$ expel amine to form the ester‡ while T^{-} could expel the alkoxide ion only with the consequent formation of amide.§¶

The results that we have obtained in the hydrolysis of imidate salts **134**, **135**, **136** and **137** in acidic and slightly basic media can be explained by the preceding mechanism. However, the observed results in strongly basic medium cannot be rationalized by the same mechanism. The exclusive formation of the ester-amine products from imidate salts **136** and **137** cannot be explained. Similarly, this mechanism does not offer an explanation for the partial formation of the ester-amine products in the basic hydrolysis of imidate salts **134** and **135**. New parameters must be considered in order to explain the observed apparent anomalies. Clearly, the conformation of the

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†The breakdown of $T^{\pm}$ should be much easier than that of T°. The R_2NH^+ group in $T^{\pm}$ is a much better leaving group than the R_2N group in T°. Also, the negatively charged oxygen in $T^{\pm}$ must be an extra driving force to facilitate the cleavage of the intermediate. Since $T^{\pm}$ and T° are kinetically equivalent, T° can therefore be neglected.

‡The R_2NH^+ group is a better leaving group than the OR group, so the cleavage of the C–N bond in T^{+} and $T^{\pm}$ should be a more facile process than that of the C–OR bond.

§The OR group is a better leaving group than the R_2N group, so the cleavage of the C–OR bond in T^{-} should be easier than that of the C–N bond.

¶It has also been suggested that the cleavage of some intermediates could occur prior to the proton transfer equilibrium giving different results.[30]

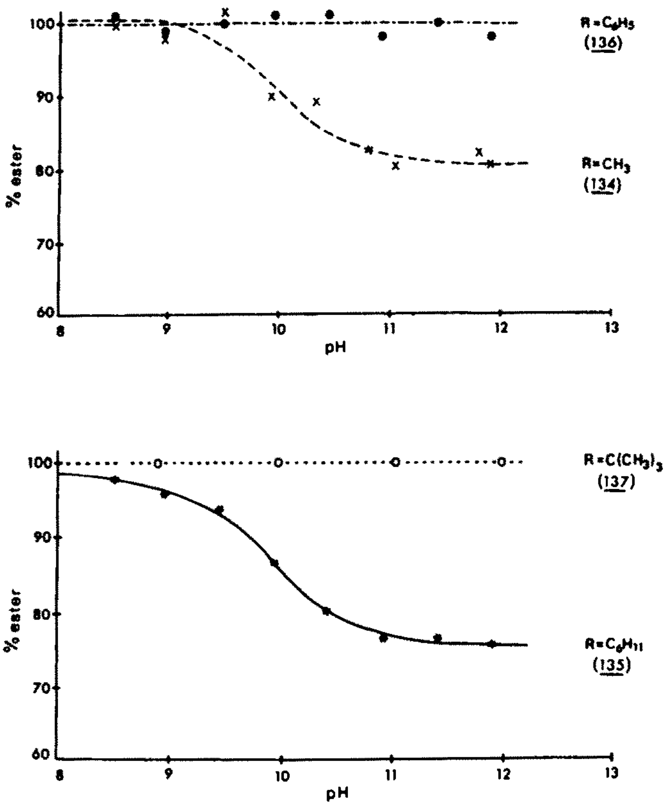
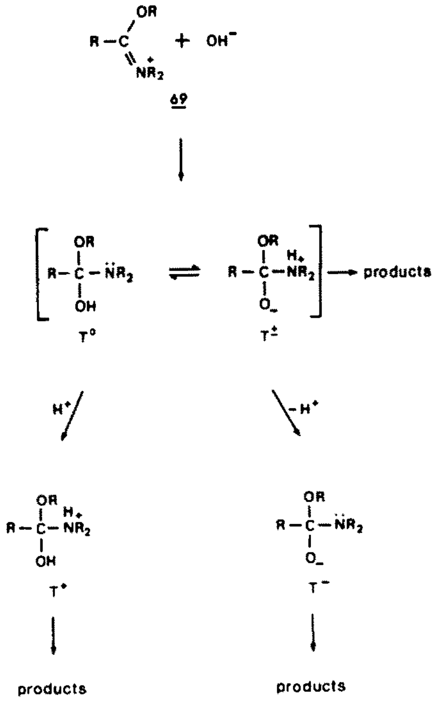


Fig. 1. Products of the hydrolysis of salts **134** (×), **135** (∗), **136** (●) and **137** (○) as a function of pH. Buffer concentrations were 0·05 M (except for NaOH buffers) and the ionic strength was 1·0 M (maintained with KCl). In the case of **135**, the amide was assayed and the percentage ester was obtained by subtraction from 100.

tetrahedral intermediate must be one of the key points. Indeed, the application of the stereoelectronic theory which we have developed appears to offer a complete explanation of the observed results.

We will first consider an imidate salt having an *anti* conformation such as **69A**. **69A** will form the intermediate **68A** (Scheme 39). In acidic medium, **68A** will exist as the protonated form T^+, in slightly basic medium (near the pK_a of T°, pH $\simeq$ 10), it will exist as $T^\pm$ and in basic medium (pH > 11), it will exist as T^-. Again, $T^\pm$ is considered to be equivalent to T°, thus T° can be neglected. Conformer **68A** in the ionic form T^+, $T^\pm$ and T^- has proper orbital orientation to break down via stereoelectronic control to yield the ester-amine products only. *Anti* imidate salts should therefore yield the ester-amine products only regardless of the pH of the reaction media.

The imidate salts **136** and **137** are considered to exist in the *anti* conformation and indeed they give ester and amine as products of their hydrolysis over the completely range of pH. We have already described the hydrolysis in mixed aqueous-organic solvent of several cyclic imidate salts which can only exist in the *anti* conformation and these salts gave the ester-amine products exclusively under basic or neutral conditions.†



Scheme 38.

When an imidate salt is in the *syn* conformation, it will first form the tetrahedral conformer **68B** which will exist either as the T^+, $T^\pm$ or T^- form depending on the pH of the reaction medium. Since conformer **68B** cannot break

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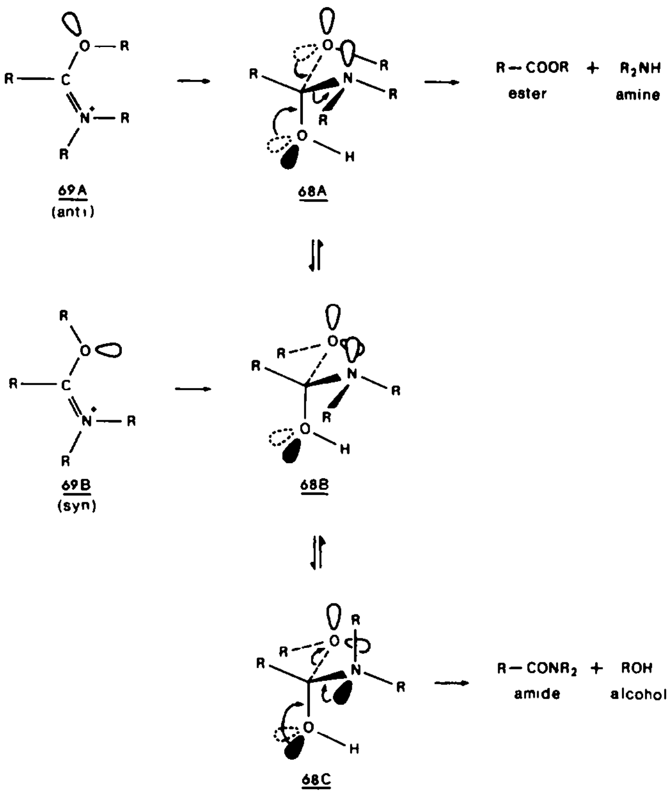
†A study of the pH-product profile in an aqueous solution cannot be conveniently carried out with these cyclic salts. Under basic conditions, the ester-amine products which are formed from these salts are very rapidly transformed into their corresponding amide-alcohol products directly in the reaction mixture. It is therefore difficult to analyze the products resulting from the reaction under kinetically controlled conditions.



Scheme 39.

down via stereoelectronic control, conformational changes by rotation to give **68A** (C–O bond rotation) or **68C** (C–N bond rotation) will occur prior to cleavage.

When conformer **68C** is in the T^+ or $T^\pm$ ionic form, it cannot be cleaved with stereoelectronic control because the nitrogen of the hemi-orthoamide is sufficiently basic to be always protonated and its lone pair orbital is therefore not available to expel the OR group. Consequently, in media which favor T^+ or $T^\pm$, conformer **68B** can be either converted to **68A** or **68C** but cleavage with stereoelectronic control can occur with conformer **68A** only. Thus, under those conditions, *syn* imidate salt should yield the ester-amine products only.

When intermediate **68C** exists in the T^- ionic form, it can be cleaved with stereoelectronic control. Consequently, in media which favor T^-, conformer **68B** can be either converted to **68A** or **68C**, **68A** yielding the ester-amine products and **68C** the amide-alcohol products. Thus, in strong basic medium, *syn* imidate salts can give the amide-alcohol as well as the ester-amine products.

Thus, in acidic or neutral media which favor the formation of T^+ and $T^\pm$, *syn* imidate salts should only give the ester-amine products. When the reaction medium becomes basic enough to allow the existence of T^-, the amide-alcohol products should start to be formed. When the medium becomes strongly basic, T^- is then the only ionic species which should yield, both the ester-amine and amide-alcohol products, at a constant ratio for a given substrate. The ratio of products will depend on the relative energy barriers of rotation of the C–O and C–N bonds. One should therefore expect that the value of the ratio will vary with different *syn* imidate salts.

The imidate salts **134** and **135** are considered to exist in the *syn* conformation† and they do indeed exhibit the following behavior. They give the ester-amine products in acidic and neutral conditions, and starting at pH 8·5, the amide-alcohol products which reach a constant maximum yield at pH 11 and above. In our previous investigation with mixed aqueous-organic solvent, we have described the basic hydrolysis of some cyclic imidate salts which can only exist in the *syn* conformation and mixture of ester-amine and amide-alcohol products was obtained under basic conditions. Under neutral or acidic conditions, they gave the ester-amine products exclusively.

We would like to emphasize that the stereoelectronic theory permits the understanding of why a tetrahedral intermediate would prefer to eject the R_2N group in presence of the OR group, a normally better leaving group under basic conditions. Thus, the application of the postulate of conformational changes in tetrahedral intermediates combined with the theory of stereoelectronic control on the various ionic forms T^+, $T^\pm$ and T^- of such intermediates provide a very attractive mechanism to explain the products formed in the hydrolysis of imidate salts at various pH.

In the course of the presentation of this new theory, we had to make several postulates concerning conformational changes during reactions and also about the relative energy barriers of bond rotation and cleavage of the intermediate.[31] These postulates remain to be supported by direct experimental evidence.

We have postulated that the energy barrier for the stereoelectronic cleavage of a tetrahedral intermediate

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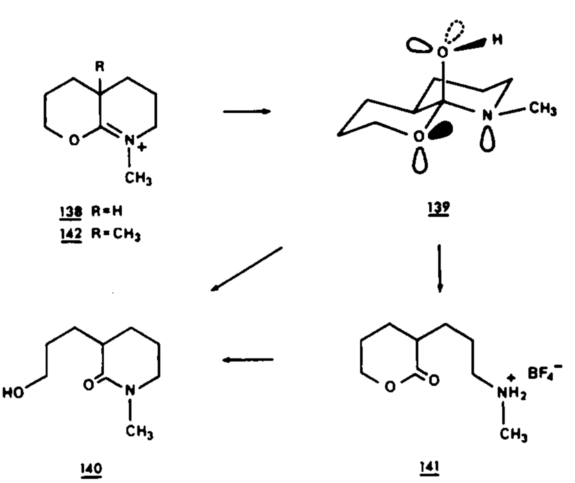
†It is possible that the salts **134** and **135** exist to some extent in the *anti* form which would be in equilibrium with the *syn* form. This new situation does not change the above conclusion. The *syn* form would still produce the amide-alcohol products and a certain percentage of the ester-amine products. The remaining portion of ester-amine products observed would come from the *anti* form.

such as **68A** and **68C** in the T^- ionic form, is much lower than that for rotation to give other conformers. The fact that *anti* imidate salts (which generate **68A**) give the ester-amine products, can be considered as an experimental evidence for that postulate. However, it would be desirable to find out an experiment which can show that conformational changes does not take place in the hydrolysis of *anti* imidate salts. Also, we have not yet obtained any experimental support that conformer **68C** in the ionic form T^- behaves in a similar way. Good arguments can be brought to show that the energy barrier for the cleavage of **68C** should be lower than that for **68A**, thus, indicating that if **68A** does not undergo conformational changes, **68C** will certainly not. The cleavage of the C–OR bond in **68C** ought to be easier than that for the C–NR_2 bond in **68A**. It is also reasonable to assume that the lone pair orbital of the nitrogen in **68C** must be a more powerful one to eject a leaving group than that of the oxygen of the OR group in **68A**.

We have also postulated that the energy barrier for a nonstereoelectronically controlled cleavage of a tetrahedral intermediate is higher than that for rotation to give new tetrahedral conformers. Experimental evidence for the conformational change of **68B** in the T^+ or $T^\pm$ forms has not yet been obtained. If the stereoelectronic theory is neglected, one can still predict on the basis of the ability of the two leaving groups than an intermediate such as **68B** should yield the ester-amine products exclusively under acidic or slightly basic conditions. So, the fact that *syn* imidate salts yield only the ester-amine products under those conditions does not constitute evidence for a conformational change of the tetrahedral intermediate prior to cleavage.

Similarly, we have not yet described an experiment to show that when conformer **68B** exists in the ionic form T^-, it prefers to undergo conformational changes to **68A** and **68C** prior to cleavage.† The fact that *syn* imidate salts yield a mixture of products under basic conditions is very well explained by this postulate and the present level of knowledge does not offer any alternative explanation. The hydrolysis of imidate salt **110** (Scheme 33) provides additional evidence for conformational changes. This *syn* salt produces a tetrahedral intermediate which is equivalent to **68B**. However, only the C–O bond rotation is allowed in this intermediate, as the C–N bond rotation is a much more difficult process. Therefore, the intermediate can change only to new conformers which can produce the ester-amine products. Indeed, the basic hydrolysis of this salt gave the ester-amine **113** only, despite its *syn* conformation.

We have also studied the hydrolysis of the bicyclic imidate salt **138**. Reaction of **138** with hydroxide ion should give the intermediate **139** which cannot break down in a stereoelectronically controlled fashion unless considerable twisting of the molecule can occur. It was therefore of interest to find out if the tetrahedral intermediate **139** could be detected in the reaction mixture since the energy barrier for its breakdown must be abnormally high. The hydrolysis of **138** in aqueous sodium carbonate gave the lactam-alcohol **140**, whereas under acidic conditions, it gave the lactone-ammonium salt **141**.



Scheme 40.

When **141** was treated with aqueous sodium carbonate, it gave directly the lactam-alcohol **140**. This result shows that the products of the basic hydrolysis of **138** were those of thermodynamic control. We have obtained similar results in the hydrolysis of the imidate salt **142**.

These results indicate that cleavage without stereoelectronic control can occur. The energy barrier of such a cleavage is simply higher than that for a cleavage with stereoelectronic control. However, when conformational changes to new conformers is possible, such high energy processes are of course avoided.

We would like to emphasize that when a tetrahedral intermediate such as **68A** exists in the T^- ionic form, it does not first eject the amide ion to be protonated by the solvent to give the secondary amine. Both, the protonation and the ejection processes must be synchronized.[32] In aqueous solution, the nitrogen lone pair orbital of **68A** must first be H-bonded with the solvent. When the cleavage starts to occur, the C–N bond becomes longer and weaker, the nitrogen atom becomes more basic, the N–H bond must become shorter and stronger. When the cleavage is almost complete, the nitrogen–hydrogen bond must be near a full bond, so that the group can leave as a secondary amine.

CONCLUSION

The results that we have described on the ozonolysis of acetals, on the hydrolysis of orthoesters and imidate salts constitute enough experimental evidence to take the stereoelectronic theory seriously. However, we believe that more experiments are still necessary to establish it completely.

We have stressed the fact that conformational changes prior to cleavage in some tetrahedral intermediate have not yet been established experimentally. We think that this should be done because it is a fundamental principle of the stereoelectronic theory. This principle of conformational change can become a crucial point when the stereoelectronic theory is applied to the mechanism of hydrolysis by enzymes. For instance, it could lead to the prediction that conformational changes are necessary for the stereoelectronic assistance of hydrolysis by enzymes.

Finally, we would like to point out that the oxidation of acetals and the cleavage of hemi-orthoester and of hemi-orthoamides are isolated examples of a general chemical process. The reactions described in Scheme 41 also belong to the same class: (*a*) the haloform reaction,

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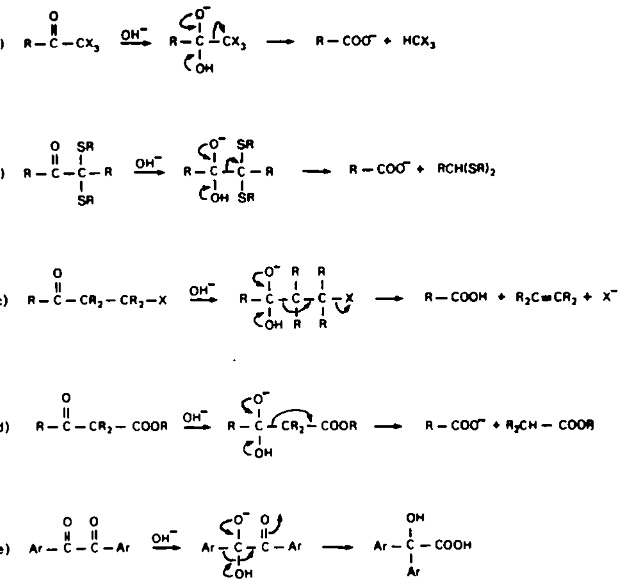
†When **68B** exists as T^-, the energy barrier for its cleavage must be higher than when it exists as $T^\pm$ (and possibly as T^+). The R_2N group in T^- is a poorer leaving group than the R_2NH^+ group in $T^\pm$. Thus, conformational change is more likely to occur when **68B** exists as T^-.



Scheme 41.

(b) the basic fragmentation of α-diketone monothioketals,[33] (c) the Grob fragmentation with two heteroatoms[34] and related reactions,[35] (d) the retro-Claisen condensation and (e) the benzilic acid rearrangement. The Cannizzaro reaction, the facile opening of cyclopropanones (Favorski rearrangement) and the cleavage of non-enolizable ketone by sodium amide[36] (Haller–Bauer reaction) and by hydroxide ion[37] can also be added to the preceding list of reactions. The combination of two hetero-atoms with proper orbital orientation is a very powerful driving force for expelling a leaving group.[33,37] The reaction should be easier if one of the two heteroatoms is negatively charged; if both heteroatoms can bear a negative charge, it should proceed with even greater ease and work with an even poorer leaving group.

Thus, this general chemical process can take place whenever two heteroatoms (oxygen and/or nitrogen) and a leaving group are linked to the same carbon. The only requirement is a stereoelectronic one where each heteroatom should have a lone pair orbital oriented antiperiplanar to the leaving group.†

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†For further experimental and theoretical studies related to this subject, see Ref. 38.

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