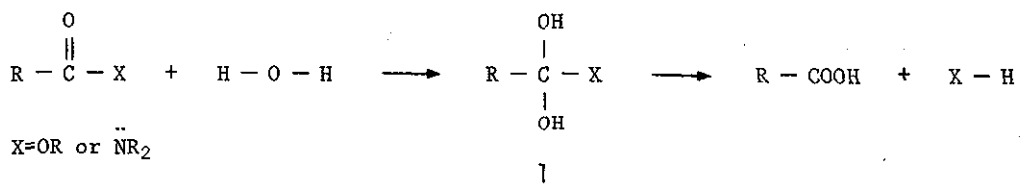STEREOELECTRONIC CONTROL IN HYDROLYTIC REACTIONS[†§]

Pierre Deslongchamps

Département de chimie, Université de Sherbrooke, Sherbrooke, Québec, J1K 2R1

Experiments are described which show that the stereochemistry and the ionic state of tetrahedral intermediates, the orientation of non-bonded electron pairs, and the relative energy barriers for cleavage and for molecular rotation are the key parameters in the stereoelectronically controlled cleavage of tetrahedral intermediates formed in the hydrolysis of esters and amides.

It is generally accepted that the most common mechanism for the hydrolysis of esters and amides proceeds through the formation of a tetrahedral intermediate 1.

$$R - \overset{\overset{\textstyle O}{\|}}{C} - X \; + \; H - O - H \longrightarrow R - \overset{\overset{\textstyle OH}{|}}{\underset{\underset{\textstyle OH}{|}}{C}} - X \longrightarrow R - COOH \; + \; X - H$$

X=OR or $\ddot{N}R_2$

$\underline{1}$

Since 1971 (1), we have elaborated a new theory in which the stereochemistry of tetrahedral intermediates plays a major role in their cleavage. We have postulated that the precise conformation of the tetrahedral intermediate is

---

transmitted into the product of the reaction and that the specific decomposition of such an intermediate is controlled by the orientation of the non-bonded electron pairs (lone pair orbitals) of the heteroatoms[1]. A cleavage with stereoelectronic control of a tetrahedral intermediate is defined in the following way: specific cleavage of a carbon-oxygen or a carbon-nitrogen bond occurs when two heteroatoms (oxygen or nitrogen) of the tetrahedral intermediate each have one non-bonded electron pair oriented antiperiplanar to the departing O-alkyl or N-alkyl group. This implies that a cleavage with stereoelectronic control, represented by 2A, is a sufficiently low energy process that a cleavage without stereoelectronic control, represented by 2B, cannot effectively compete with it.

2A   **2B**
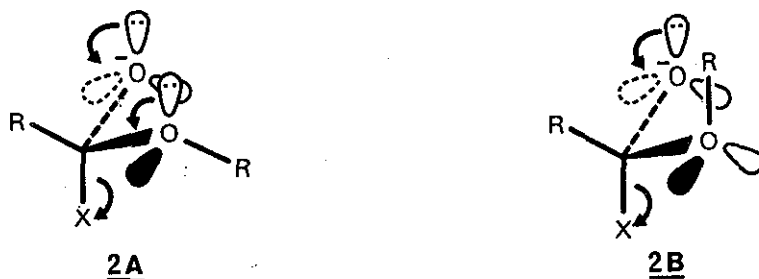
What we are trying to prove in this investigation is that the stereochemistry of species which have an extremely short lifetime is a very important parameter in relation to their reactivity. At the same time, we are trying to show that the orientation in space of non-bonded electron pairs on heteroatoms, is also crucial in order to understand the reactivity of these species. Rigorous experimental evidence to prove these points is not easily obtainable and cannot be obtained by a single experiment.
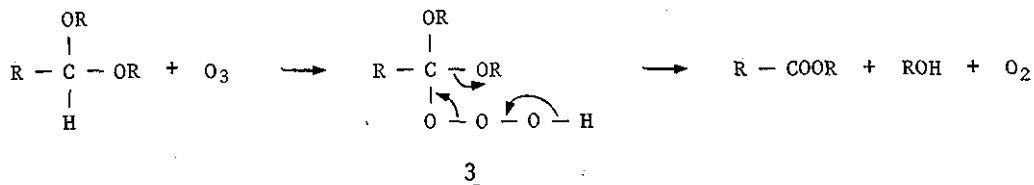
---

[1] We therefore assume that the oxygen atom of an ether function has the idealized sp3 hybridization. We now prefer the term "non-bonded electron pair" in place of "lone pair orbital" as it expresses more precisely the basis for the reactivity of tetrahedral intermediates.

Evidence which we have already reported (1), in favor of this theory, has been obtained from three different types of experiments: the oxidation of acetals by ozone (2), the acid hydrolysis of cyclic orthoesters (3) and the basic hydrolysis of N,N-dialkylated imidate salts (4). Each of these different types of experiments has provided some evidence for the several postulates that we have made and taken ensemble, they provide rather convincing arguments in favor of stereoelectronic control.

A brief description of these three different types of experiment will be presented in which we shall indicate the information gained from them, as well as their limitations. We shall then present new experimental results using completely different methods which are a) concurrent carbonyl oxygen exchange in the hydrolysis of esters and amides (5), b) cleavage of conformationally rigid bicyclic vinyl orthoesters, c) ozonolysis of tetrahydropyranyl alcohol and d) basic hydrolysis of N-(2,6-dimethylphenyl)-N-methylformamide and its imidate salts. These new methods give results which confirm our earlier findings and furthermore provide some answers that could not be obtained by our previous methods. Consequently, we think they have helped us to gain a better and more complete understanding of the fragmentation of tetrahedral intermediates.

OZONOLYSIS OF ACETALS

In our work on the ozonolysis of acetals (2), we found that only the corresponding ester and alcohol are produced. We explained this reaction by postulating the formation of a tetrahedral intermediate (an hemi-orthoester (3)) which breaks down to give the products of the reaction.

$$\underset{H}{\overset{OR}{R - C - OR}} \; + \; O_3 \longrightarrow \underset{O - O - O - H}{\overset{OR}{R - C - OR}} \longrightarrow R - COOR \; + \; ROH \; + \; O_2$$

$$\underline{3}$$

We then studied the relationship between the reactivity and the conformation of acetals. Appropriate chemical models representing the six possible gauche conformers of the acetal function were available and we found, as shown in Scheme 1, that only three of these conformers ($\underline{A}$, $\underline{C}$, and $\underline{F}$) were reactive toward ozone.

These results clearly demonstrate that there is a relationship between the conformation of the acetal function and its reactivity toward ozone. They also led us to postulate that a reactive conformer must have on each oxygen atom one pair of non-bonded electrons oriented antiperiplanar to the C — H bond of the acetal function.

During the course of this work, we had also observed that the ozonolysis of tetrahydropyranyl ethers gave the corresponding hydroxy-esters exclusively.

$$\underline{4}$$
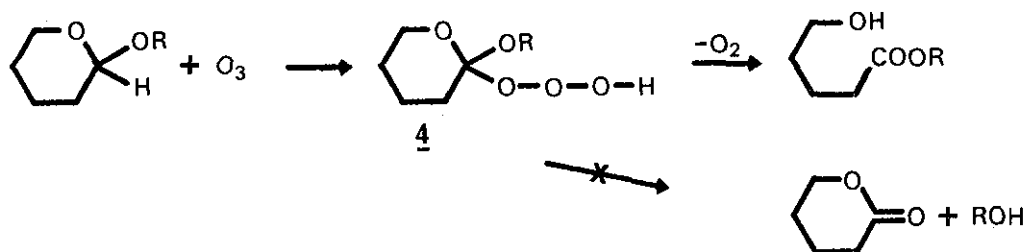
This result indicates that the tetrahedral intermediate $\underline{4}$, formed from the tetrahydropyranyl ether, cleaved in a completely specific manner since the other possible products of the reaction, the lactone and alcohol, were never observed. We have been able to rationalize these results by extending our ideas on electron pair orientation and reactivity to the cleavage of tetrahedral intermediates.

A

B

C

D

F

E
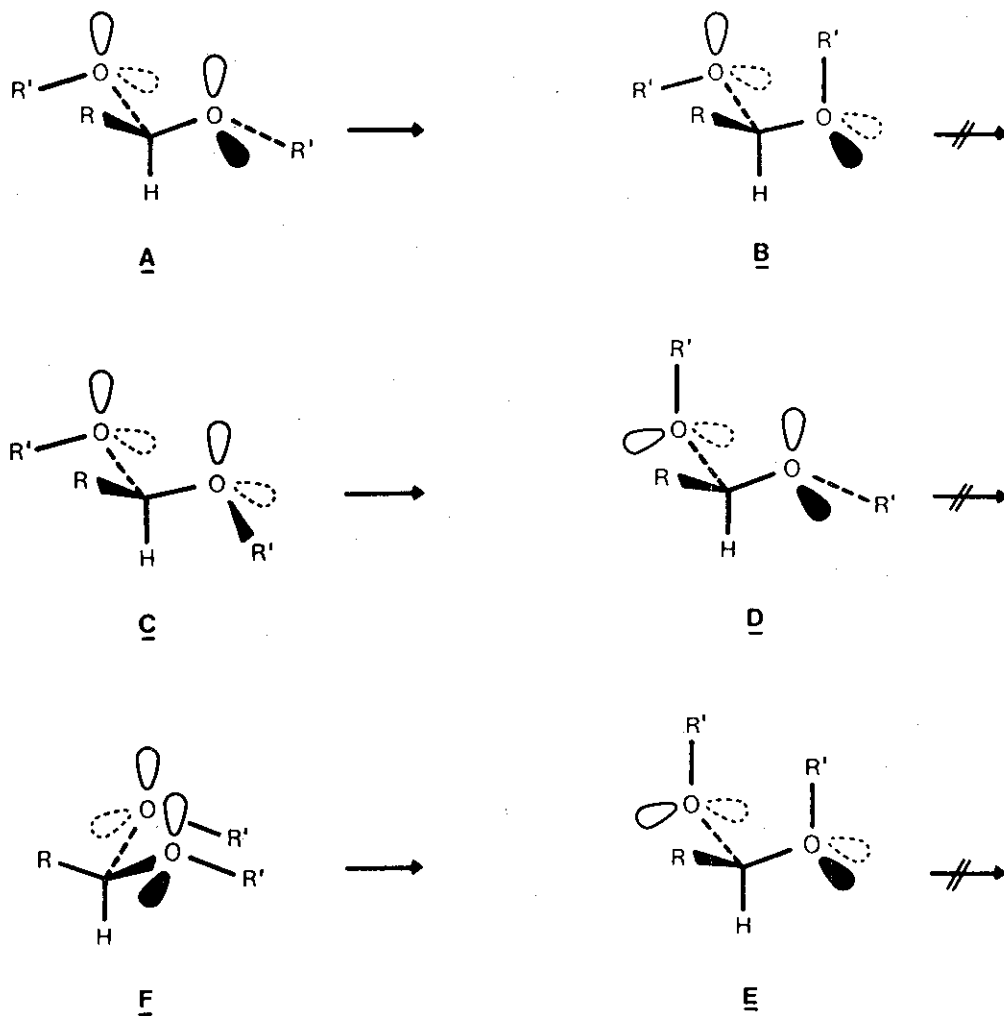
SCHEME 1

For instance, a tetrahydropyranyl ether could react with ozone *via* the conformer 5 (Scheme 2), giving specifically the tetrahedral intermediate 6. This intermediate has the proper electron pair orientation to give the hydroxy-ester only. Indeed, loss of the OR group to generate the lactone is not possible with stereoelectronic control because the non-bonded electrons of the ring oxygen are not properly aligned.
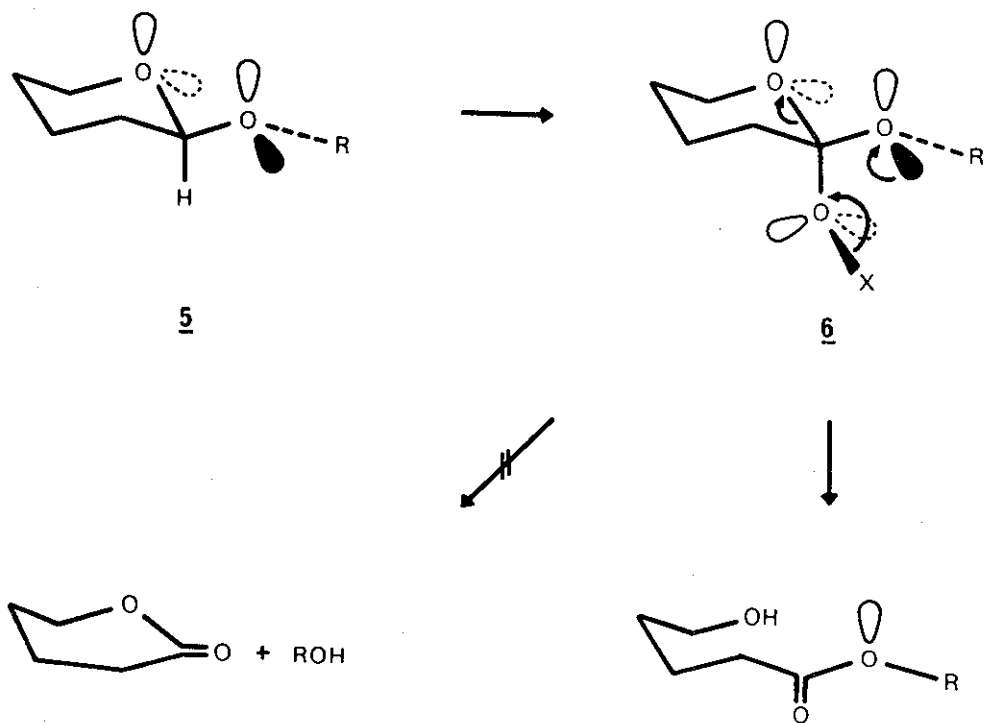
In this manner, we could explain our results, but we had to make several postulates: a) the ozonolysis reaction proceeds through the formation of an hemi-orthoester type of tetrahedral intermediate! b) the ozonolysis of a tetrahydropyranyl ether proceeds *via* the desired conformer 5! c) the conformation of 5 is transposed into the tetrahedral intermediate 6! d) the tetrahedral intermediate remains in the conformation 6, it does not undergo conformational changes prior to cleavage! However, the basic postulate is that hemi-orthoesters such as 6 cleave specifically and that such cleavage is stereoelectronically controlled. This postulate had to be verified *a priori*.

It is experimentally difficult to demonstrate that the ozonolysis of acetals proceeds *via* the formation of a hemi-orthoester intermediate[2]. Thus, the results obtained from the ozonolysis could be utilized to propose the stereoelectronic theory but not to verify it. Consequently, it was necessary to find other methods to generate tetrahedral intermediates in order to confirm that specific cleavage does indeed take place.
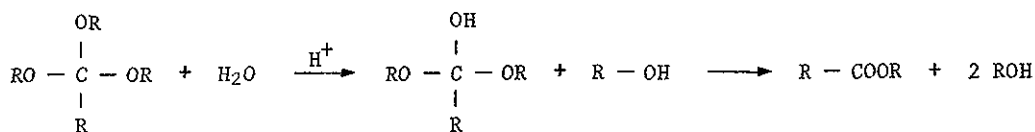

HYDROLYSIS OF ORTHOESTERS

It is accepted that the formation of esters from the mild acid hydrolysis of orthoesters proceeds through the formation of a hemi-orthoester intermediate as described in the following equation (7).

---

[2] Recent work on ozonolysis of aldehyde and ether functions (6) provides compelling evidence for the formation of a hydrotrioxide hemi-orthoester intermediate.

SCHEME **2**   (X = H or OOH)

$$\begin{array}{c} \text{OR} \\ | \\ \text{RO} - \text{C} - \text{OR} \\ | \\ \text{R} \end{array} + \text{H}_2\text{O} \xrightarrow{\text{H}^+} \begin{array}{c} \text{OH} \\ | \\ \text{RO} - \text{C} - \text{OR} \\ | \\ \text{R} \end{array} + \text{R} - \text{OH} \longrightarrow \text{R} - \text{COOR} + 2\ \text{ROH}$$

Thus, the hydrolysis of a cyclic orthoester such as $\underline{7}$ should give the hemi-orthoester $\underline{8}$ which, if it has the correct conformation, should produce the hydroxy-ester product only; no lactone plus alcohol should be observed under kinetically controlled conditions. This prediction was verified experimentally by a study of the mild acid hydrolysis of several cyclic orthoesters.
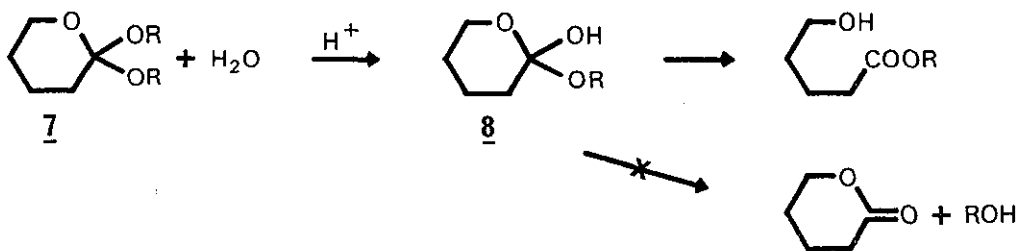
In order to explain these results, we had to make the assumption that although a cyclic orthoester can exist in principle in nine different gauche conformations, it prefers to hydrolyse *via* the conformer $\underline{9}$ only! (Scheme 3) Indeed, a stereoelectronically controlled cleavage of $\underline{9}$ gives the dioxolenium salt $\underline{10}$ which reacts with water to form the hemi-orthoester $\underline{11}$ (the equivalent of $\underline{6}$) which can only give the hydroxy-ester product.

Experimental support for this assumption was obtained by showing that conformationally rigid cyclic orthoesters such as $\underline{13}$ which has two different alkoxy groups does hydrolyse to give specifically the hydroxy-ester $\underline{14}$ with loss of the axial alkoxy group only. In addition, the stereospecific synthesis of $\underline{13}$ by reaction of sodium methoxide on the dioxolenium salt $\underline{12}$ provided further evidence for stereoelectronic control.
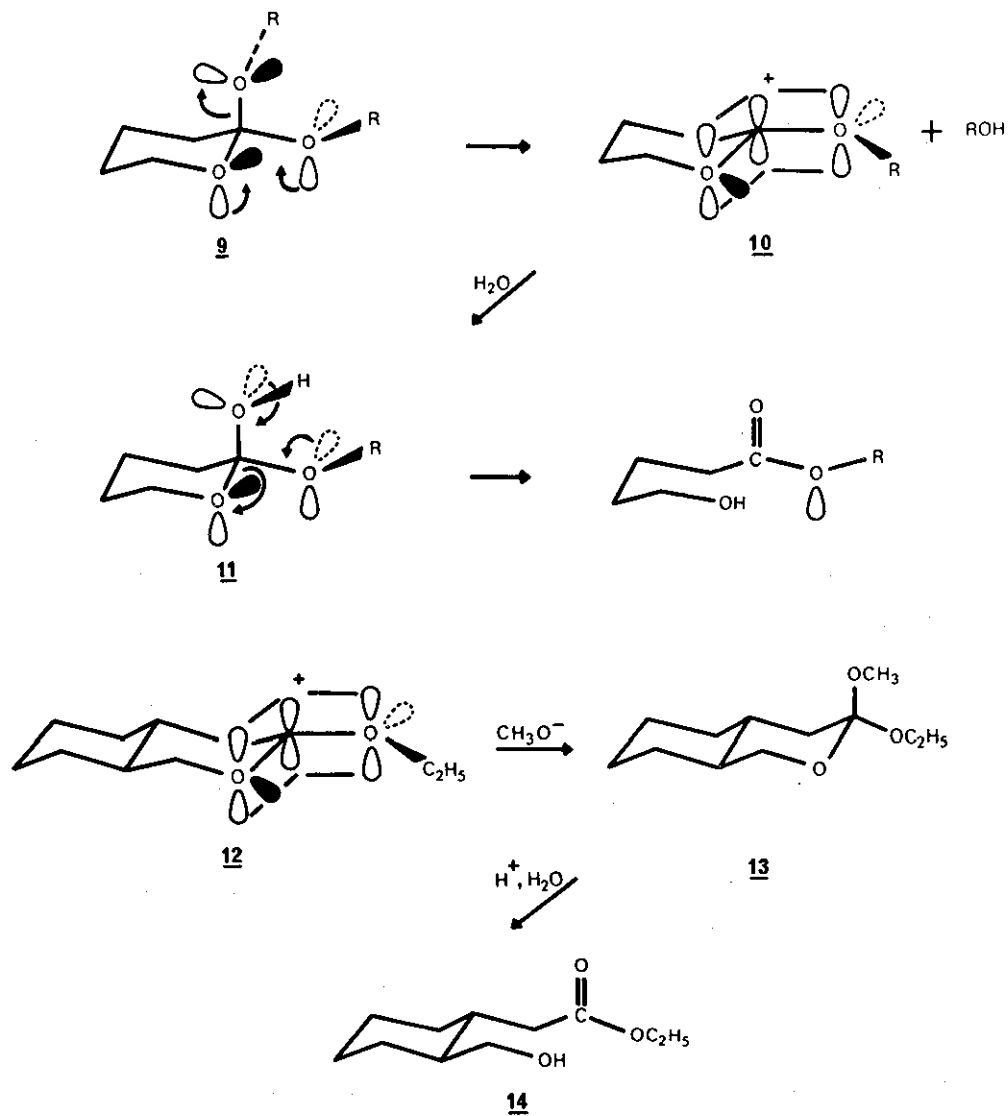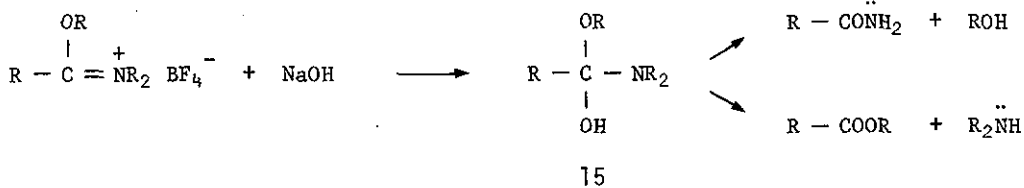
SCHEME 3

We concluded from this work that a) hemi-orthoesters do cleave in a highly specific manner, b) these results are in accord with the idea of stereoelectronic control. However, we considered that the postulates a) transmission of conformation from the starting orthoester (9) to the intermediate 11 and b) breakdown of the tetrahedral intermediate prior to any conformational change remained to be verified.

## HYDROLYSIS OF N,N-DIALKYLATED IMIDATE SALTS

We have undertaken a study of the basic hydrolysis of N,N-dialkylated imidate salts in order to provide evidence that there is also stereoelectronic control in the cleavage of hemi-orthoamides (4). N,N-dialkylated imidate salts can be considered to be activated amides, and it is known (8) that they are rapidly hydrolysed under basic conditions to give the ester-amine or the amide-alcohol as products. These reactions occur through the formation of the tetrahedral intermediate 15 (a hemi-orthoamide).

$$
R-\overset{\overset{\displaystyle OR}{|}}{C}=\overset{+}{N}R_2 \; BF_4^- \;+\; NaOH \;\longrightarrow\; R-\overset{\overset{\displaystyle OR}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}-NR_2
\nearrow R-CONH_2 \;+\; ROH
\searrow R-COOR \;+\; R_2NH
$$

$$\underline{15}$$

Imidate salts are planar[3] and can exist in two different conformations, the Z (*anti*) (16A) or the E (*syn*) (16B) form (Scheme 4). The principle of stereoelectronic control was then applied to each type of imidate salt.

In the case of Z imidate salt (16A), it led to the fascinating prediction, that under basic conditions the ester-amine should be produced exclusively;

---

[3] Unpublished results of X-ray crystallography by Dr G.I. Birnbaum, NRC (Ottawa).
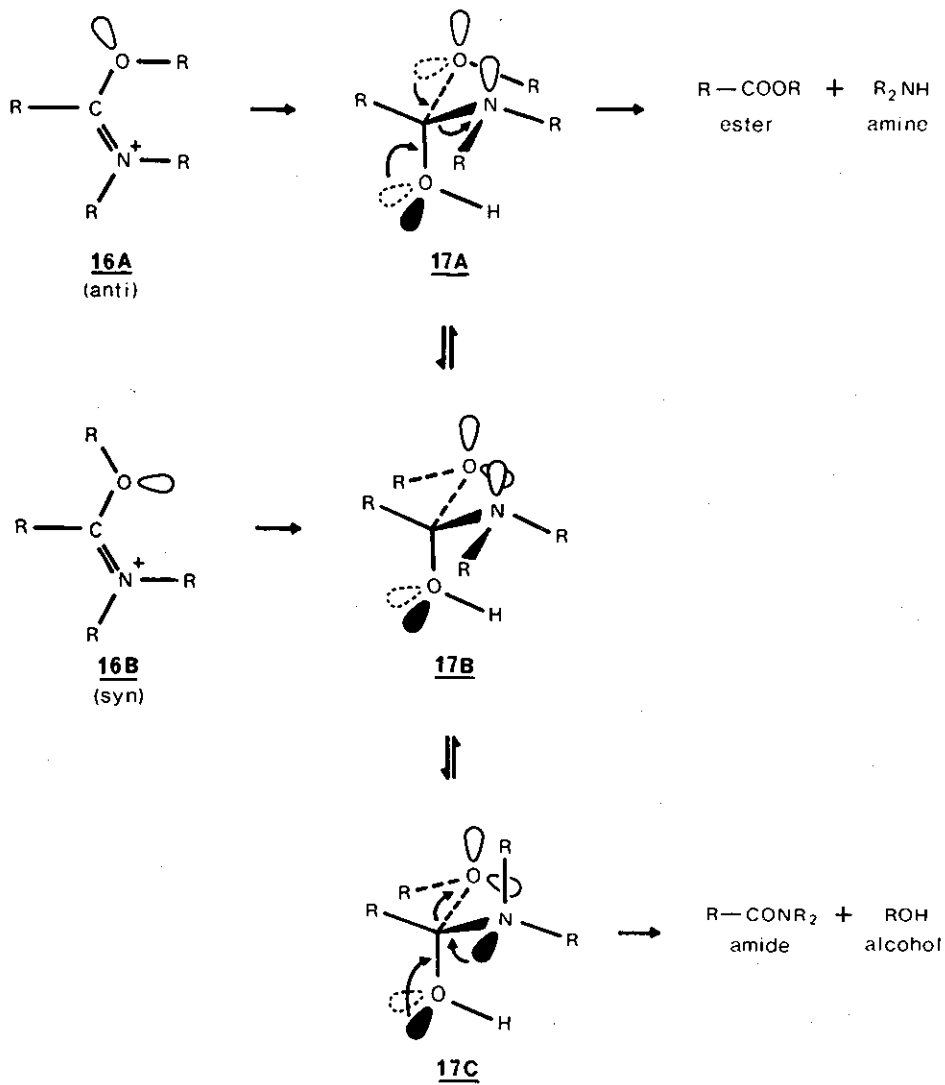
SCHEME **4**

a reaction of hydroxide ion on 16A with stereoelectronic control should give
17A which has proper electron pair orientation to eject the amino group only.
Should this prediction correspond to reality, it would be a very powerful
argument for the idea of stereoelectronic control. It would also permit an
understanding of why a tetrahedral intermediate would prefer to eject the NR_2
group in presence of the OR group, normally a much better leaving group under
basic conditions.

In the case of E imidate salt (16B), a mixture of ester-amine and amide-
alcohol products was predicted. Reaction of hydroxide ion with an imidate salt
(16B) should form the intermediate 17B specifically. Since 17B cannot break
down to the products of the reaction with stereoelectronic control, we have
postulated that its barrier for cleavage would now be higher than that for
conformational changes. Thus, 17B would prefer to undergo either C — O or
C — N bond rotation to give either 17A or 17C. 17A would again give the ester-
amine product and 17C has proper electron pair orientation to give the amide-
alcohol product.

These predictions have been verified experimentally by a study of the basic
hydrolysis of several N,N-dialkylated imidate salts. Z imidate salts gave the
ester-amine product exclusively while E imidate salts gave mixtures of ester-
amine and amide-alcohol products.

We have also studied some E imidate salts which should form an intermediate
such as 17B in which the C — N bond rotation was highly disfavored (17B✗17C).
In those cases, 17B could be converted easily into 17A only, and as predicted,
these salts yielded the ester-amine product exclusively under kinetically
controlled conditions.

These results led us to the following conclusions:

a) strong evidence in favor of stereoelectronic control was obtained because
Z imidate salts gave the ester-amine product,

b) the fact that $\underline{Z}$ and $\underline{E}$ imidate salts behave differently supported the idea that conformational change does not occur when the tetrahedral intermediate can break down with stereoelectronic control to give the products of the reaction.

In the course of this investigation, one new postulate was necessary to explain the results with $\underline{E}$ imidate salts. It was postulated that when a tetrahedral intermediate cannot break down with stereoelectronic control, the barrier for its cleavage becomes higher than that for conformational changes. Experimental support had been obtained which showed that the amino group had to undergo a conformational change but no experiments had been carried out to show that the OR group also, has to rotate prior to break down.
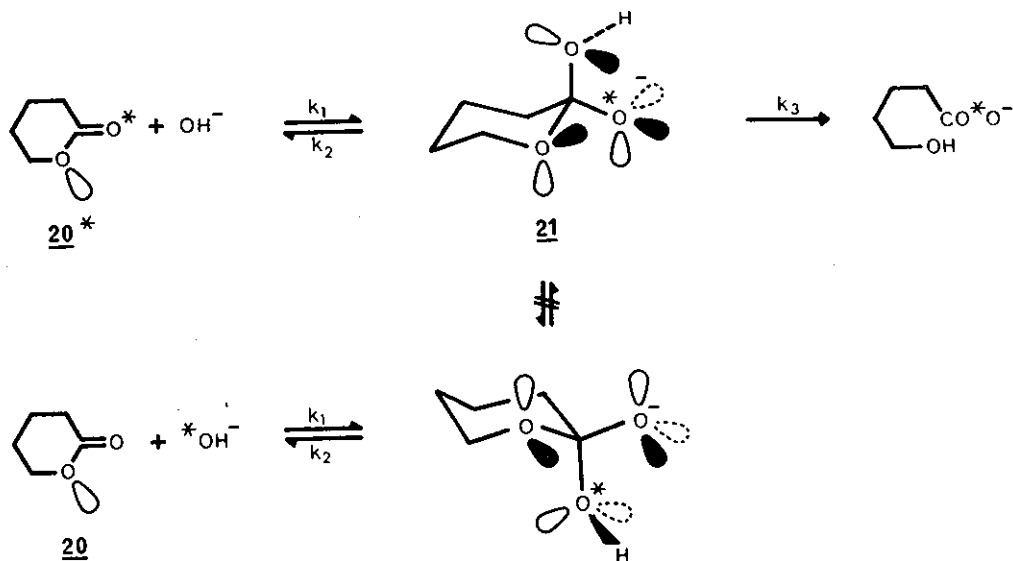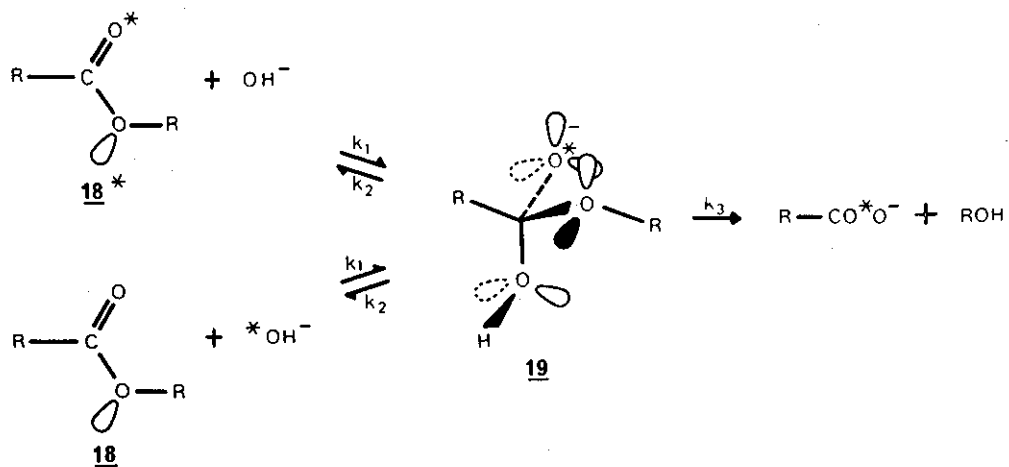
CONCURRENT OXYGEN-EXCHANGE AND HYDROLYSIS

Concurrent carbonyl-oxygen exchange and hydrolysis have been demonstrated to occur in esters by using oxygen-18 labelling (9).
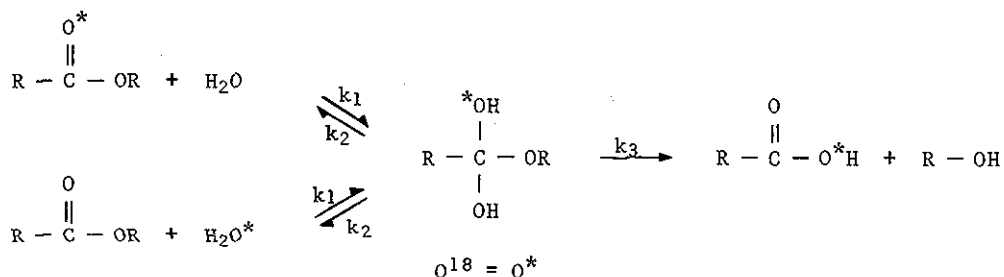
Most substrates which have been studied show concurrent oxygen exchange but there are exceptions. It has been postulated that reactions in which oxygen exchange is not detected still conform to the general mechanism described above; in those cases, no oxygen exchange is observed because the ratio of k_3/k_2 is greater than 100.

If it is indeed true that there is no conformational change in the tetrahedral intermediate when stereoelectronically controlled cleavage is allowed, then

SCHEME 5 $(O^* = O^{18})$

concurrent carbonyl-oxygen exchange during hydrolysis can be used as an experimental technique to demonstrate both the lack of conformational change and the stereoelectronic theory.

Application of these postulates to the hydrolysis of esters led to the following predictions: Z esters can undergo carbonyl-oxygen exchange but E esters cannot.

With a Z ester ($\underline{18}^{*}$, Scheme 5), reaction with hydroxide ion should give the tetrahedral intermediate $\underline{19}$ which has the required orientation of electron pairs[4] to break down in the three possible directions to give the starting labelled ester $\underline{18}^{*}$, the unlabelled ester $\underline{18}$ and the product of the reaction. Consequently, the hydrolysis of Z esters should always occur with carbonyl-oxygen exchange with the solvent. The extent of exchange can vary depending on the relative values 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 described in the literature for Z esters (11).

With an E ester ($\underline{20}^{*}$, Scheme 5), reaction with hydroxide ion should give the tetrahedral intermediate $\underline{21}$ which has the required orientation of electron pairs to break down in two directions only to give the starting labelled ester $\underline{20}^{*}$ and the product of the reaction. Since, $\underline{21}$ cannot yield the unlabelled ester $\underline{20}$, carbonyl-oxygen exchange should not occur with E esters. This prediction is in accord with our experimental results (5) as well as those previously described in the literature (12) which show that lactones do not undergo carbonyl-oxygen exchange.
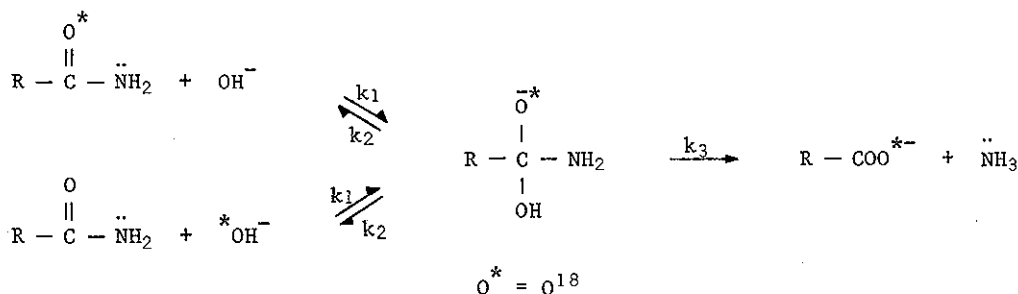
We could draw the following conclusions from this work:

a) the fact that Z esters do undergo carbonyl-oxygen exchange is in accord with the stereoelectronic theory but it does not constitute a proof for it, b) the

---

[4] An O — H bond is considered equivalent to a non-bonded electron pair
($- \ddot{O} - H = - \ddot{O}\colon$), since proton transfer is a very fast process (10).

fact that no carbonyl-oxygen exchange occurs in the hydrolysis of $\underline{E}$ esters (lactones) can be easily understood on the basis of stereoelectronic control. However, if one neglects stereoelectronic control, the results with lactones could still be explained by using a kinetic argument (if k_3/k_2 is greater than 100).

In order to be completely rigorous, we had to find some experiments where the kinetic argument could not be applied. It appeared possible to obtain such experimental conditions by a study of carbonyl-oxygen exchange in the course of the basic hydrolysis of labelled amides.

$$
\begin{array}{l}
\overset{*}{O} \\
\parallel \quad \cdot\cdot \\
R - C - NH_2 \quad + \quad OH^-
\end{array}
\underset{k_2}{\overset{k_1}{\rightleftarrows}}
\qquad
\begin{array}{l}
\overset{-*}{O} \\
| \\
R - C - NH_2 \\
| \\
OH
\end{array}
\xrightarrow{k_3}
\quad R - COO^{*-} \quad + \quad \overset{\cdot\cdot}{N}H_3
$$

$$
\begin{array}{l}
O \\
\parallel \quad \cdot\cdot \\
R - C - NH_2 \quad + \quad {}^*OH^-
\end{array}
\underset{k_2}{\overset{k_1}{\rightleftarrows}}
$$

$$O^* = O^{18}$$

It has been observed that there is considerable carbonyl-oxygen exchange in the basic hydrolysis of primary amides (13) and this result was correctly explained by the fact that k_2 should always be greater than k_3 because an OH group is a much better leaving group than an NH$_2$ group.

Application of the theory of stereoelectronic control to the basic hydrolysis of labelled amides led to the following predictions: a) primary and secondary amides should undergo considerable carbonyl-oxygen exchange, b) tertiary amides as well as secondary and tertiary lactams should not undergo carbonyl-oxygen exchange.

With a primary amide ($\underline{22}^*$, R' = H, Scheme 6), reaction with hydroxide ion should form the tetrahedral intermediate $\underline{23}$ (R' = H) which has the required
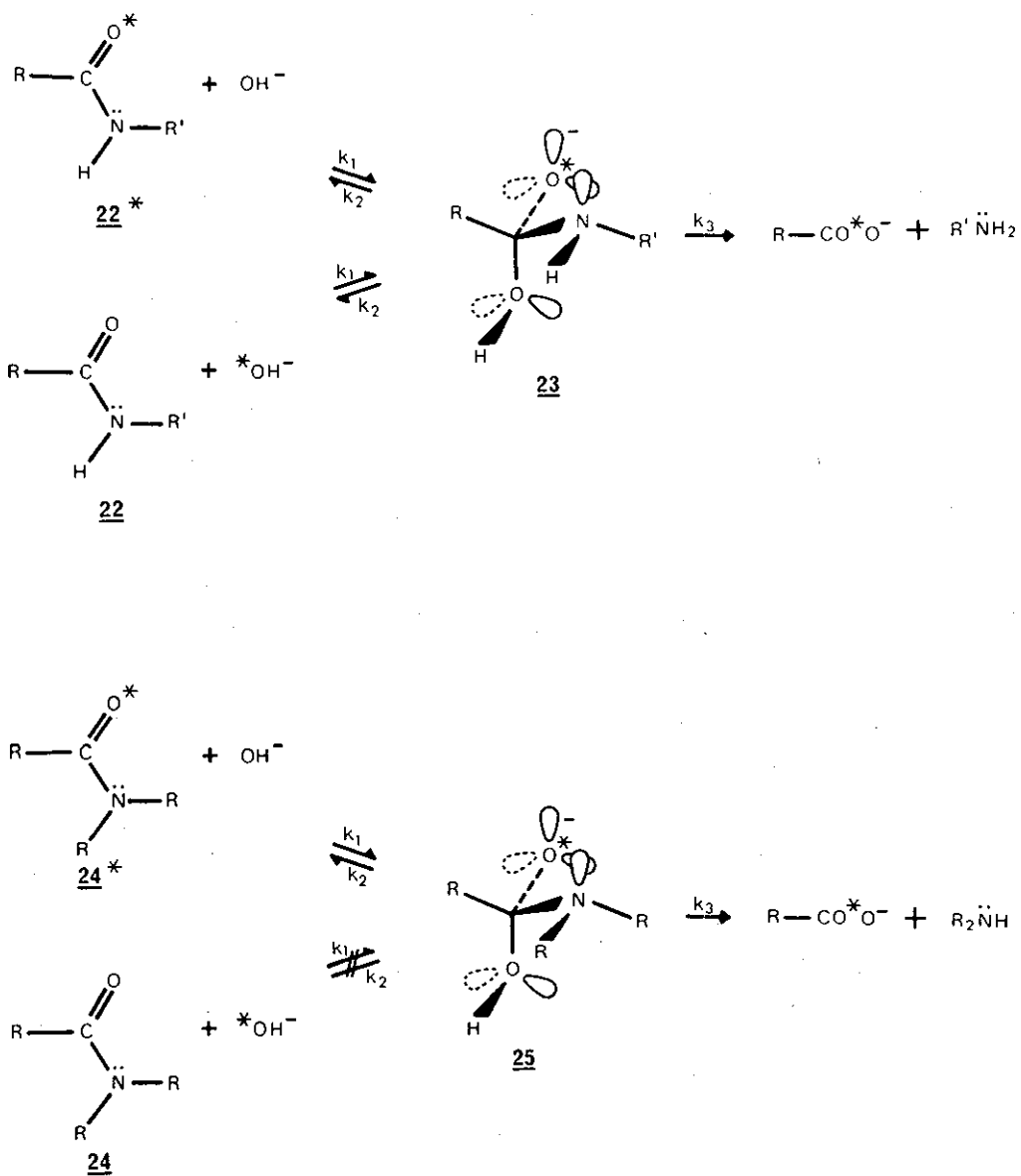
SCHEME 6

orientation of electron pairs[5] to break down in the three possible directions to give the labelled amide $\underline{22}^{*}$, the unlabelled amide $\underline{22}$ and the hydrolysis products. Thus, considerable carbonyl-oxygen exchange should be observed with primary amides.

Since a secondary amide exists in the conformation $\underline{22}$ (R' = alkyl) (14), it will form the intermediate $\underline{23}$ which can also break down in the three possible directions, thus carbonyl-oxygen exchange also should occur in this case.

With a tertiary amide $(\underline{24}^{*})$, reaction with hydroxide ion should give the tetrahedral intermediate $\underline{25}$ which has the required orientation of electron pairs to break down in two directions only to give the labelled amide $\underline{24}^{*}$ and the hydrolysis products. Intermediate $\underline{25}$ cannot break down with stereoelectronic control to give the unlabelled amide $\underline{24}$. Thus, carbonyl-oxygen exchange should not be observed with a tertiary amide. The same conclusion can be reached for tertiary lactams which are cyclic tertiary amides (Scheme 7): a labelled tertiary lactam such as $\underline{26}^{*}$ will form the intermediate $\underline{27}$ which can either give back $\underline{26}^{*}$ or the hydrolysis product, but it cannot yield unlabelled $\underline{26}$.

Since secondary lactams have a different conformation than secondary amides, they constitute a very interesting case to show the importance of conformation: a labelled secondary lactam such as $\underline{26}^{*}$ (R = H) should give the intermediate $\underline{27}$ (R = H) which can only give the labelled $\underline{26}^{*}$ or the hydrolysis product. Although the nitrogen of $\underline{27}$ (R = H) has two non-bonded electron pairs (N̈ — H), they are not properly oriented to eject the equatorial oxygen to give unlabelled $\underline{26}$. Thus, carbonyl-oxygen exchange should not be observed.

Bunton, Nayak and O'Connor (15) have studied carbonyl-oxygen exchange during the basic hydrolysis of a primary, a secondary and a tertiary amide. They have

---

[5] An N — H bond is considered equivalent to an electron pair ($-\overset{..}{\underset{|}{N}} - H = - \overset{\overset{H}{|}}{\underset{|}{N}}:$) since proton transfer is a very fast process (10).

R = H or CH$_3$
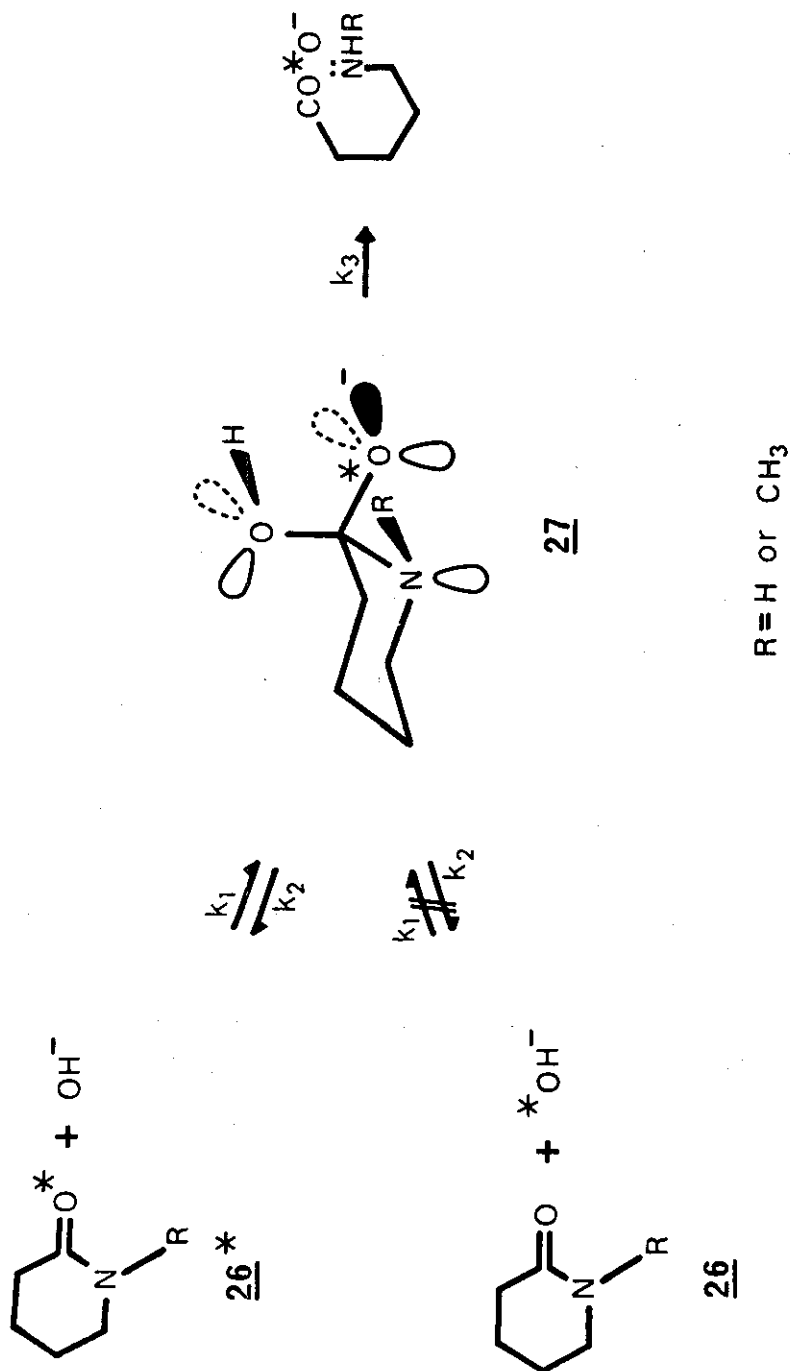
SCHEME 7

observed that the alkaline hydrolysis of benzamide and N-methylbenzamide

but not of N,N-dimethylbenzamide, is accompanied by extensive oxygen exchange.

We have studied the carbonyl-oxygen exchange during the basic hydrolysis of

N-methylacetamide, 2-piperidone and N-methyl-2-piperidone. We have found

that there is no carbonyl-oxygen exchange with 2-piperidone and N-methyl-2-

piperidone. Under similar conditions, carbonyl-oxygen exchange was observed

with N-methylacetamide (5).

Consequently, experiments have been carried out which show that the alkaline

hydrolysis of primary and secondary amides, but not of tertiary amides,

secondary and tertiary lactams, is accompanied by oxygen exchange.

The following conclusions can be drawn from these results:

a) there is stereoelectronic control in the cleavage of hemi-orthoamide

tetrahedral intermediates, b) in the case of hemi-orthoamide tetrahedral inter-

mediates, conformational change does not occur when stereoelectronically

controlled cleavage can take place under basic conditions.

CLEAVAGE OF VINYL-ORTHOESTERS

The main objective of our work is to prove that stereoelectronic control is

an important parameter in the cleavage of tetrahedral intermediates. The

results obtained by the four preceding experimental methods are in accord with

stereoelectronic control, but there is some ambiguity as the theory is used

to describe the precise configuration and conformation of an intermediate which

is then used to "test" the same stereoelectronic theory. A new strategy to

generate a tetrahedral intermediate in which the assignment of configuration

and conformation is independent of the stereoelectronic theory, could con-

fidently be considered as proof for the stereoelectronic theory, provided that

the intermediate behaved in the predicted manner.
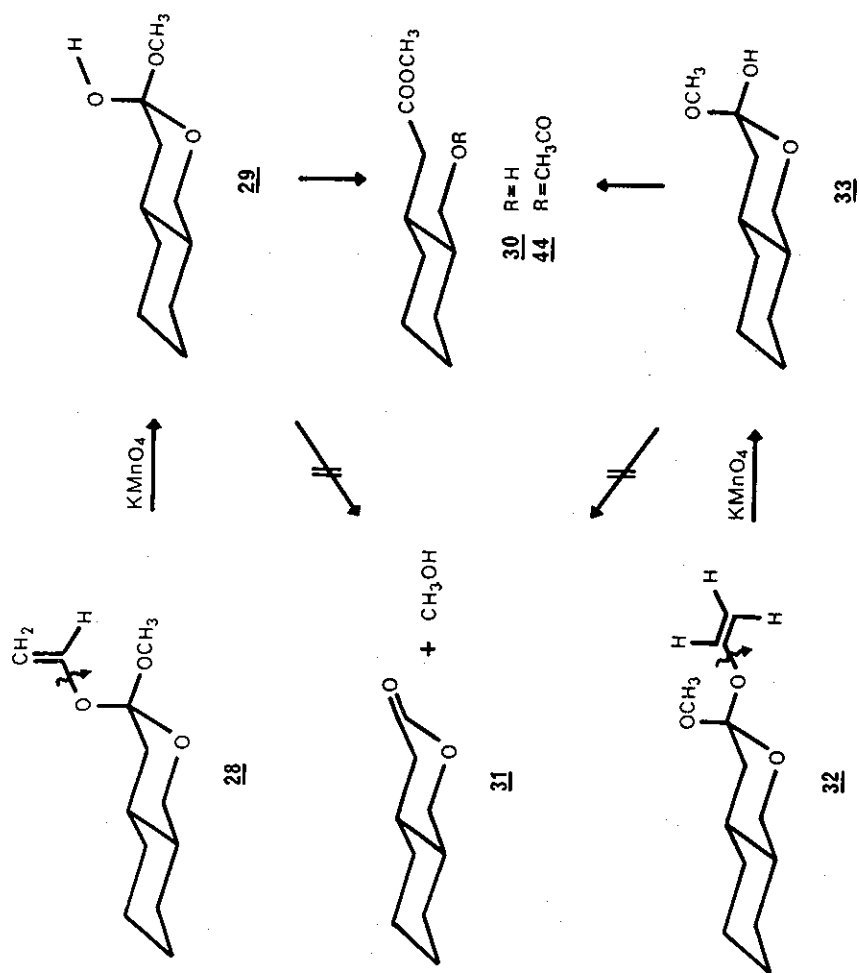
SCHEME 8

Such an experiment appeared conceivable using the bicyclic axial-vinyl orthoester 28 (Scheme 8) with a reagent to transform 28 into the intermediate 29. The intermediate 29 with the OH group in the axial position is equivalent to the intermediate which we have postulated in the ozonolysis of acetals (6) and in the hydrolysis of orthoesters (11), and should thus behave similarly during its cleavage to give the hydroxy-ester 30 only.

This new approach was also very interesting because the other possible bicyclic equatorial-vinyl orthoester 32 could presumably also be prepared and could give by an appropriate reaction, the intermediate 33 having now an equatorial OH group. This new method would therefore not only permit us to confirm the behavior of intermediate 29, but it would also be valuable for the complementary experiment of observing the fragmentation behavior in the intermediate 33.

The specific syntheses of 28 and 32 have been realized (16) and are described in Scheme 9. Reaction of the known dioxolenium salt 35 (3) with chloroethanol in dichloromethane containing triethylamine at -78°C gave the bicyclic axial chloroethyl orthoester 36. Treatment of 36 with potassium t-butoxide in tetrahydrofuran at reflux for one hour gave the pure bicyclic axial vinyl-orthoester 28. The dichloroethyl dioxolenium fluoroborate salt 38 was prepared *in situ* by reaction of boron trifluoride etherate and tri-chloroethyl ortho-formate 37 (17) and its reaction with the bicyclic lactone 31 gave the corresponding *chloroethyl lactonium salt 39. Reaction of crude 39 with* methanol in dichloromethane containing triethylamine gave the bicyclic equatorial chloroethyl orthoester 40. Treatment of 40 with potassium t-butoxide in tetrahydrofuran gave the bicyclic equatorial vinyl-orthoester 32.

The study of the cleavage of these vinyl orthoesters was carried out with potassium permanganate in a buffered aqueous solution (pH = 10, NaOH-NaHCO$_3$)
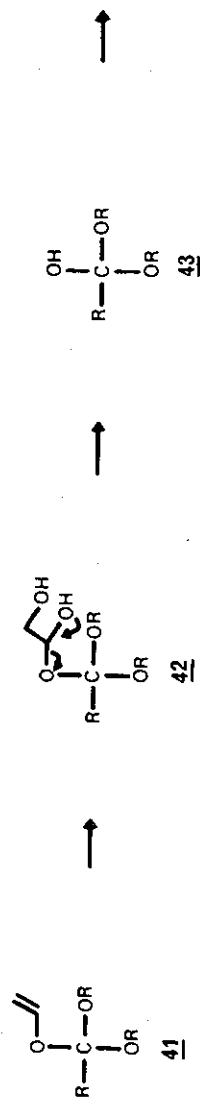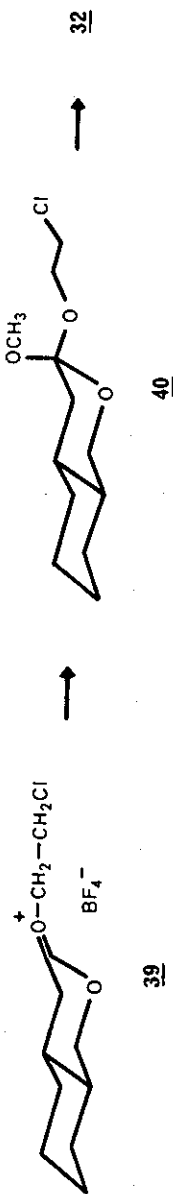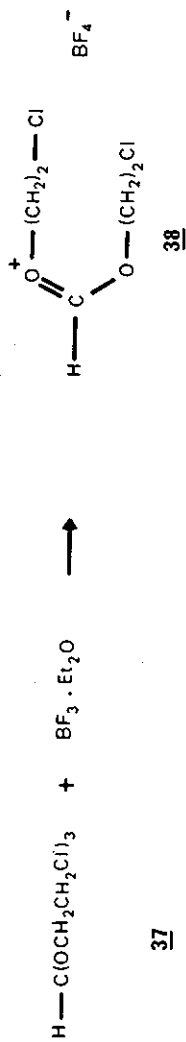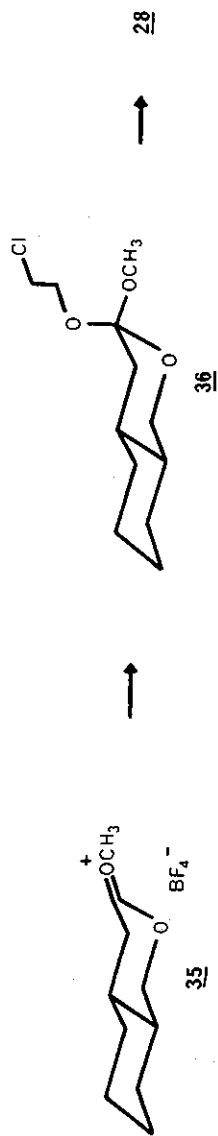
SCHEME 9

mixed with an equal amount of acetonitrile[6]. The reaction mixture was treated with an excess of acetic anhydride and pyridine to transform the resulting hydroxy-ester 30 into the acetoxy-ester 44. Both vinyl orthoesters 28 and 32 gave identical results: ⩾95% of acetoxy-ester 44 and ⩽5% of lactone 31. These results show that both 28 and 32 gave essentially a quantitative yield of hydroxy-ester 30, no lactone 31 being produced[7].

The permanganate oxidation experiments were repeated with a buffer containing oxygen-18 labelled water in order to confirm that the desired transformation 41 → 42 → 43 had taken place: for the axial vinyl orthoester 28, an incorporation of 53% of oxygen-18 was found in the acetoxy-ester 44; for the equatorial vinyl orthoester 32, an incorporation of 40% was observed in 44. The ideal result should have been 0% incorporation. However, in order to completely invalidate our experiments, the oxygen-18 incorporation should have been quantitative[8]. The 50% non-incorporation of the solvent demonstrates that the intermediates 29 and 33 were respectively formed partly with retention of the oxygen of the vinyl ether group and that they undergo specific cleavage to 30.

The specific cleavages of 28 and 32 into 30 has now to be analyzed. In the case of hemi-orthoester 29, the analysis is straightforward. When 29 is

---

[6] It is anticipated that potassium permanganate reacts with the vinyl ortho-ester function (41) to give the intermediate diol orthoester (42) which then yields the desired intermediate 43 (18).

[7] We have previously shown (3) that treatment of pure hydroxy-ester 30 with pyridine and acetic anhydride gives ⩾95% of 44 and ⩽5% of 31. Thus, when there is less than 5% of lactone 31 in the reaction mixture, it indicates that the hydroxy-ester 30 is the only product formed.

[8] The oxygen-18 incorporation can be explained in the following way: when 28 and 32 react with potassium permanganate, a competitive process could occur leading to the formation of the dioxolenium salt 35 which would react with water giving the intermediate 29 which then gives the hydroxy-ester 30 containing oxygen-18.

produced from the axial vinyl orthoester 28, it can exist in the three confor-

mations 45, 46, and 47 (Scheme 10). Stereoelectronically controlled cleavages

for these conformers are the following: 45 can only give the hydroxy-ester 30

in the Z conformation 30A, 46 cannot break down and 47 can only produce the

hydroxy-ester 30 in the E conformation 30B[9]. It can be concluded from this

experiment that additional evidence has been obtained for stereoelectronic

control.

The next analysis has to deal with the specific cleavage of intermediate 33

to give the hydroxy-ester 30. For the first time, an hemi-orthoester with an

equatorial OH group is considered and it also gives the hydroxy-ester 30 only.

When 33 is produced from the equatorial vinyl orthoester 32, it can exist in

the two conformations 48 and 49 (Scheme 10). Stereoelectronically controlled

cleavages for these conformers are the following: 48 can cleave to yield both

the hydroxy-ester 30 having a Z conformation 30C and the lactone 31; 49 can

break down in only one direction to yield the lactone 31. Thus, we have a case

here where two stereoelectronically controlled cleavages are allowed and only

one is observed experimentally. Consequently, this result cannot be taken as

evidence for stereoelectronic control and it could even be taken against it,

unless a logical explanation can be provided to demonstrate that a stereo-

electronically controlled cleavage leading to a Z ester is a lower energy

process then that leading to an E ester.

It has been experimentally demonstrated (19), that Z esters are much more

stable than E esters by more than 3 kcal/mol. This difference in stability

could also exist in the transition state leading to an E and a Z ester.

However, in the present case, it is difficult to accept this kind of argument

---

[9] In the following discussion, it will be shown that 47 → 30B cannot compete
with 45 → 30A.
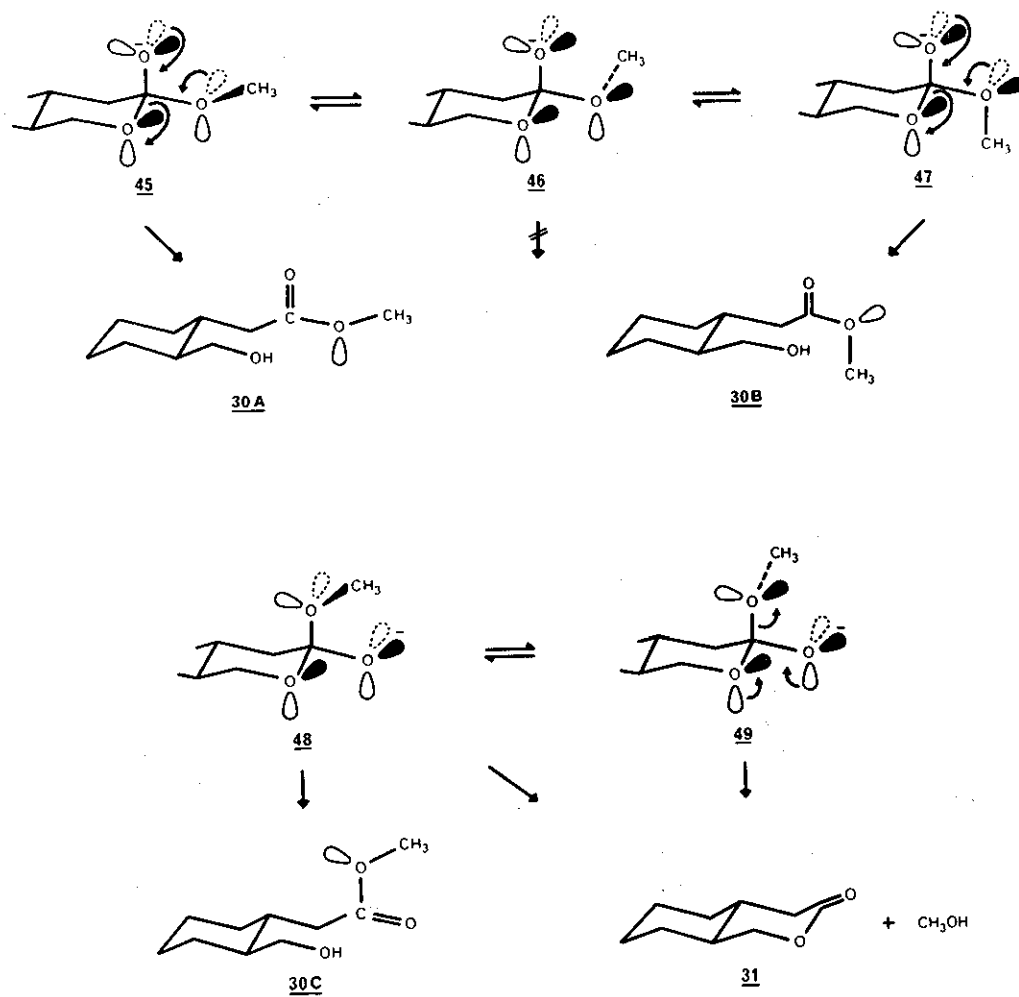
SCHEME 10

because the transition state must be close to the tetrahedral intermediate,

the intermediate being at a higher energy level than the reaction products (20).

The explanation must therefore lie in the tetrahedral intermediate itself

indicating that of the two possible bonds to be broken, the one leading to

the Z ester should be an easier operation. We think that such a logical

explanation can be found if the orientations in space of all the electron

pairs of the heteroatoms are taken into consideration.

In Scheme 11, the formulas 50 and 51 express the factors in the tetrahedral

intermediate 48 which we believe are operative in the transition states leading

to a Z (30C) and an E (31) ester respectively. In "transition state" 50, the

electronic effects are: a) the equatorial and the axial oxygen each have an

electron pair (represented by ⟨ ⟩), which are antiperiplanar to the C — O

bond of the ring, therefore this C — O bond can be cleaved with stereoelectronic

control, b) the remaining electron pair of the axial oxygen (⟨⟩) is anti-

periplanar to the polarized C — O⁻ bond, thus because of the anomeric effect

(⟩) (21)[10], the C — OR bond will have double bond character and will be

stronger than a normal single C — OR bond, c) there is also one electron pair

on the equatorial oxygen (⟨⟩) which is antiperiplanar to the C — OR bond,

this electron pair, because of the anomeric effect, (⟩) will also give double

bond character to the C — O⁻ bond. In transition state 51, the electronic

effects are: a) the equatorial and the ring oxygen each have an electron pair

(⟨⟩) which is antiperiplanar to the carbon-axial oxygen bond, thus this C — O

bond can be cleaved with stereoelectronic control, b) there is one electron pair

---

[10] We accept the view that the anomeric effect is a "stabilizing effect"
(double bond - no bond resonance) (22) on the more stable conformer. We
neglect the other view that the anomeric effect is a destabilizing effect
due to electron pairs repulsion ("rabbit ear effect (23) and/or dipole-
dipole repulsion (24) on the less stable conformer. If we take into account
the second view, we arrive however at the same conclusion.

50 ≡ 51

30C 31 + ROH

59 ≡ 60

61 ≡ 62

30A
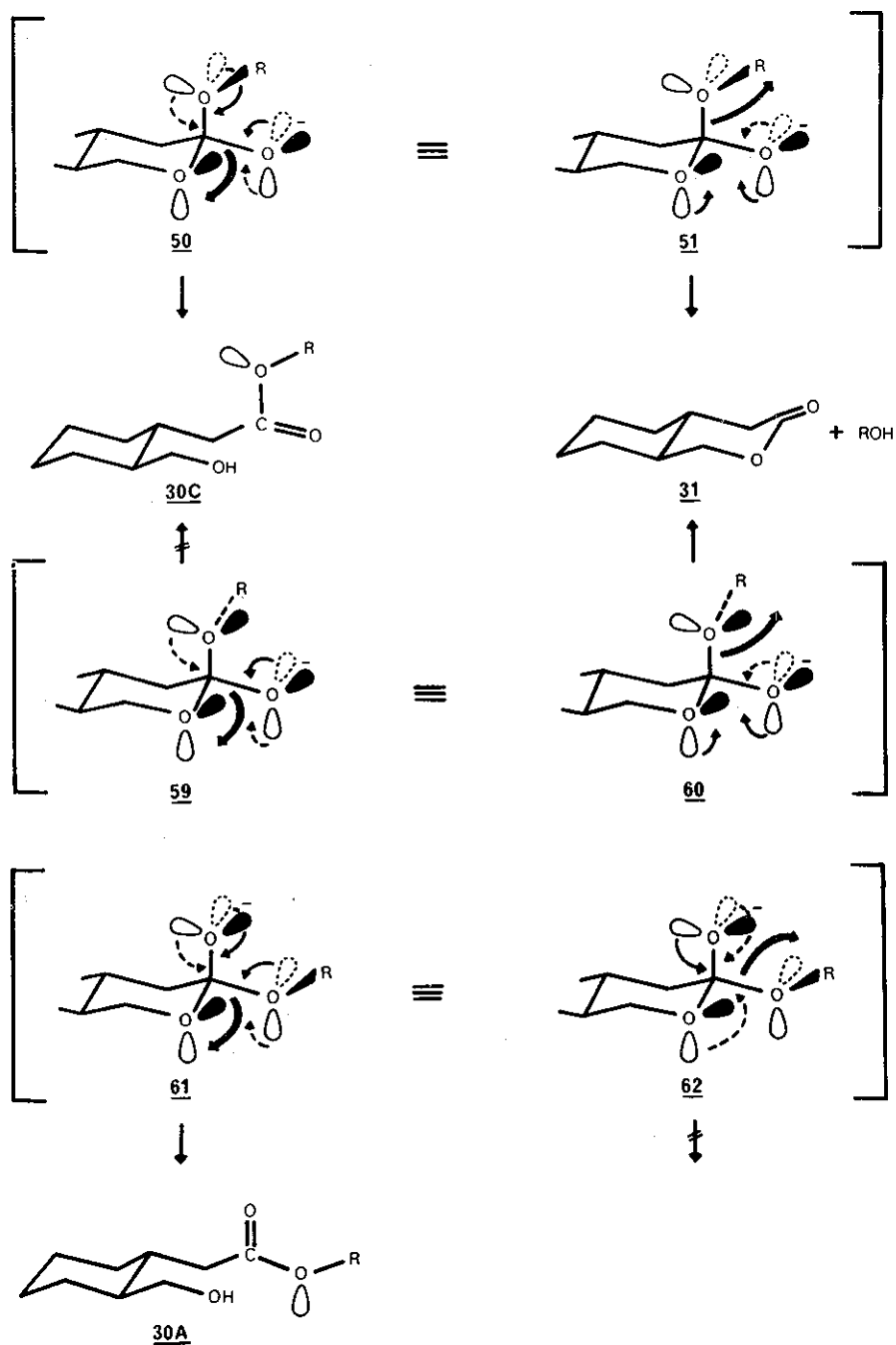
SCHEME 11

($:\overset{\frown}{\underset{\smile}{}}:$) on the equatorial oxygen which is antiperiplanar to the C — O bond of the ring, giving double bond character to the C — O$^-$ bond, c) the remaining electron pair (⬤) of the ring oxygen is not properly oriented to give double bond character to the C — O bond of the ring.

Thus, both transition states can occur with "primary" stereoelectronic control (factor a), but in 50 there are two anomeric effects and only one in 51. The former (50) should therefore be favored energetically. Thus, the energy difference between the transition states leading to E and Z esters is due to the anomeric effect[11].

The relative role and importance of primary and secondary (anomeric effect) stereoelectronic control can also be understood by the examination of these two effects on the geometries and relative stabilities of E and Z esters.

Stereoelectronic control is responsible for the planar geometry of an ester function: two pairs of electrons, one on each oxygen are used to construct the π system; this is usually expressed by the resonance structures 52, 53, and 54 (Scheme 12). This electronic delocalisation conveys sp$_2$ character to the two oxygens as well as to the central carbon of the ester function and is

---

[11] It is interesting to note that stereoelectronic control can also influence the leaving group ability of an alkoxide group. In transition state 50, the oxygen of the ring is the leaving group, this oxygen has one of its electron pairs oriented antiperiplanar to the axial C — O bond, the C — O bond of the ring therefore has a double bond character. The remaining electron pair of the ring oxygen is not properly oriented to give a second double bond character: thus, in 50, the leaving group has one double bond character. In the competing transition state 51, the leaving group is the axial oxygen. The two electron pairs of this oxygen are both oriented antiperiplanar to a C — O bond. Thus, this leaving group in 51 (the axial alkoxy group) has two double bond characters due to the anomeric effect, it is therefore a poorer leaving group than the one of the competing transition state 50. This again is in favor of transition state 50. However, we prefer at the present stage to neglect the anomeric effect on the leaving group.
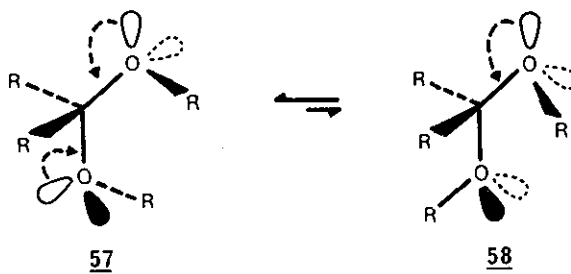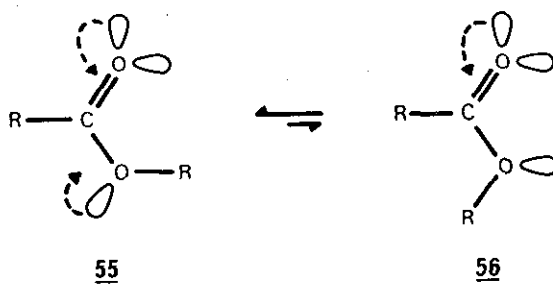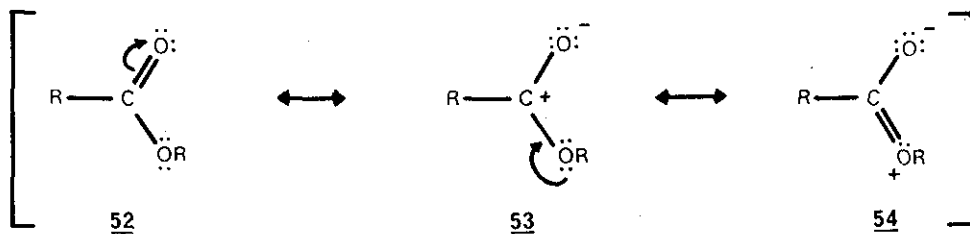
SCHEME **12**

also responsible for the two geometrical forms 55 (Z) and 56 (E) of an ester function.

The main role of the anomeric effect deals with the relative stability of these two forms. At the same time, it can impart double bond and triple bond character to the C — OR and the C = O bonds, respectively, of the ester function.

Both Z (55) and E (56) esters have one electron pair of the carbonyl oxygen oriented antiperiplanar to the C — OR bond and an anomeric effect should therefore exist which gives triple bond character to the carbonyl group [Ö = C — ÖR ⟷ Ö ≡ C ÖR]. The C — OR bond of an ester function is more polarized than that of an acetal C — OR bond and the magnitude of the anomeric effect in the carbonyl group should therefore be more important.

In Z esters (55), there is the possibility for a second anomeric effect: the ether oxygen has an electron pair antiperiplanar to the C = O bond. The magnitude of this anomeric effect should be much more important than the previous one, because a carbonyl C = O bond [C = O ⟷ C$^+$ — O$^-$] is much more polarized than the C — OR bond in the ester function. We think that this amplified anomeric effect must be responsible for the greater stability of Z relative to E esters[12]. It also provides an explanation for the difference in stability between Z and E esters (≈3.0 kcal/mol (18)) which is larger than that observed between two acetal conformers such as 57 and 58 (≈1.4 kcal/mol (25)).

The anomeric effect which can be relatively weak in the intermediate becomes quite strong in the ester products. It is therefore less important in the

[12] To my knowledge, Professor A. Eschenmoser (E.T.H.) was the first to explain the relative stability of E and Z esters by application of the modern version of the anomeric effect. Private communication with the author.

transition state than in the product, nevertheless, it should be stronger in the transition state than in the tetrahedral intermediate.

The preference of tetrahedral intermediates to yield $\underline{Z}$ esters is a very important result from which two important conclusions can be drawn: A) The stereoelectronic theory is further extended and becomes more complete, B) it also allows us to make a very appropriate adjustment to the postulate of the lack of conformational change prior to the breakdown. At the same time, it permits us to take into consideration another important parameter which is the ionic state of the intermediate (*vide infra*).

A) Extension of the stereoelectronic theory: Two effects must now be considered in the stereoelectronic theory: primary stereoelectronic control as previously defined and secondary stereoelectronic control as defined by the anomeric effect. This classification is justified by the fact that these two effects have their origin in the same chemical principle, orientation in space of non-bonded electron pairs!

In primary stereoelectronic control, the two electron pairs which are antiperiplanar to the leaving group in the tetrahedral intermediate are used to expel the leaving group and to form the two electron pairs of the π system of the ester function. In secondary stereoelectronic control (or anomeric effect), the electron pairs of the tetrahedral intermediate, which are not antiperiplanar to the leaving group, but are antiperiplanar to the two C — O bonds of the "incipient" ester function, serve to give double bond character to these bonds in the transition state. Since a more complete double bond character is obtained in a transition state leading to a $\underline{Z}$ ester, it is of lower energy than the one leading to a $\underline{E}$ ester.
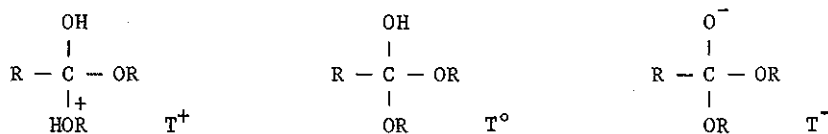
Transition states leading to $\underline{E}$ and $\underline{Z}$ esters with stereoelectronic control can be compared with transition states which lack primary stereoelectronic control (Scheme 11).

59 and 60 represent two possible transition states of the same conformer

(49). Transition state 60 can yield an E ester 31 with the help of primary

and secondary (one anomeric effect) stereoelectronic control. Transition state

59 has secondary electronic control (two anomeric effects) but there is no

primary stereoelectronic control[13]. Thus, 60 is a better transition state

than 59, and a tetrahedral intermediate having that rigid conformation should

therefore give 31. 61 and 62 represent two possible transition states of the

same conformer (45). Transition state 61 can yield a Z ester 30A with the

help of primary and secondary (two anomeric effects) stereoelectronic control.

Transition state 62 also has secondary stereoelectronic control (two anomeric

effects) but there is no primary stereoelectronic control. Thus, an inter-

mediate having that conformation should break down through transition state

61, not 62.

B) Conformational change, breakdown and ionic state of the intermediate:

The fact that hemi-orthoesters 29 and 33 always prefer to give the hydroxy-ester

indicates that it is not necessary to postulate the lack of conformational

change prior to the breakdown of the intermediate. We think that this postulate

of lack of conformational change is valid only when the intermediate exists as

a positively or a negatively charged species, but it should not be valid in the

case of a neutral intermediate.

A hemi-orthoester intermediate can exist in three different ionic forms T^+,

T°, and T^- depending on the acidity or the basicity of the medium.

```
    OH                      OH                      O⁻
    |                       |                       |
R — C — OR            R — C — OR              R — C — OR
    |+                      |                       |
    HOR      T⁺             OR      T°              OR      T⁻
```

---

[13] Transition state 59 has an electron pair (the electron pair of the equa-
      torial oxygen (:O:)) antiperiplanar to the leaving group, it is better
      than none, but we think it is not sufficient. Primary stereoelectronic
      control requires two electron pairs oriented antiperiplanar to the leaving
      group.

In acidic or neutral medium, it will exist in the T^+ and T^o forms. In slightly basic medium (relative to the pKa of the intermediate) it will exist in the T^o and T^- forms. In strong basic medium, it will exist in the T^- form only. The energy barrier for conformational change of a given intermediate should remain about the same in the three ionic forms T^+, T^o, and T^- but the energy barrier for the cleavage will vary, it will be quite low for the T^+ and the T^- forms and quite high for the neutral form T^o (26).

It is therefore conceivable that when a tetrahedral intermediate can cleave with stereoelectronic control, there will be no conformational change prior to the breakdown only in cases where the intermediate will exist entirely in the T^+ or T^- form. Whenever, the pH of the medium allows the presence of the neutral form T^o, conformational changes should be allowed.

In the ozonolysis of simple tetrahydropyranyl ether (Scheme 13) as well as in the mild acid hydrolysis of monocyclic orthoesters, the intermediate will exist mainly in the T^o form, conformational changes can therefore occur but the hydroxy-ester will still be the only product formed. In those cases, there will be a transmission of configuration and conformation of the starting product (5 or 9) into the intermediate which should first exist in conformation 63. The specific configuration and conformation 63 may be lost by rotation and ring inversion to give all the possible conformers (63 - 68). But this loss of conformation is not important, since the hydroxy-ester will still be the kinetic product.

In cases where the tetrahydropyranyl ether and the cyclic orthoester become partly rigid because of the presence of another ring as in the case of 69 and 70, there will be again, first a transmission of configuration and conformation of the starting product into the intermediate (5 → 63 and 9 → 63). The intermediate 63 may then loose its specific conformation (63 ⇄ 64 ⇄ 65) but its specific configuration will be maintained (63 - 65⧸⧸66 - 68).
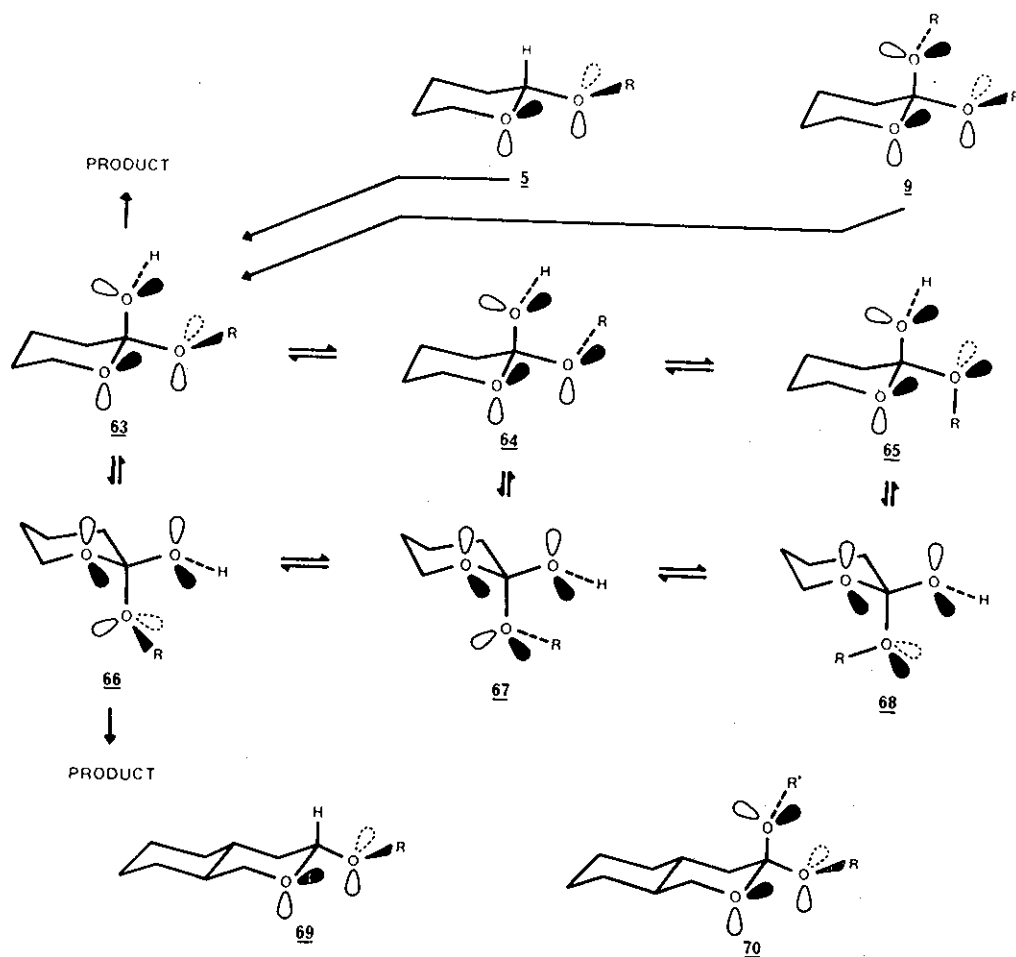
SCHEME 13

The preceding discussion which introduces interesting new elements in the cleavage of tetrahedral intermediate is based on one single experiment, the oxidative cleavage of the equatorial vinyl orthoester 32. It is therefore important to find new experiments to confirm that it is indeed true that a) it is easier to produce a Z than an E ester, b) conformational change is allowed when the tetrahedral intermediate exists in the T° form.

OZONOLYSIS OF TETRAHYDROPYRANYL ALCOHOL

We have carried out the ozonolysis of tetrahydropyranyl alcohol 71 in ethyl acetate at −78°C (Scheme 14). We have found (27) that this reaction proceeds very well to yield the hydroxy-acid 74 in essentially quantitative yield. 71 should give the intermediate 72 which we consider to be equivalent to 73, thus, 73 prefers to cleave to yield the hydroxy acid 74 (a carboxylic acid has the same geometry as a Z ester) instead of δ-valerolactone. This result demonstrates again that there is no need to postulate the lack of conformational change in the ozonolysis of acetals and mild acid hydrolysis of orthoesters. It is also an experiment which shows that the transition state leading to a Z ester is of lower energy than the one leading to an E ester.

This result, taken with the observation that there is no oxygen-exchange in the carbonyl group during the mild acid hydrolysis of γ-butyrolactone (12), further demonstrates that k_3 is much larger than k_2 in the case of tetrahedral intermediates derived from lactones.
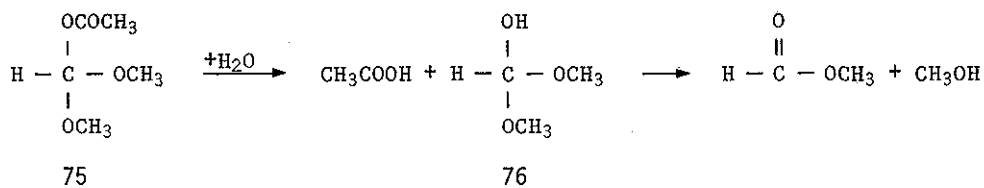
SOLVOLYSIS OF ACETOXY DIMETHOXYMETHANE

Capon and his collaborators (28) have recently carried out a remarkable experiment which shows that a neutral tetrahedral intermediate (T°) can exist in solution: acetoxydimethoxymethane (75) in a mixture of acetone and water
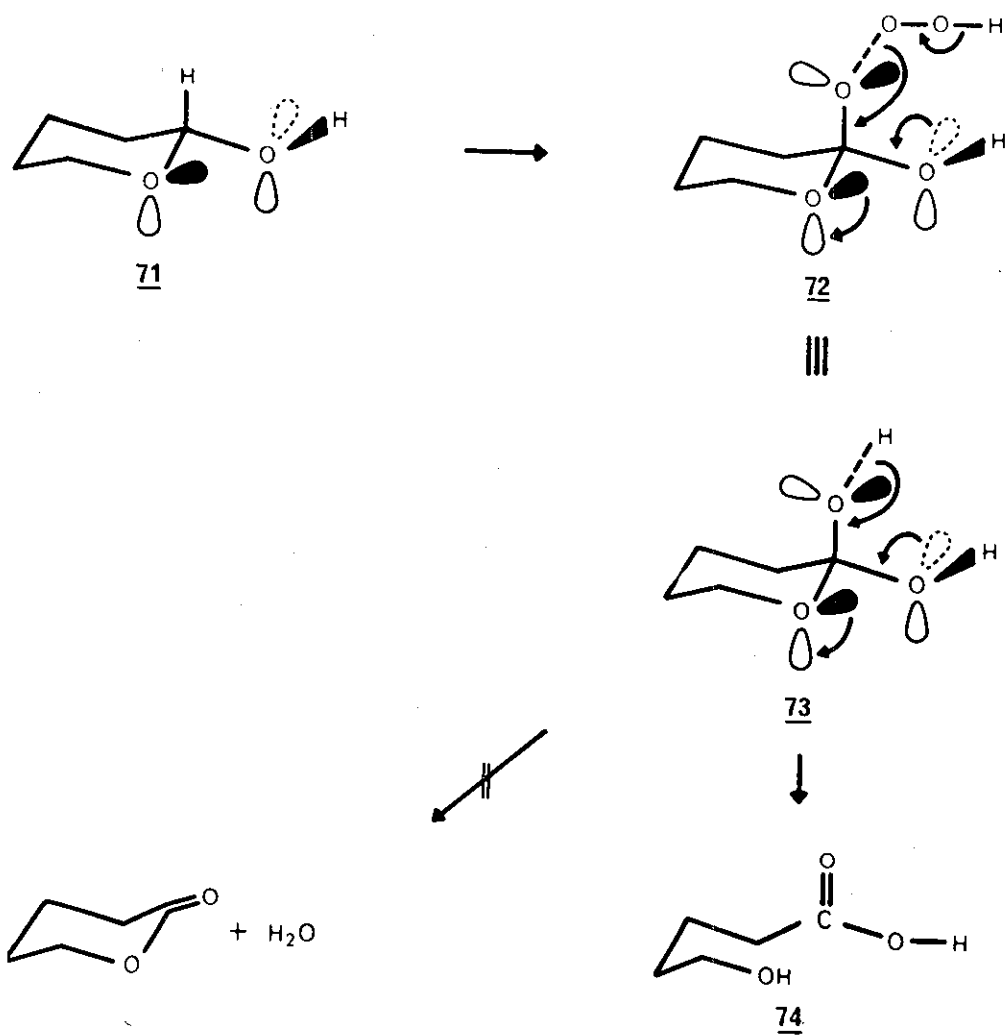
SCHEME 14

reacts at -30°C to give the intermediate 76 and acetic acid which can be easily detected by nmr spectroscopy. Disappearance of the intermediate was then observed to give the reaction products.

$$
\begin{array}{c}
OCOCH_3 \\
| \\
H - C - OCH_3 \\
| \\
OCH_3 \\
\underline{75}
\end{array}
\quad\xrightarrow{+H_2O}\quad
CH_3COOH \;+\;
\begin{array}{c}
OH \\
| \\
H - C - OCH_3 \\
| \\
OCH_3 \\
\underline{76}
\end{array}
\quad\longrightarrow\quad
\begin{array}{c}
O \\
\| \\
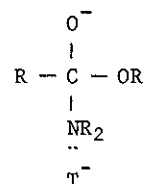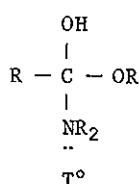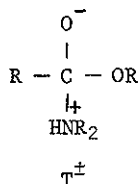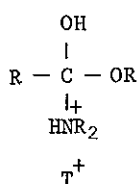H - C - OCH_3
\end{array}
\;+\; CH_3OH
$$

If a neutral intermediate can be detected in solution, molecular rotation has to occur in this intermediate. It therefore demonstrates that the barrier for cleavage is higher than that for rotation when the intermediate exists in the neutral T° form.

HYDROLYSIS OF MIXED IMIDATE SALTS

We have carried out a series of experiments which constitute a direct proof that in the case of hemi-orthoamides, when they can exist in the neutral T° form, the barrier for cleavage is higher than that for molecular rotation.

In the hydrolysis of N,N-dialkylated imidate salts, the tetrahedral inter-mediate can take several ionic forms, T^+, $T^\pm$, T°, and T^- depending on the pH of the reaction medium. In acidic medium, it will exist in the T^+ form, in slightly basic medium (near the pKa of the intermediate, pH $\approx$ 10), it will exist in the $T^\pm$ and in basic medium (pH > 11), it will exist as T^-. In systems where the nitrogen can be easily protonated, T° will not be significant, since it can be easily transformed into the $T^\pm$ form. Again, the energy barriers for the cleavage of T^+, $T^\pm$, and T^- must be low and the one for T° must be high (26).

$$
\begin{array}{cccc}
\text{OH} & \text{O}^- & \text{OH} & \text{O}^- \\
| & | & | & | \\
\text{R} - \text{C} - \text{OR} & \text{R} - \text{C} - \text{OR} & \text{R} - \text{C} - \text{OR} & \text{R} - \text{C} - \text{OR} \\
|+ & |+ & | & | \\
\text{HNR}_2 & \text{HNR}_2 & \text{NR}_2 & \text{NR}_2 \\
& & \cdot\cdot & \cdot\cdot \\
\text{T}^+ & \text{T}^\pm & \text{T}^\circ & \text{T}^-
\end{array}
$$

In acidic and neutral media which favor the formation of T^+ and $T^\pm$, E and Z imidate salts should always give the ester-amine product. In basic medium, which favors the formation of T^-, the formation of products will depend on the conformation of T^- : Z imidate salt should give the ester-amine product only and E imidate salts should give a mixture of ester-amine and amide-alcohol products.

We have shown that this is indeed the case by carrying out several experiments on both E and Z imidate salts at different pH values and the results did confirm entirely our predictions (4).

We have however found an exception to this general behavior in the case of imidate salts which have a 2,6-dimethylphenyl group as one of the N-alkyl groups (30).

The E imidate salt 77 having the 2,6-dimethylphenyl group *cis* to the formamide hydrogen has been obtained pure by crystallization (Scheme 15). An X-ray diffraction analysis[3] of the salt 77 shows that it is a planar system with the OCH_3 group *cis* to the formamide hydrogen. The phenyl ring is also perpendicular to the plane of the imidate salt. We have also obtained its geometrical isomer, the salt 78 where the $N - CH_3$ group is *cis* to the formamide hydrogen[14].

---

[14] Reaction of N-(2,6-dimethylphenyl)-N-methylformamide with trimethyl oxonium tetrafluoroborate (29) gave a mixture of salts 77 and 78. The salt 77 was obtained completely pure by fractional crystallization. Using the same technique, the salt 78 has not been obtained completely pure, it was contaminated by a small percentage ($\approx$4%) of the isomer 77.
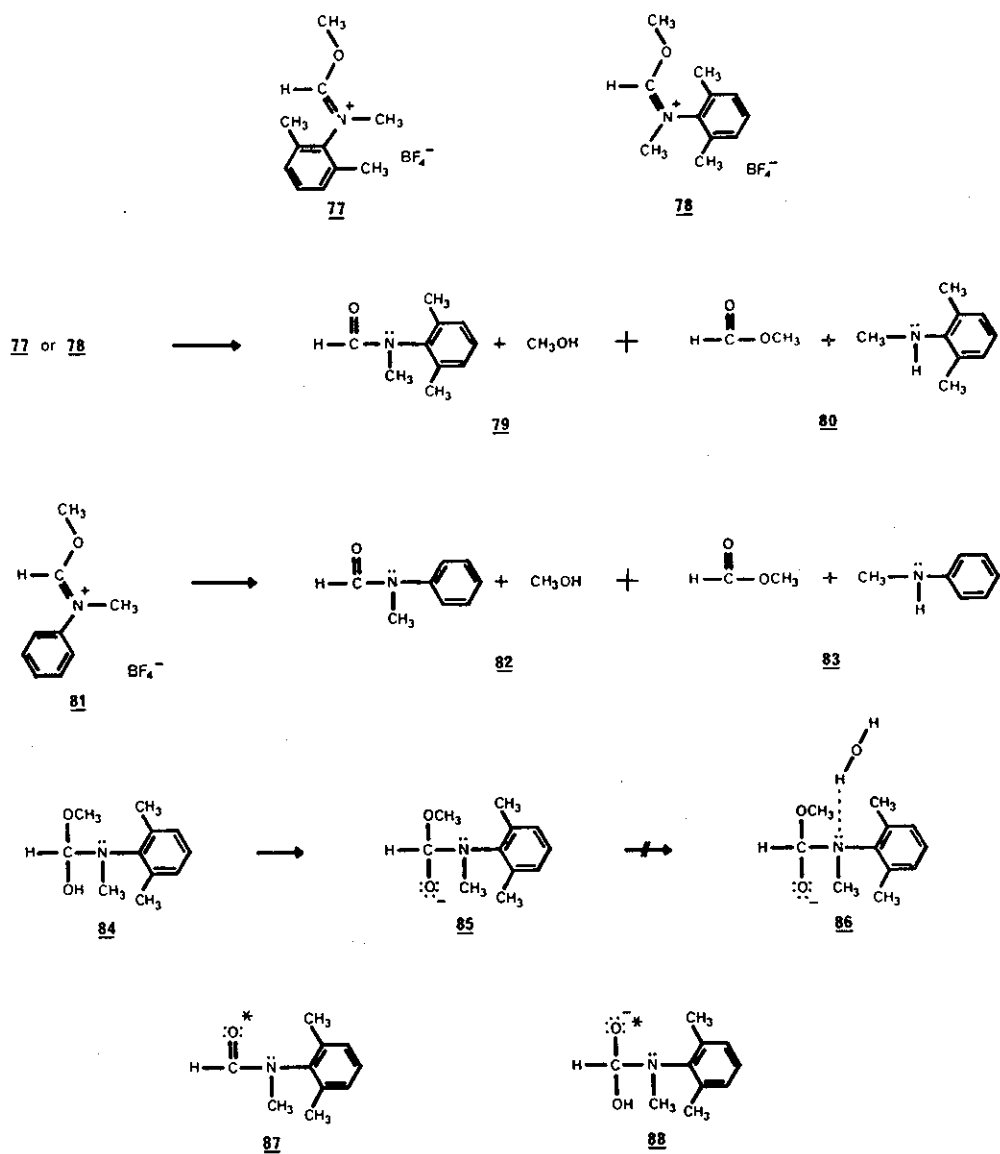
SCHEME 15

The imidate salt _77_ under basic conditions gave 100% of the amide-alcohol

product _79_; under acidic conditions it gave 70% of the amide-alcohol product

_79_ and only 30% of the ester-amine product _80_. This result is completely

different from what we have observed with other E imidate salts. For

instance, the closely related E imidate salt _81_ gave under acidic conditions

100% of the ester-amine product _83_; under basic conditions, it gave 50% of

the ester-amine product _83_ and 50% of the amide-alcohol product _82_. Also,

when the acid hydrolysis of _77_ was repeated with oxygen-18 labelled water,

there was a complete incorporation of the oxygen label in the amide product,

showing that this hydrolysis reaction proceeds normally, through the formation

of a tetrahedral intermediate, as in the case of imidate salt _81_.

These interesting results can best be interpreted in the following manner:

water reacts with the imidate salt _77_ to give the intermediate hemi-orthoamide

_84_ in the T° form. However, due to the severe steric hindrance, caused by the

presence of the two methyl groups of the phenyl ring (which is parallel to the

nitrogen lone pair), it is very difficult to protonate the nitrogen. Even

under strong acidic conditions, the protonation of the nitrogen of T° to give

T^{+} is not complete prior to break down since a large percentage of amide is

observed. Under basic conditions, T° can be converted into T^{-} (_85_), but the

electron pair of the nitrogen cannot easily become hydrogen bonded with the

solvent (_85_ ⇥ _86_), the intermediate would thus have to eject an amide ion

which must be a high energy process. Since the C — N bond cleavage cannot

compete with the C — OR bond cleavage, the amide is the only product formed

under such conditions.

We have confirmed this result in the following way: when the oxygen-18

labelled N-(2,6-dimethylphenyl)-N-methylformamide _87_ was heated at 90°C for

70 hr with aqueous sodium hydroxide (30), we have observed that the hydrolysis

reaction does not take place, but the amide looses its label completely.
These results demonstrate a) that the hemi-orthoamide 88 is formed under basic
conditions, b) that the nitrogen electron pair has to be hydrogen bonded with
the solvent in order to observe the cleavage of the C — N bond.

The preceding results show that the $T^{\circ} \to T^{\pm}$ conversion is prohibited in the
hemi-orthoamide intermediate 84, it thus should undergo conformational change
prior to the breakdown in a neutral medium.

When the imidate salt 77 is treated with water, the hydrolysis reaction is
slow. It can easily be observed that under those conditions, the salt 77 is
transformed into the isomeric salt 78, with which it reaches a thermodynamic
equilibrium, before the hydrolysis reaction to give 79 is complete.
The same phenomenon is observed starting with the imidate salt 78. 78 does
reach a thermodynamic equilibrium with 77 before the hydrolysis reaction is
complete.

These results can be rationalized in the following way: imidate salts 77
and 78 react with water to form the intermediates 89 and 90, respectively
(Scheme 16). These two intermediates have different configurations, they
cannot be interconverted by rotation of the C — N bond, but can be intercon-
verted by a nitrogen inversion followed by C — N bond rotation of 180°C
[91 = 89 $\rightleftarrows$ 92 $\rightleftarrows$ 93 = 90].

These experiments show that a hemi-orthoamide tetrahedral intermediate in
the form T° has a sufficient half-life to permit molecular rotation. It
therefore confirms that the barrier for cleavage of such intermediates is
higher than that for conformational change.
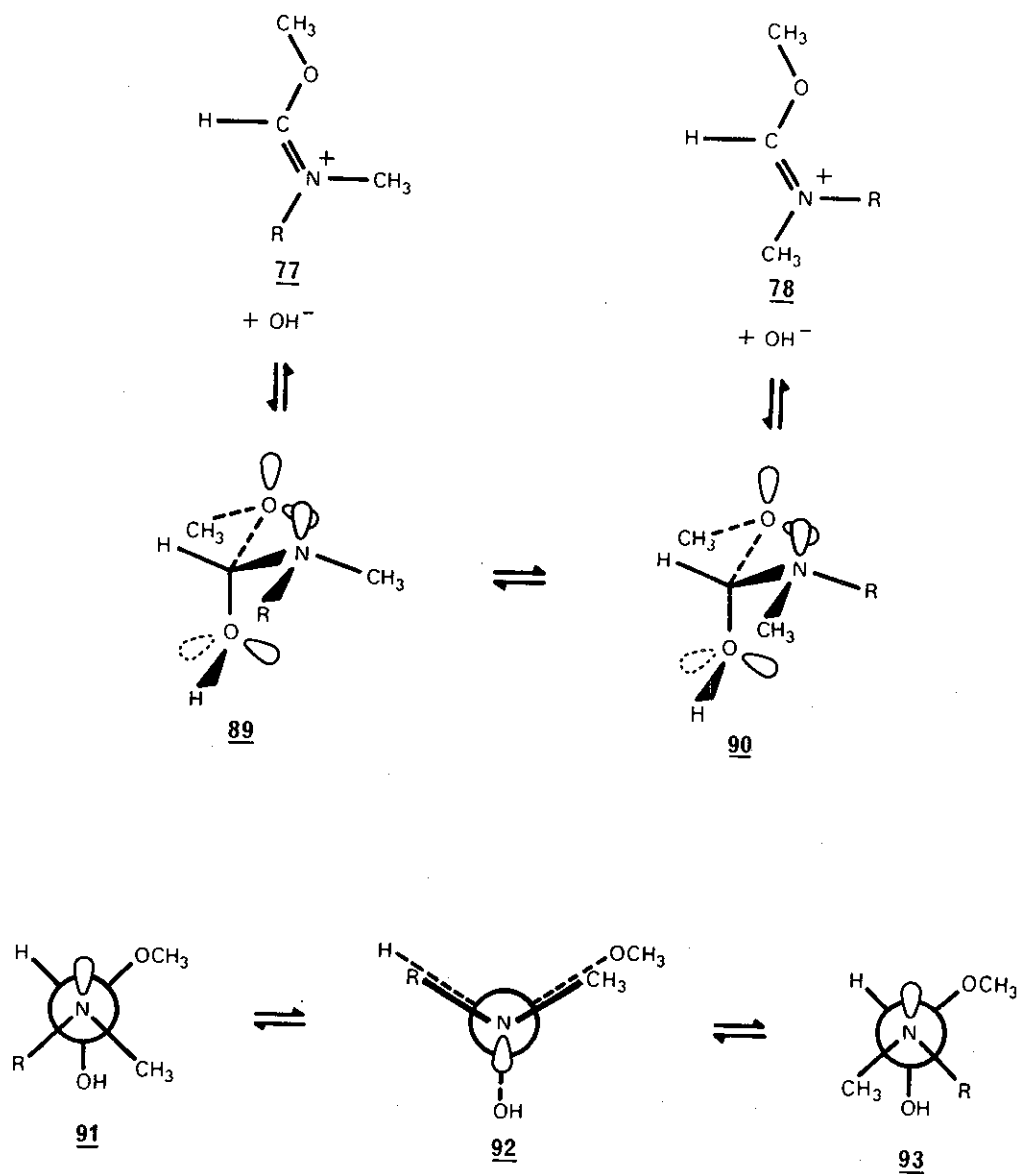
SCHEME **16**

CONCLUSION

The preceding experiments show that:

a) Conformational change is allowed in neutral tetrahedral intermediates (T^o).

b) Conformational change does not occur in basic tetrahedral intermediates (T^-) when they can break down with stereoelectronic control to yield $\underline{Z}$ esters or amides (except for the intermediate $\underline{88}$ derived from formamide $\underline{87}$[15]).

c) Cleavage of an intermediate to a $\underline{Z}$ ester is easier than to an $\underline{E}$ ester.

d) The stereoelectronic theory has been further extended to primary and secondary (anomeric effect) stereoelectronic control.

As a general conclusion, these investigations have led to a better under-standing of the main parameters which govern the cleavage of tetrahedral inter-mediates. These parameters are the stereochemistry of tetrahedral intermediates which include the orientation of non-bonded electron pairs, the ionic state of the tetrahedral intermediate (T^+, T^o, $T^{\pm}$, T^-) which includes its capacity for hydrogen bonding with the solvent, the relative barrier for conformational change and breakdown of the tetrahedral intermediate, and the application of primary and secondary (anomeric effect) stereoelectronic control.

----

15 We have also found that oxygen-18 exchange occurs during the basic hydrolysis of another formamide (N-benzyl-N-methylformamide). Therefore, molecular rotation can occur in formamide derived tetrahedral intermediate in the T^- ionic form. The typical behavior of formamide-derived tetrahedral inter-mediates can be explained by two factors: a) the barrier for molecular rotation must be lower in these intermediates because the hydrogen atom is a small group, b) the barrier for cleavage must also be higher, because these intermediates lack the steric decompression factor which is present when H is replaced by a bigger group.

REFERENCES

1 P. Deslongchamps, <u>Pure Appl. Chem.</u>, 1975, 43, 351; P. Deslongchamps,

<u>Tetrahedron</u>, 1975, 31, 2463.

2 P. Deslongchamps and C. Moreau, <u>Can. J. Chem.</u>, 1971, 49, 2465; P. Deslongchamps,

C. Moreau, D. Fréhel, and P. Atlani, <u>Can. J. Chem.</u>, 1972, 50, 3402; P. Deslong-

champs, P. Atlani, D. Fréhel, A. Malaval, and C. Moreau, <u>Can. J. Chem.</u>, 1974,

52, 3651; P. Deslongchamps, C. Moreau, D. Fréhel, and R. Chênevert, <u>Can. J. Chem.</u>

1975, 53, 1204.

3 P. Deslongchamps, P. Atlani, D. Fréhel, and A. Malaval, <u>Can. J. Chem.</u>, 1972,

50, 3405; P. Deslongchamps, R. Chênevert, R.J. Taillefer, C. Moreau, and J.K.

Saunders, <u>Can. J. Chem.</u>, 1975, 53, 1601.

4 P. Deslongchamps, C. Lebreux, and R.J. Taillefer, <u>Can. J. Chem.</u>, 1973, 51,

1665; P. Deslongchamps, S. Dubé, C. Lebreux, D.R. Patterson, and R.J. Taillefer,

<u>Can. J. Chem.</u>, 1975, 53, 2791; P. Deslongchamps and R.J. Taillefer, <u>Can. J. Chem.</u>,

1975, 53, 3029.

5 P. Deslongchamps, U.O. Cheriyan, A. Guida, and R.J. Taillefer, <u>Nouveau J. de</u>

<u>Chimie</u>, 1977, 1, 235.

6 F.E. Stary, D.E. Emge, and R.W. Murray, <u>J. Am. Chem. Soc.</u>, 1974, 96, 5671.

7 E.H. Cordes, 'Progress in Physical Organic Chemistry', eds. by A. Streitwieser

and R.W. Taft, Interscience, New York, N.Y., 1967, vol. 4, p. 1; E.H. Cordes and

H.G. Bull, <u>Chem. Rev.</u>, 1974, 74, 582.

8 G.L. Schmir and B.A. Cunningham, <u>J. Am. Chem. Soc.</u>, 1965, 87, 5692; G.M.

Blackburn and W.P. Jencks, <u>J. Am. Chem. Soc.</u>, 1968, 90, 2638; G.L. Schmir,

<u>J. Am. Chem. Soc.</u>, 1968, 90, 3478; T.C. Pletcher, S. Koehler, and E.H. Cordes,

<u>J. Am. Chem. Soc.</u>, 1968, 90, 7072.

9 M.L. Bender, <u>Chem. Rev.</u>, 1960, 60, 53; S.L. Johnson, 'Advances in Physical

Organic Chemistry', ed. by V. Gold, Academic Press, London, 1967, vol. 5,

p. 237.

10 M. Eigen, Angew. Chem. Internat. Ed. Engl., 1964, 3, 1.

11 M.L. Bender and R.J. Thomas, J. Am. Chem. Soc., 1961, 83, 4189; M.L. Bender, H. Matsui, R.J. Thomas, and S.W. Tobey, J. Am. Chem. Soc., 1961, 83, 4139; M.L. Bender and H. d'A. Heck, J. Am. Chem. Soc., 1967, 89, 1211; S.A. Shain and S.F. Kirsch, J. Am. Chem. Soc., 1968, 90, 5848.

12 F.A. Long and L. Friedman, J. Am. Chem. Soc., 1950, 72, 3692; Y. Pocker and E. Green, J. Am. Chem. Soc., 1973, 95, 113; Y. Pocker and E. Green, J. Am. Chem. Soc., 1974, 96, 166.

13 C.A. Bunton, T.A. Lewis, and D.H. Llewellyn, Chem. and Ind., (London), 1954, 1154; M.L. Bender, R.D. Ginger, and K.C. Kemp, J. Am. Chem. Soc., 1954, 76, 3350; M.L. Bender and R.D. Ginger, J. Am. Chem. Soc., 1955, 77, 348; H. Ladenheim and M.L. Bender, J. Am. Chem. Soc., 1960, 82, 1895.

14 R. Huisgen and H. Walz, Chem. Ber., 1956, 89, 2616; L.A. Laplanche and M.T. Rogers, J. Am. Chem. Soc., 1964, 86, 337.

15 C.A. Bunton, B. Nayak, and C. O'Connor, J. Org. Chem., 1968, 33, 572.

16 R. Chênevert, C. Moreau, R.A. Dickinson, and N. Beaulieu, Unpublished results, this laboratory.

17 H. Meerwein, K. Bodenbenner, P. Borner, F. Kunert, and K. Wunderlich, Ann. Chem., 1960, 632, 38.

18 K.B. Wiberg and K.A. Saegebarth, J. Am. Chem. Soc., 1957, 79, 2822.

19 R. Huisgen and H. Ott, Tetrahedron, 1959, 6, 253; G.I. Jones and N.L. Owen, J. Mol. Struct., 1973, 18, 1.

20 G.S. Hammond, J. Am. Chem. Soc., 1955, 77, 334.

21 R.U. Lemieux, Pure Appl. Chem., 1971, 25, 527.

22 C. Romers, C. Altona, H.R. Buys, and E. Havinga, Top. Stereochem., 1969, 4, 39; C.A. Jeffrey, J.A. Pople, and L. Radom, Carbohydr. Res., 1972, 25, 117; S. David, O. Eisenstein, W.J. Here, L. Salem, and R. Hoffman, J. Am. Chem. Soc., 1973, 95, 3806; J.M. Lehn and G. Wipfe, J. Chem. Soc. Chem. Commun., 1975, 800.

23 E.L. Eliel, <u>Angew. Chem. Internat. Ed. Engl.</u>, 1972, 11, 739.

24 R.U. Lemieux and P. Chu, <u>Abstr. Pap. Amer. Chem. Soc.</u>, 1958, 133 Meeting,

p. 31N; R.U. Lemieux, 'Molecular Rearrangements', ed. by P. de Mayo, Interscience,

New York, N.Y., 1964, p. 723 ff; J.T. Edward, <u>Chem. Ind.</u>, (London), 1955, 1102.

25 C.B. Anderson and D.T. Sepp, <u>Tetrahedron</u>, 1968, 24, 1707; D.T. Sepp and

C.B. Anderson, <u>Tetrahedron</u>, 1968, 24, 6873; A.J. de Hooz, H.R. Buys, C. Altona,

and E. Navinga, <u>Tetrahedron</u>, 1969, 25, 3365; A.J. de Hooz and H.R. Buys,

<u>Tetrahedron Lett.</u>, 1969, 4175.

26 J.P. Guthrie, <u>J. Am. Chem. Soc.</u>, 1973, 95, 6999; J.P. Guthrie, <u>J. Am. Chem.</u>

<u>Soc.</u>, 1974, 96, 3608.

27 D. Fréhel and N. Beaulieu, Unpublished results, this laboratory.

28 B. Capon, J.H. Gall, and D. Mcl.A. Grieve, <u>J. Chem. Soc. Chem. Comm.</u>, 1976,

1034.

29 H. Meerwein, <u>Org. Synth.</u>, 1966, 46, 113, 120.

30 U.O. Cheriyan and J.P. Pradère, Unpublished results, this laboratory.

31 A. Guida, Unpublished results, this laboratory.