The Hydrolysis of Imidate Salts. Stereoelectronic Control in the Cleavage of the Hemiorthoamide Tetrahedral Intermediate

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A new stereoelectronic theory for the cleavage of the tetrahedral intermediate (hemiorthoamide) in the hydrolysis of amides is presented. In this new theory, the precise conformation of the tetrahedral intermediate controls the nature of the hydrolysis products. It is postulated that the breakdown of the tetrahedral intermediate depends upon the orientation of the lone pair orbitals of the heteroatoms. Specific cleavage of a carbon–oxygen or a carbon–nitrogen bond in any conformer is allowed only if the other heteroatoms (oxygen and nitrogen) each have an orbital oriented antiperiplanar to the leaving *O*-alkyl or *N*-alkyl group. Experimentally, a study of the basic hydrolysis of a variety of *N,N*-dialkylated imidate salts having either a *syn* or an *anti* conformation demonstrates clearly that there is a stereoelectronic control in the cleavage of the hemiorthoamide.

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Une nouvelle théorie stéréoélectronique sur la décomposition de l'intermédiaire tétrahédrique (hémi-orthoamide) au cours de l'hydrolyse des amides est présentée. Dans cette nouvelle théorie, il y a une relation directe entre la conformation précise de l'intermédiaire tétrahédrique et la nature des produits d'hydrolyse. Il est aussi postulé que c'est l'orientation des paires d'électrons libres sur les hétéroatomes qui contrôle la décomposition de l'intermédiaire. La coupure d'un lien carbon–oxygène ou d'un lien carbone–azote d'un intermédiaire est permise lorsque les deux autres hétéroatomes possèdent chacun une orbitale d'électrons libres orientée d'une manière antipériplanaire au groupe partant (*O*-alkyl ou *N*-alkyl). On démontre expérimentalement par l'hydrolyse en milieu basique sur des sels imidates ayant une conformation *syn* ou *anti* qu'il y a effectivement un contrôle stéréoélectronique lors de la décomposition d'un hémiorthoamide.

Introduction

We have recently reported a new stereoelectronic theory for the hydrolysis of esters (1, 2) and amides (2, 3). In this new theory, the nature of the products formed from the hydrolysis of an ester or amide depends upon the conformation of the tetrahedral hemiorthoester or hemiorthoamide intermediate formed in the reaction. It is further postulated that the breakdown of a tetrahedral conformer depends upon the orientation of the lone pair orbitals of the heteroatoms; specific cleavage of a carbon–oxygen or a carbon–nitrogen bond being allowed only if the other two heteroatoms (oxygen or nitrogen) of the tetrahedral intermediate each have an orbital oriented antiperiplanar to the leaving *O*-alkyl or *N*-alkyl group.

We have reported in detail our experiments which show that there is indeed a stereoelectronic control in the cleavage of hemiorthoesters (1). We have also obtained experimental evidence that there is a stereoelectronic control in the cleavage of hemiorthoamides (3), based on a study of the basic hydrolysis of some *N,N*-dialkylated imidate salts. These results were published in a preliminary form (3). We have now completed this work with a variety of imidate salts and wish to detail our results.[2]

When we started this investigation, it was clear to us that we could obtain experimental evidence for the new stereoelectronic theory by observing the products formed from the cleavage of a hemiorthoamide such as **2**. Consequently, it was first important to find a method for the generation of a hemiorthoamide which would then break down to products (ester or amide) in an irreversible manner. It is not possible to produce

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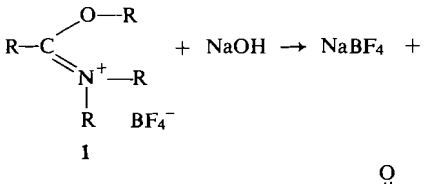
[2]For recent experimental and theoretical studies related to this subject, see refs. 4–6.

such a hemiorthoamide in a mild and 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 hydrolyzed under basic conditions, at room temperature, to give ester and amine or amide and alcohol as products (7).



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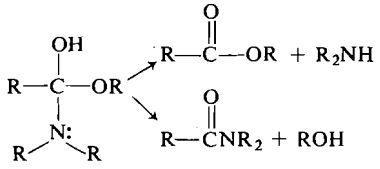


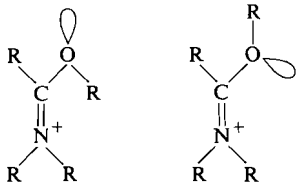
2

When a fluoroborate imidate salt such as **1** reacts with sodium hydroxide, it forms sodium fluoroborate and the intermediate **2** 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 **2**. If ester and amine are obtained as products, it is clear that it is the result of kinetically controlled cleavage of **2** 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 **2**. In such a circumstance, it is in principle possible to use the result as evidence for the new 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 **2**.

It is experimentally very difficult to know the precise conformation of a hemiorthoamide such as **2**. However, the conformation of **2** can be obtained indirectly by the utilization of the new stereoelectronic theory and the knowledge of the precise conformation of the starting imidate salt **1**. If a good correlation between the proposed conformation of **2** and its cleavage is obtained, it constitutes experimental evidence in favor of the new stereoelectronic theory. Thus, the conformation of the imidate salts must first be taken into consideration.

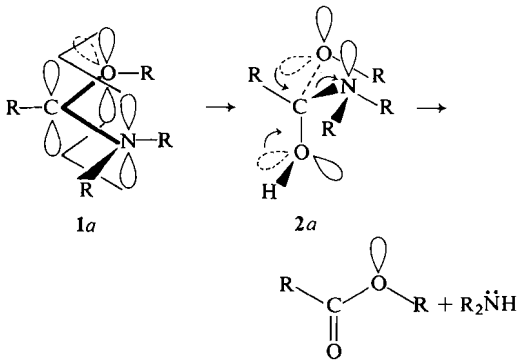
Stereoelectronic Control in the Cleavage of Hemiorthoamide

We believe that imidate salts are planar and thus can exist in two different conformations, the *anti* (**1***a*) or the *syn* (**1***b*) form. In the *anti* conformation **1***a*, the O—R bond is antiperiplanar to the C—R bond. In the *syn* conformation **1***b*, the O—R bond is *cis* to the C—R bond. Application of the new stereoelectronic theory on each type of imidate salt leads to the following predictions concerning the precise conformation of the intermediate **2** and to the manner by which each conformer of **2** should then break down.



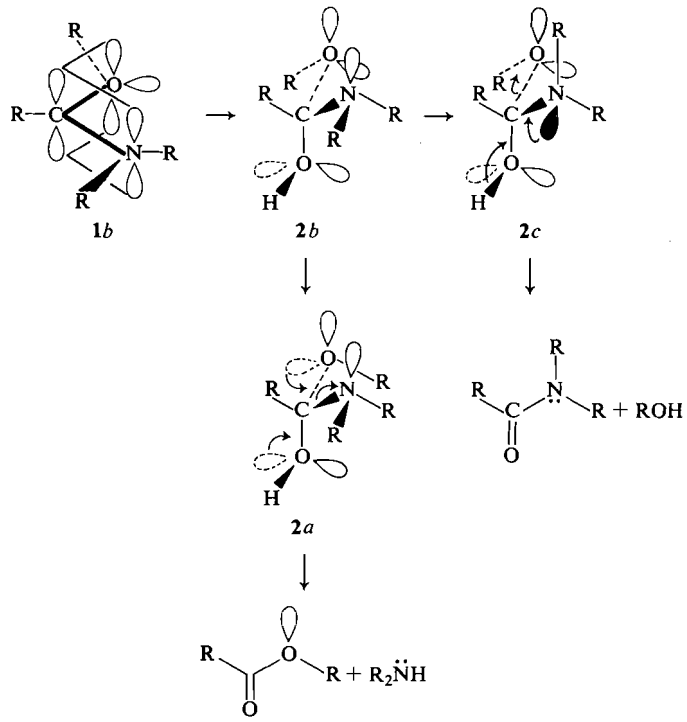
1*a* **1***b*

According to this theory, the reaction of hydroxide ion with the *anti* form **1***a* of an imidate salt should give the tetrahedral conformer **2***a* specifically (Scheme 1). Conformer **2***a* is the



1*a* **2***a*

SCHEME 1



SCHEME 2

result of hydroxide ion attack perpendicular to the plane of the salt **1***a*. The conformation of the starting imidate salt **1***a* is thus transposed to the intermediate **2***a*; the R—C bond in **2***a* is antiperiplanar to the O—R bond and to one of the N—R bonds as in the *anti* imidate **1***a*.[3] 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 carbon–oxygen bond. Thus, the reverse reaction, the ejection of the hydroxyl group can be achieved by an orbital assisted mechanism because there are two heteroatoms 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 **2***a* is higher than the energy barrier for its breakdown. With such a condition, no tetrahedral conformer other than **2***a* must be taken into consideration.

Examination of the orientation of the lone pair orbitals in **2***a* 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 **1***a* of an imidate salt should lead to the exclusive formation of ester and amine as a result of the cleavage of conformer **2***a*.

If the preceding stereoelectronic theory is valid, the reaction of hydroxide ion on the *syn* form **1***b* will give specifically the conformer **2***b* (Scheme 2). Again, **2***b* is the result of an attack perpendicular to the plane of the salt **1***b* by hydroxide ion. The conformation of **1***b* has also been retained in the intermediate **2***b*. There are lone pair orbitals on

[3]In principle, hydroxide ion attack on the imidate can either lead to conformer **2***a* 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 (8). 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.

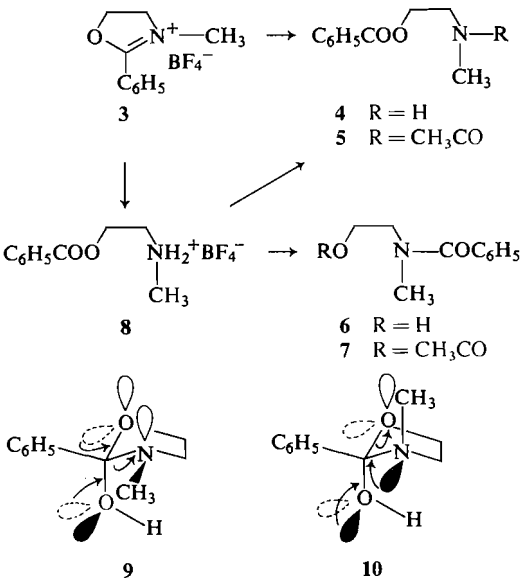
the nitrogen and on the oxygen of the OR group which are each oriented antiperiplanar to the C—OH bond.

It is interesting to note that conformer **2***b* cannot break down to products by an orbital assisted mechanism; the nitrogen nonbonded orbital is not antiperiplanar to the C—OR bond. Similarly, the oxygen atom of the OR group does not have a nonbonded 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 **2***b* becomes more facile than its breakdown to products and new conformers must be considered. If these new conformers have their orbitals properly oriented, they will break down immediately to give products. The energy barrier for carbon–nitrogen 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 carbon–nitrogen bond, conformer **2***b* can give a new conformer such as **2***c*. In conformer **2***c*, the hydroxyl oxygen and the nitrogen each have a lone pair orbital oriented antiperiplanar to the C—OR bond. Intermediate **2***c* should thus immediately produce the amide and alcohol products. By rotation of the C—OR bond in **2***b*, a new conformer such as **2***a* can also be obtained. We have already described that **2***a* should give the ester and amine products. Other conformers can be obtained by other rotations in **2***b*. The relative proportions of ester and amine products *vs.* amide and alcohol products will thus depend on the new conformers that will be formed by bond rotation in conformer **2***b*. Consequently, it is predicted that the basic[4] hydrolysis of the *syn* form **1***b* of an imidate salt will give in principle mixtures of products.

Hydrolysis of *Anti* Imidate Salts

We will first describe the results obtained from the basic hydrolysis of imidate salts having an *anti* conformation. The first substrate selected was the five-membered ring imidate salt **3** in which the *anti* conformation is assured by the cyclic structure. Hydrolysis of **3** with 3 equiv. of sodium carbonate in a mixture of acetonitrile and water gave the benzoate amine **4** exclusively. The reaction was followed by proton n.m.r. spectroscopy and was complete after 10 min at room temperature. Compound **4** was isolated as the acetamide derivative **5** by treating the reaction mixture with an excess of pyridine and acetic anhydride. If the reaction mixture was left at room temperature for a period of 24 h, the aminobenzoate **4** was completely converted into the more stable benzamide alcohol **6**. This product was isolated also as its acetate derivative **7**.



3 **4** R = H; **5** R = CH_3CO

8 **6** R = H; **7** R = CH_3CO

9 **10**

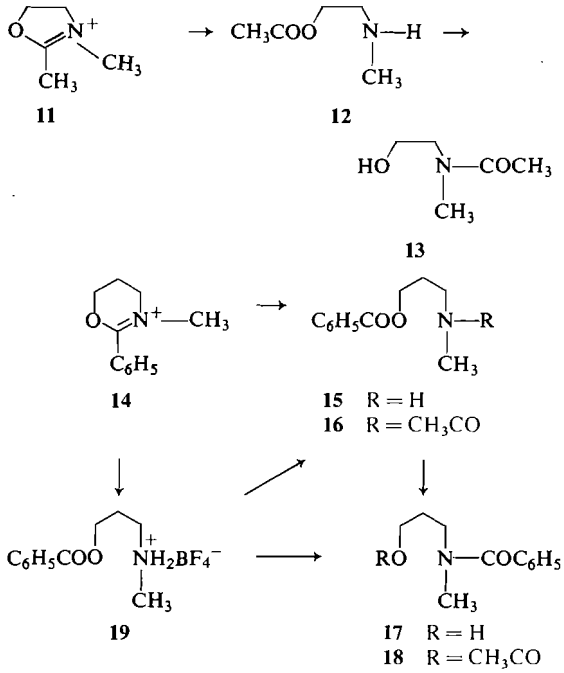
These experimental results can be easily explained by the stereoelectronic theory. The salt **3** forms the hemiorthoamide intermediate **9** in which the energy barrier for fragmentation is lowered by the alignment of the orbitals on both oxygen atoms. Indeed, under kinetically controlled conditions, the ester amine product **4** is the only product formed.[5] It is possible that the ex-

[4]It should be emphasized that this prediction is valid in basic medium only. This condition is important because the protonation of the basic nitrogen of the tetrahedral intermediate effectively ties up its lone pair orbital (7). Thus the nitrogen atom cannot participate in an orbital assisted decomposition of the tetrahedral intermediate under acidic conditions.

[5]The basic hydrolysis of **3** was also carried out with sodium hydroxide. Under these conditions, the imidate salt **3** gave directly the benzamide alcohol **6**, while the benzoate amine **4** was not detected. This unexpected result can be explained if the transformation of the benzoate amine **4** into the more stable benzamide alcohol **6** is very rapid in the presence of sodium hydroxide. This assertion was shown to be true in the following way. The benzoate ammonium salt **8** was prepared by the hydrolysis of **3** in neutral water. When the ammonium salt **8** was treated with sodium hydroxide under the conditions described for the hydrolysis of **3**, it gave directly the benzamide alcohol **6**. Treatment of **8** with sodium carbonate gave the benzoate amine **4**.

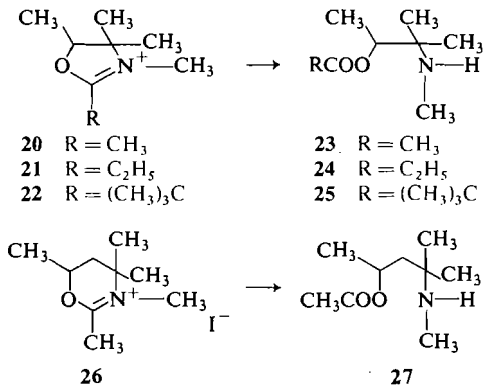
perimental conditions used favor the reformation of tetrahedral intermediates by an attack of the amino group on the ester function of **4**. Compound **4** can either reform **9** or form a new intermediate such as **10**, which has its orbitals properly aligned to yield the more stable product, the amide alcohol **6**. 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 h with sodium carbonate; they were immediately obtained when sodium hydroxide was utilized.[5]

The hydrolysis of imidate salt **11** was also carried out with sodium carbonate. After 10 min, it gave mainly the acetate amine **12** which was then slowly converted into the acetamide alcohol **13** after standing for 1.5 h at room temperature. It is interesting to note that the conversion of **12** into **13** in the presence of sodium carbonate occurs at a much faster rate than the conversion of **4** into **6** under similar conditions. This result, however, can be easily explained by the fact that **12** is an acetate ester, thus more reactive than **4** which is a benzoate ester.



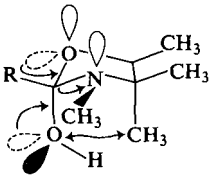
The basic hydrolysis of a six-membered ring imidate salt was also performed. After 15 min at room temperature, the hydrolysis of **14** with sodium carbonate gave the benzoate amine **15** exclusively. The presence of benzamide alcohol **17** was not detected in the reaction mixture even after a period of 5 h. Compound **15** was isolated and characterized as its corresponding acetamide derivative **16**.

The hydrolysis of **14** was also carried out with sodium hydroxide. The imidate salt was completely hydrolyzed after a few minutes and it yielded mainly the benzoate amine **15** (≃95%) with a small quantity of the benzamide alcohol **17** (≃5%). After standing for a period of 30 min at room temperature, the reaction mixture consisted of the benzamide alcohol **17** only, which was isolated as its acetate derivative **18**. This result indicates again that the ester **15** is first formed and then converted into the more stable amide product **17**. This assumption was verified by treating the ammonium salt **19** under identical basic conditions. Like the imidate **14**, **19** also gave the benzoate amine **15** first, which was then completely converted into the benzamide alcohol **17** within a period of 30 min. The ammonium salt **19** had been obtained by the hydrolysis of **14** in neutral water.



The basic hydrolysis of the imidate salts **20**, **21**, and **22** has been previously reported by Allen and Ginos (9). These salts gave the corresponding ester amine products **23**, **24**, and **25** in basic conditions. We have also carried out the basic hydrolysis of imidate salt **26** (10) and it gave the ester amine **27**. There are two factors which help the cleavage of the C—N bond in the hydrolysis of **20**, **21**, **22**, and **26**. According to the theory, **20**, **21**, and **22** should form the intermediate **28** which has proper orbital alignment to yield the corresponding ester amine products. In **28**, 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 carbon–nitrogen bond. Compound **26** should give the intermediate **29** in which there is again a

similar steric compression factor. This, combined with the orbital orientation factor, favors the carbon–nitrogen bond cleavage.



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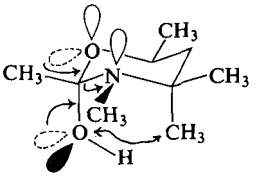

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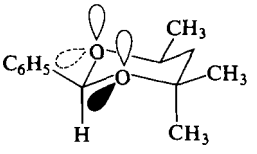

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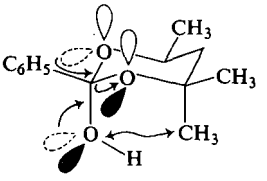

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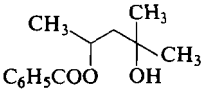

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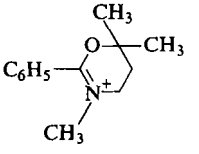
It was of interest to find out if this steric compression factor was important enough to direct the cleavage of the intermediate exclusively in one direction. We have verified experimentally that this factor is indeed important by carrying out the ozonolysis of the acetal **30** (11). Oxidation of **30** by ozone gave the ester **32** exclusively. During this reaction, it is postulated that the intermediate **31** is formed. In **31** the orientation of the nonbonded 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 **31** is strong enough to allow a specific cleavage in one direction. This result is in agreement with the minimum value of 2.4 kcal/mol which has been estimated for 1,3-diaxial interaction between a hydroxyl and a methyl group.[6]

Having a good estimate for the importance of 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 **33** was therefore prepared for that purpose. Its reaction with hydroxide ion should give the intermediate **34**, 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 **33** with sodium carbonate gave exclusively the ester amine product **35** which was characterized as its acetamide derivative **36**. Additionally, salt **37** was also prepared. Its hydrolysis yielded first the ester amine **38** which was rapidly transformed under the experimental conditions into the benzamide alcohol **39**. In the above examples, the reaction was still specific despite an opposing steric factor (estimated to be $\geq$2.4 kcal/mol) which had first to be surmounted. It is considered that a reaction path is specific when it is favored by at least 2.4 kcal/mol. The minimum value for the orbital orientation effect can therefore be estimated to be at least 5 kcal/mol.

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



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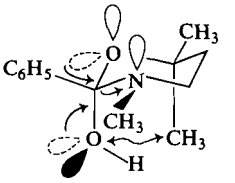

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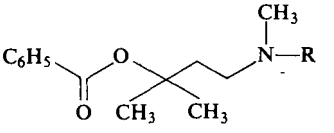
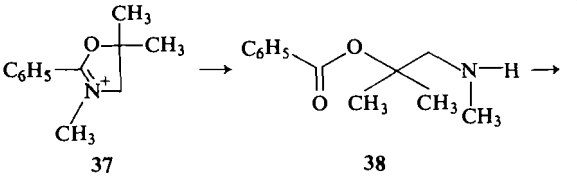


35 R = H
36 R = CH_3CO



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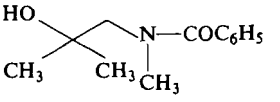

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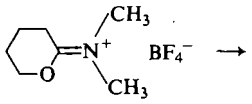
[6]The energy difference between the two conformers of *cis*-3-methylcyclohexanol can be estimated at about 3.8 kcal/mol and an experimental value of 2.4 kcal/mol (12) is taken as the basis for the 1,3-diaxial methyl–hydroxyl interaction (13).

clearly demonstrate that, indeed, the ester amine products are the only products observed under kinetically controlled conditions. We must conclude that orbital orientation is an important factor in lowering the energy barrier for the breakdown of a tetrahedral intermediate. In fact, we believe that it is the determining factor.

Hydrolysis of *Syn* Imidate Salts

We have also undertaken the basic hydrolysis of the imidate salts **40** and **41** which have a *syn* conformation owing to their cyclic structure. The hydrolysis of **40** should give the intermediate **42** which is equivalent to **2***b*. Thus, **42** cannot break



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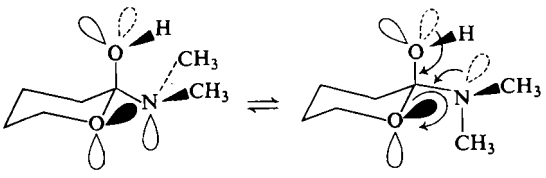
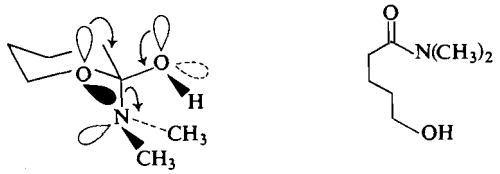
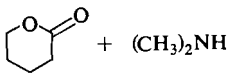


42 **43**



44 **46**



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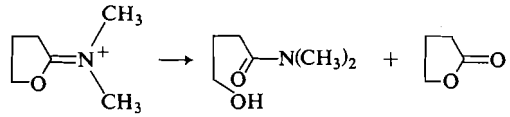
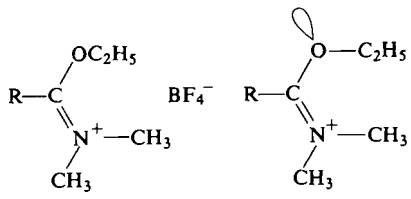
down easily if the stereoelectronic theory is valid. However, intermediate **42** can undergo conformational changes to yield either **43** by carbon–nitrogen rotation or **44** by chair inversion. Conformer **43** has its orbitals properly oriented to give the hydroxy amide **46** whereas conformer **44** should yield the lactone **45** and dimethylamine. Thus, the stereoelectronic theory predicts a mixture of products **45** and **46** from the basic hydrolysis of **40**. The hydrolysis of **40** was carried out with sodium hydroxide in aqueous acetonitrile. Indeed, the imidate salt **40** gave a mixture of hydroxy amide **46** (66%) and δ-valerolactone (**45**, 33%) and dimethylamine (33%). The relative proportion of products was determined directly in the reaction mixture by measuring (n.m.r.) the relative proportion of dimethylamine and *N*,*N*-dimethylamide produced. Likewise, the hydrolysis of the imidate salt **41** gave a one to one mixture of the corre-



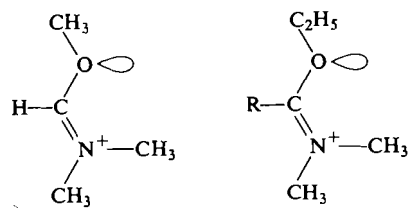
41 **47** **48**

sponding hydroxy amide **47** and γ-butyrolactone (**48**).

We have also studied the basic hydrolysis of a series of imidate salts **49**, in which the R group was varied (R = hydrogen, methyl, isopropyl, cyclohexyl, *t*-butyl, and phenyl). Such salts can exist in principle in the *anti* (**49***a*) or the *syn* (**49***b*) form. 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 R group and the ethyl group in the *syn* form *b*. There is also a 1,3-synperiplanar 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, when R is a large group such as



49 **49***a*



50 **49***b*

TABLE 1. Basic hydrolysis of imidate salts **49***†

R	%ester	%amide
H	50	50
CH_3	81	19
C_6H_{11}‡	50	50
$(CH_3)_3C$	100	0
C_6H_5	100	0

*Hydrolysis was carried out with NaOH (1–2 *N*) in a mixture (≃ 1:1) CD_3CN–H_2O in an n.m.r. tube.
†Yields were estimated by n.m.r. spectroscopic analysis.
‡Yields were estimated by v.p.c. analysis.

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 **49** (R = H) exists mainly as the *syn* form. A nuclear Overhauser effect study on the salt **50** indicates that it exists mainly in the *syn* conformation.[7] When R is a methyl, an isopropyl, or a cyclohexyl group, **49** 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, **49** would exist in the pure *anti* form.

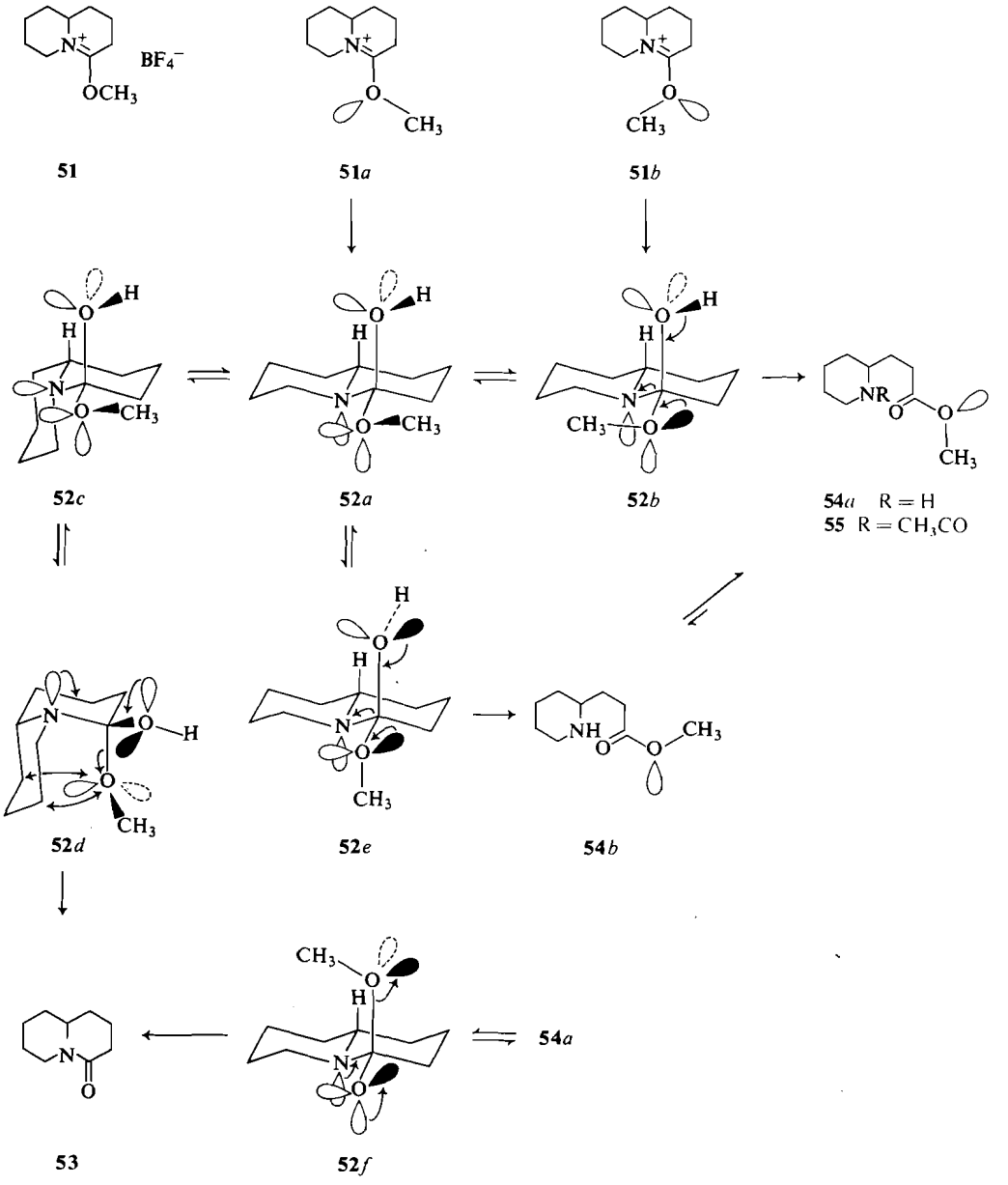
The above reasoning, in conjunction with stereoelectronic theory predicts that mixtures of ester amine and amide alcohol products should be observed in the hydrolysis of **49** when R is a hydrogen, a methyl, an isopropyl, and a cyclohexyl group. It also predicts that the basic hydrolysis of **49** when 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 1. This data is in striking accord with the preceding discussion.

We have also studied the bicyclic imidate salt **51**; imidate **51** can exist either in the *syn* (**51***a*) or the *anti* (**51***b*) form. Steric interactions in **51** are similar to those of salt **49** (R = CH_3). Application of the stereoelectronic theory to this system leads to the following conclusions. We assume that the *syn* conformation **51***a* must be predominant. Reaction of **51***a* with hydroxide ion should yield the conformer **52***a* specifically. Since conformer **52***a* cannot break down by an orbital assisted mechanism, conformational changes should take place. Nitrogen inversion is possible in **52***a* to give the new conformer **52***c*. However, this new conformer, like **52***a*, does not have proper orbital orientation to break down. Since **52***c* is equivalent to a *cis*-decalin system, it can undergo a chair inversion to give conformer **52***d*. Conformer **52***d* should break down to give the lactam product **53** in a stereoelectronically controlled fashion. However, in conformer **52***d*, there are two severe 1,3-diaxial steric interactions between two methylene groups of ring A and the oxygen of the OCH_3 group. The energy barrier for the conversion of **52***a* into **52***d* will be increased accordingly. Thus, if **52***a* 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 **52***d* can be eliminated from consideration.

Conformer **52***a* can also change its conformation by rotation of the O—CH_3 bond. In this fashion, it can give either **52***b* or **52***e*. (In principle, **52***b* could also be obtained directly from the *anti* form **51***b*.) These two conformers have proper orbital orientation to break down to yield the ester amine product **54**. The magnitude of the anomeric effect (15), which occurs whenever two lone pair orbitals are in a 1,3-synperiplanar arrangement is approximately the same in **52***b* and **52***e*. However, on steric grounds, **52***e* should be more stable than **52***b* since there is a 1,3-synperiplanar interaction[8] between the OCH_3 group and the methylene group adjacent to the nitrogen atom in **52***b*. Conformer **52***b* should give the ester amine in its thermodynamically more stable *E* form (**54***a*), whereas **52***e* should yield the same product in its less stable *Z* form **54***b* (14). If the route **52***a* → **52***e* → **54***b* were operative, **54***b* would be converted by bond rotation into the more stable *E* form **54***a*. If the instability of the *Z* ester relative to the *E* ester (11) is transposed to the energy barrier for the cleavage of the more stable conformer **52***e*, one must conclude that the hydrolysis of **51** could very well occur via both intermediates **52***b* and **52***e*. These two intermediates lead to the ester

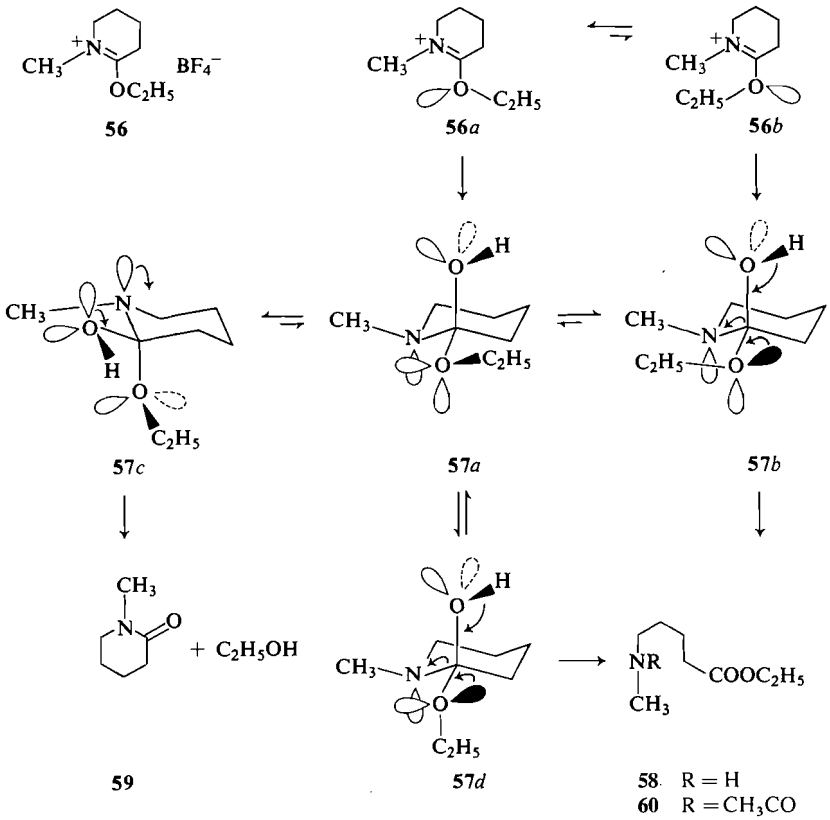
[7]Saturation of the OCH_3 absorption (δ = 4.8) causes an area enhancement of 15% of the methine proton (δ = 8.8). Irradiation of the N—CH_3 group *cis* to the methine proton (doublet, J = 2 Hz, δ = 3.6) resulted in a 16% area increase of this absorption, whereas saturation of the *trans* N—CH_3 group (singlet, δ = 3.8) had no effect. We are grateful to professor J. K. Saunders for this experiment.

[8]A 1,3-synperiplanar interaction is identical to a 1,3-diaxial interaction in a cyclohexane ring.



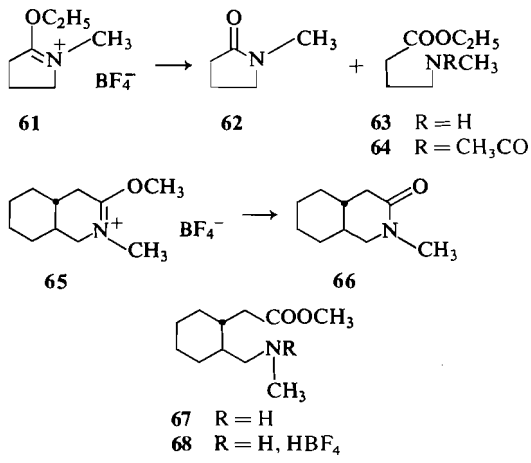
amine **54***a*. Formation of **54***a* via **52***b* and **52***e* is an easier process than formation of the lactam **53** via the sterically unfavored **52***d*. The kinetic product of the hydrolysis reaction of **51** must therefore be the ester amine **54***a*.

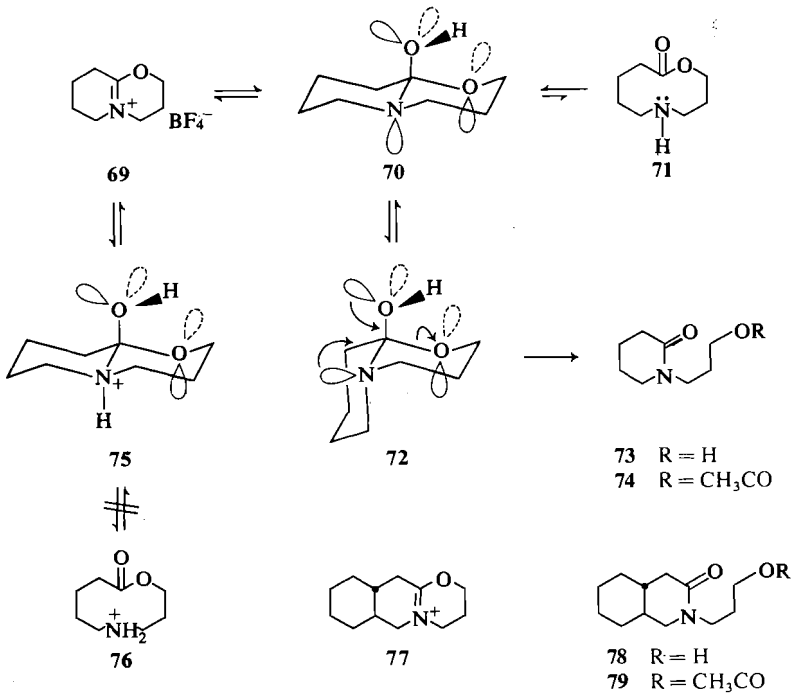
In the experiment, the imidate salt **51** was hydrolyzed with sodium carbonate and gave the ester amine **54***a* exclusively after 15 min of reaction. The ester amine **54***a* was then slowly converted into the lactam **53** in the reaction mixture (66% of conversion after 76 h). In another experiment, the hydrolysis of **51** was allowed to proceed for 15 min, then the reaction mixture was treated with a large excess of acetic anhydride and pyridine. The ester amine **54***a* was trapped as the acetamide ester **55** in good yield. Thus, it appears that the formation of lactam **53** via stereoelectronic control must occur by the new tetrahedral conformer **52***f* which can be easily formed from the ester amine **54***a*.



The hydrolysis of the imidate salt **56** was also carried out. It gave a mixture of ester amine **58** (83%) and lactam **59** (17%). The ester amine **58** was isolated as its acetamide derivative **60**. The salt **56** can be considered as the monocyclic version of the bicyclic salt **51** that gives tetrahedral intermediates (**52**) which cannot undergo a proper nitrogen inversion without creating severe steric interactions. The salt **56** can form tetrahedral intermediates (**57***a*, *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 **56**. This prediction is in agreement with the experimental result. A similar result was obtained from the hydrolysis of the salt **61** which also gave a mixture of ester amine **63** (65%) and lactam **62** (35%). The ester amine **63** was isolated and characterized as its acetamide derivative **64**.

The hydrolysis of the bicyclic imidate salt **65** was also investigated. Its hydrolysis with aqueous sodium carbonate gave directly the lactam **66**, while none of the expected amine ester **67** was detected. However, hydrolysis of **65** in aqueous acid gave the ester ammonium salt **68**. On treatment of **68** with aqueous sodium carbonate only the lactam **66** was obtained. The amine ester **67** was not observed. Consequently, the above result cannot be used against the stereoelectronic theory, because the basic hydrolysis of **65** gives directly the thermodynamic product (**66**) under





conditions where the kinetic product (**67**) cannot long survive.

Hydrolysis of Bicyclic Imidate Salts 69 and 77

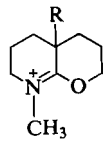
The hydrolysis of the *anti* bicyclic imidate salt **69** was also examined. If the stereoelectronic rule is followed, the salt **69** should give the intermediate **70** which has its orbitals properly aligned to yield the amino lactone **71**. The presence of the large ring in **71** keeps the nitrogen in close proximity to the carbonyl of the ester function. It is therefore logical to expect that the reformation of intermediate **70** from **71** should be especially facile. If **70** has a sufficient lifetime because it is in mobile equilibrium with **71**, it can undergo a conformational change to **72** by nitrogen inversion. Stereoelectronically controlled cleavage of **72** yields the hydroxy lactam **73** which is the thermodynamic product of the reaction. So, even if the conversion of **70** into **72** is a much slower process than its breakdown into **71**, once **72** 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 **69** was carried out and it led to the exclusive formation of hydroxy lactam **73** which was characterized by its acetate derivative **74**.

On the other hand, the reaction of **69** in acidic medium should give the intermediate **75** which can break down into the lactonium ammonium salt **76** by an orbital assisted mechanism. The intermediate **75** cannot undergo a conformational change to give the protonated form of **72**; the nitrogen in **75** cannot be inverted because its lone pair orbital is now protonated. The formation of hydroxy lactam **73** should therefore not be observed in acidic medium. The hydrolysis of **69** 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 8 months. Thus, not only the hydroxy lactam product **73** was not formed but the ammonium salt **76** was not even produced. The stability of **69** in aqueous acid can be explained in two ways: (*a*) the salt **69** 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 **75** but it prefers to give back the starting salt **69**, for the reason that **69** is more stable than the ammonium salt **76**. We think that the first explanation is not valid. It is difficult to find one good reason to explain the resistance of **69** to form a tetrahedral inter-

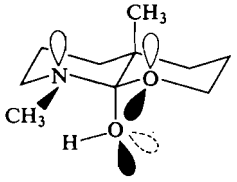
mediate in acidic medium. All other imidate salts that we have reported in this article do form an intermediate since they are all hydrolyzed in aqueous acid. We have prepared the tricyclic imidate salt **77** which has a structure similar to **69** and we should thus expect the same kind of reactivity. In aqueous base, **77** gave the expected hydroxy lactam **78** which was characterized by its acetate derivative **79**. In aqueous acid, it was found to be completely stable.

Hydrolysis of Imidate Salts 80 and 86

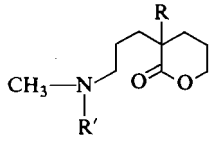
The basic hydrolysis of the bicyclic imidate salt **80** was undertaken next. Reaction of **80** with hydroxide ion should give the intermediate **81**



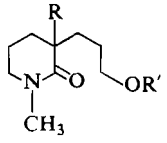
80 R = CH_3
86 R = H



81



83 R = CH_3, R′ = H, HBF_4
84 R = CH_3, R′ = CH_3CO
89 R = H, R′ = H, HBF_4
90 R = H, R′ = CH_3CO



82 R = CH_3, R′ = H
85 R = CH_3, R′ = CH_3CO
87 R = H, R′ = H
88 R = H, R′ = CH_3CO

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 **81** could be detected in the reaction mixture since the energy barrier for its breakdown must be abnormally high. The hydrolysis of **80** was carried out in aqueous sodium carbonate. This imidate gave the hydroxy lactam **82** which was also isolated as its acetate derivative **85**. We have found that **80** is hydrolyzed in aqueous acid to the lactone ammonium salt **83** which was further transformed into its acetamide derivative **84**. When **83** was treated with aqueous base, it gave directly the hydroxy lactam **82**. This result shows that the products of the basic hydrolysis of **80** were those of thermodynamic control. (The fact that **80** is hydrolyzed in aqueous acid brings additional support that **69** is in equilibrium with the intermediate **75** under the same conditions.) The specific formation of the lactone ammonium salt **83** shows that the nitrogen lone pair in the tetrahedral intermediate is always protonated under acidic conditions; the lone pair is, therefore, never available to expel an OR group. The successful hydrolysis of **80** under basic conditions indicates that the breakdown of a tetrahedral intermediate can be accomplished without the help of two lone pair orbitals acting synergistically. The tetrahedral intermediate can be cleaved through a higher energy barrier. If the cleavage of **81** had become the slow step of the reaction, its presence could have been detected.

We have also prepared the closely related imidate salt **86** and have obtained a similar result. Under basic conditions, **86** gave the hydroxy lactam **87** which was also characterized as its acetate derivative **88**. Under acidic conditions, **86** gave the lactone ammonium salt **89** which was transformed into the hydroxy lactam **87** by treatment with aqueous sodium carbonate. Treatment of the salt **89** with pyridine and acetic anhydride gave the lactone acetamide **90**.

Conclusion

The products of hydrolysis of the imidate salts examined were accurately predicted by application of the straightforward argument presented here. The application of the postulate of conformational changes combined with the principle of stereoelectronic control provide a very attractive mechanism to explain the products formed in the hydrolysis of imidate salts under basic conditions. We believe that the preceding results combined with our work on the oxidation of acetals (11) and the hydrolysis of orthoesters (1) constitute strong experimental evidence which support this new stereoelectronic theory.[9]

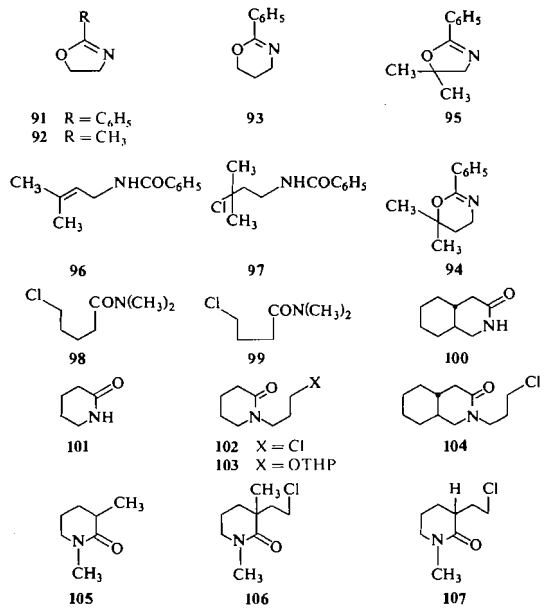
Experimental

The i.r. spectra were taken on a Perkin-Elmer 257 spectrophotometer. Proton n.m.r. spectra (δ value) were

[9]In this work, we have not taken account of the p*H* 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 had to be used. We also used mixed aqueous–organic solvents so that the products of the reaction could be conveniently analyzed by n.m.r. spectroscopy. We have also undertaken the hydrolysis of some *N,N*-dialkylated imidate salts in aqueous solution over a range of p*H* values. The results obtained confirm the conclusion of this work and will be reported in the near future.

recorded on a Varian A-60 spectrometer in solvent indicated. All chemical shifts are recorded relative to internal TMS as standard. The vapor phase chromatographic analyses were done on Varian chromatographs models 600-D and 2800. Mass spectra were run on a Hitachi-Perkin-Elmer RMU-6 spectrometer. Microanalyses were performed by Dr. C. Daesslé, Organic Microanalyses, Montreal and by Mr. J. Tamas, Laboratoire de Microanalyse, Université de Sherbrooke.

The imidate salts **3**, **11**, **14**, **33**, and **37** were obtained by alkylation with trimethyloxonium tetrafluoroborate (16) of compounds **91**, **92**, **93**, **94**, and **95**, respectively. Compound **94** was prepared from the chloroamide **97** which was obtained from the olefinic amide **96**. The imidate salt **40** was prepared from δ-valerolactone via intermediates **46** and **98**. Similarly, the salt **41** was obtained from γ-butyrolactone via compounds **47** and **99**. The imidate salts **49**, **50**, **51**, **56**, **61**, and **65** were prepared by alkylation with the appropriate trialkyloxonium tetrafluoroborate of the corresponding amides or lactams. The lactam **66** was prepared from lactam **100**. The salt **69** was prepared by cyclization of **102** which was obtained by *N*-alkylation of **101** with 1-bromo-3-chloropropane. An authentic sample of **73** was prepared by alkylation of **101** with 3-chloro-1-propanol tetrahydropyranyl ether (**103**) followed by acid hydrolysis. The salt **77** was obtained by a similar route using **100** and **104** as intermediates. The salts **80** and **86** were prepared by cyclization of **106** and **107**. *C*-Alkylation of **105** and **59** gave the chloroamides **106** and **107** respectively. Finally, alkylation of **59** gave **105** (17).



General Method of Preparation of Imidate Salts

The imino ether, amide, or lactam (1 equiv.) was treated with trialkyloxonium tetrafluoroborate (1 equiv.) in anhydrous dichloromethane. The solution was kept at room temperature for 12 h. The solvent was removed *in vacuo*. The reactions are essentially quantitative. When the imidate salt could not be obtained crystalline, it was used directly without further purification. The structure and purity of such salts can be easily verified by n.m.r. and i.r. spectroscopic analysis.[10]

A Typical Procedure for the Basic Hydrolysis of Cyclic Imidate Salts

Imidate Salt 3

Procedure A—Imidate salt **3** (50 mg, 0.20 mmol) was dissolved in deuterated acetonitrile (0.3 ml). Sodium carbonate (0.66 mmol) in deuterated water (0.3 ml) was added. After 10 min, analysis by n.m.r. spectroscopy indicated the presence only of benzoate amine **4** (n.m.r. (CD_3CN—D_2O): δ 7.55–8.05 (5H, multiplet, aromatic protons), 4.45 (2H, triplet, J = 5.5 Hz, CH_2O), 3.02 (2H, triplet, J = 5.5 Hz, CH_2N), and 2.48 (3H, singlet, CH_3N). The reaction mixture was left at room temperature for 24 h. Nuclear magnetic resonance analysis indicated the presence of benzamide alcohol **6** as the sole product. The solvent was removed *in vacuo*, brine was added, and the mixture was extracted with chloroform. The organic phase was dried over magnesium sulfate, filtered, and evaporated to dryness to yield crude benzamide alcohol **6**; i.r. ($CHCl_3$): 3520–3200 and 1615 cm^{-1}; n.m.r. ($CDCl_3$): δ 7.45 (5H, singlet, aromatic hydrogens), 3.76 (5H, multiplet, OCH_2CH_2N and OH), 3.21 (3H, singlet, CH_3N), and 3.09 (3H, singlet, CH_3N). Acetylation of benzamide alcohol **6** with pyridine and acetic anhydride gave benzamide acetate **7**; i.r. ($CHCl_3$): 1625 and 1740 cm^{-1}; n.m.r. ($CDCl_3$): δ 7.44 (5H, aromatic hydrogens), 4.33 (2H, unresolved triplet, CH_2O), 3.72 (2H, unresolved triplet, CH_2N), 3.08 (3H, singlet, CH_3N), and 2.09 (3H, singlet, CH_3CO).

Procedure B—Imidate salt **3** (200 mg, 0.8 mmol) was dissolved in acetonitrile (5 ml) and sodium carbonate (44 mmol) in water (2 ml) was added. After 10 min at room temperature, acetic anhydride (50 ml) and pyridine (10 ml) were added. The reaction was left for 12 h at room temperature. It was cooled to 0 °C and methanol (50 ml) was added. Water was then added and the mixture was extracted with dichloromethane. The organic phase was washed with water, dried, and evaporated to dryness to yield pure benzoate acetamide **5** (180 mg, 100%); i.r. ($CHCl_3$): 1635 and 1715 cm^{-1}; n.m.r. ($CDCl_3$): δ 7.55–8.10 (5H, multiplets, aromatic hydrogens), 4.50 (2H, triplet, J = 6 Hz, CH_2O), 3.70–3.80 (2H, two triplets, J = 6 Hz, CH_2N), 3.06–3.12 (3H, two singlets, CH_3N), and 2.11–2.18 (3H, two singlets, CH_3CO).

Procedure C—Imidate salt **3** (50 mg, 0.20 mmol) was dissolved in deuterated acetonitrile (0.3 ml). Sodium carbonate (0.66 mmol) in deuterated water (0.3 ml) was added. After 10 min, n.m.r. analysis indicated the presence of only benzoate amine **4**. Sodium hydroxide in deuterated water (1 *N*, 0.3 ml) was added. Nuclear magnetic resonance analysis of this solution showed only benzamide alcohol **6**.

Procedure D—Imidate salt **3** (30 mg, 0.20 mmol) was dissolved in acetonitrile (0.3 ml) and deuterated water (0.1 ml). The reaction is complete after 10 h at room temperature and gives the ammonium salt **8** n.m.r.

[10]The experimental procedures and spectroscopic data for the imidate salts and the various compounds described in this work are available, at a nominal charge, from the Depository for Unpublished Data, CISTI, National Research Council of Canada, Ottawa, Canada KIA 0S2.

(CD_3CN—D_2O): δ 7.65–8.10 (5H, multiplet, aromatic hydrogens), 4.53 (2H, multiplet, CH_2O), 3.48 (2H, multiplet, CH_2N), and 2.83 (3H, singlet, CH_3N). A solution of sodium hydroxide (0.25 ml, 1 *N*) is added. Nuclear magnetic resonance analysis indicated the presence of benzamide alcohol **6** only.

Procedure E—Imidate salt **3** (30 mg, 0.12 mmol) was dissolved in acetonitrile (0.3 ml) and deuterated water (0.1 ml). After 18 h at room temperature, sodium carbonate (0.66 mmol) in deuterated water (0.3 ml) was added. Nuclear magnetic resonance analysis indicated the presence of benzoate amine **4**. After standing for 100 h, n.m.r. analysis indicated the presence of benzamide alcohol **6**.

*Hydrolysis of Imidate Salt **11***

*Acetate amine **12***—n.m.r. (CD_3CN–D_2O): δ 4.15 (2H, triplet, J = 6 Hz, CH_2O), 2.77 (2H, triplet, J = 6 Hz, CH_2N), and 2.32 (3H, singlet, CH_3N).

*Acetamide alcohol **13***—i.r. ($CHCl_3$): 3200–3550 and 1630 cm^{-1}; n.m.r. ($CDCl_3$): δ 4.70 (1H, broad singlet, OH), 3.60 (4H, multiplet, NCH_2CH_2O), 2.95–3.10 (3H, two singlets, CH_3N), and 2.08–2.14 (3H, two singlets, CH_3CO).

*Hydrolysis of Imidate Salt **14***

*Benzoate amine **15***—n.m.r. (CD_3CN–D_2O): δ 7.55–7.90 (5H, two multiplets, aromatic hydrogens), 4.35 (2H, triplet, J = 6 Hz, CH_2O), 2.88 (2H, triplet, J = 7 Hz, CH_2N), 2.42 (3H, singlet, CH_3N), and 2.02 (2H, multiplet, CH_2).

*Benzoate acetamide **16***—i.r. ($CHCl_3$): 1630 and 1715 cm^{-1}; n.m.r. ($CDCl_3$): δ 7.57–8.10 (5H, two multiplets, aromatic hydrogens), 4.40 (2H, triplet, J = 6 Hz, CH_2O), 3.52–3.58 (2H, two triplets, J = 6 Hz, CH_2N), 2.98–3.06 (3H, two singlets, CH_3N), 2.10–2.11 (3H, two singlets, CH_3CO), and 2.11 (2H, multiplet, CH_2).

*Acetate benzamide **18***—i.r. ($CHCl_3$): 1620 and 1730 cm^{-1}; n.m.r. ($CDCl_3$): δ 7.45 (5H, singlet, aromatic hydrogens), 4.11 (2H, multiplet, CH_2O), 3.55 (2H, multiplet, CH_2N), 3.05 (3H, singlet, CH_3N), and 2.02 (5H, multiplet, CH_2 and CH_3CO).

*Benzoate ammonium salt **19***—n.m.r. (CD_3CN): δ 7.65–8.10 (5H, two multiplets, aromatic hydrogens), 4.41 (2H, triplet, J = 6 Hz, CH_2O), 3.20 (2H, triplet, J = 7 Hz, CH_2N), 2.70 (3H, singlet, CH_3N), and 2.11 (2H, multiplet, CH_2).

*Hydrolysis of Imidate Salt **26***

*Acetate amine **27***—i.r. ($CHCl_3$): 1725 cm^{-1}; n.m.r. ($CDCl_3$): δ 5.15 (1H, multiplet, CHO), 2.30 (3H, singlet, CH_3N), 2.02 (3H, singlet, CH_3CO), 1.24 (3H, doublet, J = 7 Hz, CH_3CH), and 1.05 (6H, singlet, $(CH_3)_2C$).

*Hydrolysis of Imidate Salt **33***

*Benzoate amine **35***—n.m.r. (CD_3CN–D_2O): δ 7.6–7.90 (5H, two multiplets, aromatic hydrogens), 2.32 (3H, singlet, CH_3N), and 1.60 (6H, singlet, $(CH_3)_2C$).

*Acetamide benzoate **36***—i.r. ($CHCl_3$): 1750 and 1630 cm^{-1}; n.m.r. (CD_3CN): δ 7.6–8.10 (5H, two multiplets, aromatic hydrogens), 3.52 (2H, multiplet, CH_2N), 2.86–2.98 (3H, two singlets, CH_3N), 1.95–2.04 (3H, two singlets, CH_3CO), and 1.62 (6H, singlet, $(CH_3)_2C$).

*Hydrolysis of Imidate Salt **37***

*Benzoate amine **38***—n.m.r. (CD_3CN–D_2O): δ 7.80 (5H, multiplet, aromatic hydrogens), 3.06 (2H, singlet, CH_2N), 2.52 (3H, singlet, CH_3N), and 1.62 (6H, singlet, $(CH_3)_2C$).

*Benzamide alcohol **39***—i.r. ($CHCl_3$): 3200–3600, and 1615 cm^{-1}; n.m.r. ($CDCl_3$): δ 7.45 (5H, singlet, aromatic hydrogens), 3.96 (1H, broad singlet, OH), 3.60 (2H, singlet, CH_2N), 3.10 (3H, singlet, CH_3N), and 1.28 (6H, singlet, $(CH_3)_2C$).

*Hydrolysis of Imidate Salt **40***

The n.m.r. spectrum indicated a mixture of dimethylamine (31%), the hydroxy carboxylic acid sodium salt of δ-valerolactone (**45**) and hydroxy amide **46**; n.m.r. (CD_3CN–H_2O): δ 3.57 (2H, unresolved triplet, CH_2O), 3.04–2.88 (6H, two singlets, $(CH_3)_2NCO$), and 2.27 (6H, singlet, $(CH_3)_2ND$).

*Hydrolysis of Imidate Salt **41***

The n.m.r. spectrum indicated a mixture of dimethylamine (50%), the hydroxy carboxylic acid sodium salt of γ-butyrolactone (**48**), and hydroxy amide **47**; n.m.r. (CD_3CN–D_2O): δ 3.56 (2H, triplet, CH_2O), 3.04–2.88 (6H, two singlets, $(CH_3)_2NCO$), and 2.25 (6H, singlet, $(CH_3)_2ND$).

*Hydrolysis of Imidate Salt **51***

*Ester amine **54***—n.m.r. (CD_3CN–H_2O): δ 3.68 (3H, singlet, CH_3O).

*Acetamide ester **55***—i.r. ($CHCl_3$): 1730 and 1620 cm^{-1}; n.m.r. ($CDCl_3$): δ 3.67 (3H, singlet, CH_3O), 2.36 (2H, multiplet, CH_2CO), 2.08 (3H, singlet, CH_3CO), and 1.62 (10H, broad multiplet).

*Hydrolysis of Imidate Salt **56***

*Ester amine **58** (observed in a mixture with **57**)*—i.r. (CH_2Cl_2): 1725 cm^{-1}; n.m.r. (90 MHz, CD_2Cl_2): δ 4.22 (2H, quadruplet, J = 7 Hz, OCH_2), 2.53 (2H, triplet, J = 7 Hz, CH_2N), 2.35 (3H, singlet, CH_3N), 2.28 (2H, triplet, J = 7 Hz, CH_2CO), 1.52 (2H, multiplet), and 1.21 (3H, triplet, J = 7 Hz, OCH_2CH_3).

*Lactam **59***—i.r. ($CHCl_3$): 1625 cm^{-1}; n.m.r. ($CDCl_3$): δ 3.30 (2H, unresolved multiplet, CH_2N), 2.96 (3H, singlet, CH_3N), 2.40 (2H, multiplet, CH_2CO), and 1.85 (4H, multiplet).

*Acetamide ester **60***—i.r. ($CHCl_3$): 1725 and 1630 cm^{-1}; n.m.r. ($CHCl_3$): δ 4.28 (2H, quartet, J = 7 Hz, OCH_2), 3.40 (2H, multiplet, CH_2N), 2.98–3.06 (3H, two singlets, CH_3CO), 2.35 (2H, multiplet, CH_2CO), 2.12–2.14 (3H, two singlets, CH_3N), 1.60 (4H, multiplet), and 1.26 (3H, triplet, J = 7 Hz, OCH_2CH_3).

*Hydrolysis of Imidate Salt **61***

*Ester amine **63** (observed in a mixture with **62**)*—i.r. (CH_2Cl_2): 1735 cm^{-1}; n.m.r. (90 MHz, CH_2Cl_2): δ 4.11 (2H, quartet, J = 7 Hz, OCH_2CH_3), 2.54 (2H, triplet, J = 7 Hz, CH_2N), 2.34 (3H, singlet, CH_3N), 2.30 (2H, triplet, J = 7 Hz, CH_2CO), 1.21 (3H, triplet, J = 7 Hz, OCH_2CH_3).

*Lactam **62***—i.r. (neat): 1670 cm^{-1}; n.m.r. ($CDCl_3$): δ 3.41 (2H, triplet, J = 7 Hz, CH_2N), 2.85 (3H, singlet, CH_3N), 2.30 (4H, multiplet).

*Acetamide ester **64***—n.m.r. ($CDCl_3$): δ 4.18 (2H, quartet, J = 7 Hz, OCH_2CH_3), 3.40 (2H, multiplet, CH_2N), 2.94–3.02 (3H, two singlets, CH_3N), 2.08–2.10 (3H, two singlets, CH_3CO), 2.10 (4H, multiplet), and 1.28 (3H, triplet, J = 7 Hz, OCH_2CH_3).

*Hydrolysis of Imidate Salt **65***

Basic conditions—Imidate salt **65** (93 mg, 0.345 mmol) was dissolved in acetonitrile-d_3 (300 μl) in an n.m.r. tube. Dry sodium carbonate (79 mg, 0.744 mmol) was added, along with deuterium oxide (700 μl). The heterogeneous

mixture was shaken for 10 min at room temperature. The n.m.r. spectrum at this time showed no resonances due to starting material. Solvent was removed *in vacuo* and the residue was triturated with chloroform. The triturant was concentrated *in vacuo* to leave a clear oil which was the lactam **66** (60 mg, 100%). This material was homogeneous by t.l.c. and identical to the lactam prepared via methylation of lactam **100** by n.m.r., i.r., and t.l.c. comparison.

Acidic Conditions—Imidate salt **65** (43 mg, 0.16 mmol) was dissolved in aqueous hydrochloric acid (1 *N*, 300 μl) in an n.m.r. tube. The sample was allowed to stand at room temperature for 5 days. At the end of this time no resonances due to starting material remained. New resonances characteristic of the ester ammonium salt **68** at δ 3.80 (singlet) and 2.80 p.p.m. (triplet, $J = 3$ Hz) had appeared. Solvent was removed *in vacuo*. The i.r. of the semisolid thus obtained in chloroform showed absorptions at 3500–3000 (NH), 1720, and 1625 cm^{-1}.

Ammonium ester **68** (25 mg, 0.067 mmol) was placed in an n.m.r. tube along with deuteriochloroform (300 μl). Aqueous sodium carbonate (1 *N*, 300 μl) was added and the tube was shaken vigorously. Within 3 min the n.m.r. spectrum was essentially that of lactam **66**. Solvent was removed *in vacuo*. The oily solid which remained was triturated with methylene chloride and the triturant was dried over sodium sulfate. Solvent was removed *in vacuo* to give the lactam **66** (10 mg, 90%) as a clear oil. The t.l.c., i.r., and n.m.r. characteristics of this sample were identical to an authentic sample.

Hydrolysis of Imidate Salt ***69***

Basic Conditions—Imidate salt **69** ($X = ClO_4^-$) (59 mg, 0.247 mmol) was dissolved in acetonitrile-d_3 (300 μl) in an n.m.r. tube. Aqueous sodium carbonate (4 *N* in D_2O, 250 μl, 1 mmol) was added. The heterogeneous mixture thus obtained was stirred vigorously and the progress of the reaction was followed by n.m.r. The hydrolysis was judged complete after 15 h at room temperature. The contents of the n.m.r. tube were extracted with chloroform and the extract dried over sodium sulfate. Removal of solvent *in vacuo* gave hydroxy lactam **73** in good yield. The hydroxy lactam **73** obtained from this experiment was identical to hydroxy lactam prepared from the tetrahydropyranyl ether **103**.

Imidate salt **69** ($X = ClO_4^-$) (62 mg, 0.260 mmol) was dissolved in acetonitrile-d_3 (30 μl) in an n.m.r. tube. Aqueous sodium hydroxide (4 *N*, 65 μl, 0.26 mmol) was added, and the resulting heterogeneous mixture was shaken vigorously. The progress of the reaction was followed by n.m.r. After 19 min at room temperature the salt **69** was completely hydrolyzed to hydroxy lactam **73**. As in the previous experiment, **73** was isolated in good yield. The basic hydrolysis of **69** ($X = BF_4^-$) also gives the hydroxy lactam **73**.

Acidic Conditions—Imidate salt **69** ($X = BF_4^-$) (21 mg, 0.09 mmol) was dissolved in aqueous hydrochloric acid (300 μl, 0.1 *N* in D_2O) in an n.m.r. tube. During 8 months at room temperature, there was no change in the n.m.r. spectrum of this sample. At the end of this time solvent was removed *in vacuo*. The residue (31 mg) was triturated with dichloromethane. The triturant was concentrated *in vacuo* to give the imidate salt **69** (13 mg, 62%). Crystallization from dichloromethane – ethyl ether gave pure **69** (11 mg); m.p. 161–163 °C. A 50:50 w/w mixture of authentic **69** and **69** recovered from the aqueous acidic reaction gave m.p. 162–163 °C.

Hydrolysis of Imidate Salt ***77***

Basic Conditions—Imidate salt **77** (57 mg, 0.196 mmol) was dissolved in acetonitrile-d_3 (300 μl). Aqueous sodium carbonate (4 *N* in deuterium oxide, 200 μl) was added. At this point some sodium carbonate precipitated and the solution was filtered into an n.m.r. tube. After 19 h at room temperature the salt **77** had been completely hydrolyzed, as shown by n.m.r. The resulting solution was extracted with chloroform and the extract was dried over potassium carbonate. Removal of solvent *in vacuo* left an oil (40 mg). Preparative t.l.c. (silica gel, $CHCl_3$ – 6% (v/v) CH_3OH, R_f 0.2) gave the hydroxy lactam **78** (30 mg, 70%) as a clear oil; i.r. (CCl_4): 3400 and 1630 cm^{-1}; n.m.r. ($CDCl_3$): δ 4.20 (1H, singlet, OH), 3.9–2.6 (6H, multiplet), 2.5–0.6 (14 H, multiplet); m.s.: *m/e* 211 (M^+), 193 ($M^+ - H_2O$).

Hydroxy lactam **78** (255 mg, 1.21 mmol) was dissolved in acetic anhydride (2 ml) and dry pyridine (2 ml). This mixture was stirred overnight at room temperature, under nitrogen. Solvent was removed *in vacuo* to leave a yellow oil (280 mg). Preparative t.l.c. (silica gel, $CHCl_3$ – 6% (v/v) CH_3OH, R_f 0.5) gave the acetoxy lactam **79** (240 mg, 78%). Low temperature crystallization from hexane gave **79** as a white solid; m.p. 27 °C; i.r. (CCl_4): 1745 and 1650 cm^{-1}; n.m.r. ($CDCl_3$): δ 4.15 (2H, triplet, $J = 7$ Hz, CH_2O), 3.7–2.5 (4H, multiplet), 2.4–0.8 (14 H, multiplet), and 2.05 (3H, singlet, CH_3CO); m.s.: *m/e* 253 (M^+), 210 ($M^+ - CH_3CO$), 193 ($M^+ - CH_3COOH$).

Anal. Calcd. for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15. Found: C, 66.29; H, 9.17.

Acidic Conditions—Tricyclic salt **77** (25 mg, 0.089 mmol) was dissolved in hydrochloric acid (0.1 *N* in deuterium oxide, 300 μl) in an n.m.r. tube. There was no appreciable change in the n.m.r. spectrum of this sample during 8 months at room temperature. At the end of this time solvent was removed *in vacuo* and the residue was triturated with dichloromethane. The triturant was concentrated *in vacuo* to give the imidate **77** (16 mg, 65%) as an oil. This material crystallized from cold absolute ethanol to give pure **77** (12 mg); m.p. 78–80 °C. A 1:1 (w/w) mixture of authentic **77** and **77** isolated from aqueous acid showed m.p. 78–79.5 °C.

Hydrolysis of Imidate Salt ***80***

Basic Conditions—Imidate salt **80** (60 mg, 0.236 mmol) was dissolved in deuteriochloroform (400 μl), in an n.m.r. tube. Aqueous sodium carbonate (300 μl, 0.270 mmol, 0.9 *N* in D_2O) was added and the reaction was followed by n.m.r. After 2.5 h approximately 10% of the imidate remained; after standing 12 h at room temperature, no starting material was detectable by n.m.r. Solvent was removed *in vacuo*. The residue obtained was triturated with chloroform. The triturant was concentrated *in vacuo* to leave a yellow oil (50 mg). Trituration with diethyl ether gave pure lactam alcohol **82** (33 mg, 75%) as a clear, ether soluble, oil; t.l.c.: R_f 0.5 on silica gel using $CHCl_3$ – 7% (v/v) CH_3OH eluent; i.r. (CCl_4): 3450 and 1640 cm^{-1}; n.m.r. ($CDCl_3$): δ 3.8–3.5 (2H, multiplet), 3.5–3.15 (2H, multiplet), 2.90 (3H, singlet), 2.2–1.25 (9H, multiplet), and 1.20 (3H, singlet); m.s.: *m/e* 186 (M^+).

In another experiment the hydrolysis of imidate salt **80** was carried out in aqueous sodium carbonate with no cosolvent. Work-up as described above gave the hydroxy lactam **82** in quantitative yield. The hydrolysis was complete within 5 min after mixing the reagents.

Hydroxy lactam **82** (115 mg, 0.62 mmol) was dissolved

in a mixture of acetic anhydride (1 ml) and dry pyridine (1 ml), under argon. This was allowed to stand overnight at room temperature. Solvent was removed *in vacuo* to leave a slightly yellow oil (137 mg). Short path distillation gave pure acetoxy lactam **85** (95 mg, 68%) as a clear oil; b.p. 80 °C/0.1 Torr; i.r. (CCl_4): 1740 and 1640 cm^{-1}; n.m.r. ($CDCl_3$): δ 4.2–3.9 (2H, multiplet), 3.5–3.1 (2H, multiplet), 2.90 (3H, singlet, CH_3N), 2.05 (3H, singlet, CH_3CO), 2.0–1.3 (8H, multiplet), and 1.20 (3H, singlet, CH_3C); m.s.: *m/e* 227 (M^+).

Anal. Calcd. for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31. Found: C, 63.18; H, 9.38.

Acidic Conditions—Imidate salt **90** (106 mg, 0.416 mmol) was dissolved in aqueous fluoroboric acid (86 mg, 48% HBF_4–H_2O, 0.50 mmol) in an n.m.r. tube. Deuterium oxide (300 μl) was added and the solution was allowed to stand at room temperature for 3 months. No resonances owing to starting material could be detected in the n.m.r. spectrum of the sample at this time. Solvent was removed *in vacuo* and the residue was triturated with chloroform. The triturant gave an oil (110 mg) whose i.r. spectrum in acetonitrile showed an absorption due to the presence of the lactone function at 1720 cm^{-1} corresponding to compound **83**. The oil was stirred at room temperature in a mixture of acetic anhydride (1 ml) and dry pyridine (1 ml), under argon, overnight. Solvent was removed *in vacuo* to leave a brown oil. Preparative t.l.c. (silica gel, $CHCl_3$ – 6% (v/v) CH_3OH, R_f 0.2) gave pure lactone **84** (40 mg, 43%), as a clear oil; i.r. (CCl_4): 1730 and 1640 cm^{-1}; n.m.r. ($CDCl_3$): δ 4.5–4.2 (2H, multiplet), 3.5–3.1 (2H, multiplet), 3.1–2.8 (3H, two lines due to CH_3NCO), 2.7–1.0 (11H, multiplet), and 2.10 (3H, singlet, CH_3CO); m.s.: *m/e* 227 (M^+).

Hydrolysis of Imidate Salt 86

Basic Conditions—Imidate salt **86** (21 mg, 0.091 mmol) was dissolved in acetonitrile-d_3 in an n.m.r. tube. Aqueous sodium hydroxide (4 *N* in deuterium oxide, 50 μl) was added and the n.m.r. spectrum was run immediately. Resonances due to the imidate **86** had completely disappeared. One new resonance, at 2.9 p.p.m., was particularly diagnostic of the methyl group of a 1-methyl-2-piperidone. No further changes occurred in the n.m.r. spectrum of this sample during 1 h of intermittent observation. In another experiment, imidate **86** (21 mg, 0.091 mmol) was dissolved in aqueous sodium carbonate (1 g Na_2CO_3 – 10 ml D_2O, 0.94 *N*, 300 μl) in an n.m.r. tube. The n.m.r. spectrum of this sample was run within 5 min after mixing. No resonances from **86** remained and the spectrum obtained was identical to the one obtained in the previous experiment.

To fully characterize the product of the basic hydrolysis of imidate **86**, the reaction was scaled up. Imidate salt **86** (91 mg, 0.395 mmol) was dissolved in aqueous sodium hydroxide (1 *N*, 5 ml). The mixture was stirred at room temperature for 30 min. The resulting solution was saturated with sodium chloride, then extracted with chloroform. The extract was dried over sodium sulfate, then solvent was removed *in vacuo* to leave a clear oil (75 mg). Preparative t.l.c. (silica gel, $CHCl_3$ – 5% (v/v) CH_3OH, R_f 0.2 gave the hydroxy lactam **87** ((18), 60 mg, 87%) as an oil which crystallized from cold diethyl ether; m.p. 56–56.5 °C; i.r. (CCl_4): 3400 and 1630 cm^{-1}; n.m.r. ($CDCl_3$): δ 3.85–3.55 (3H, multiplet), 2.95 (3H, singlet, CH_3N), and 2.6–1.2 (11H, multiplet); m.s.: *m/e* 153 ($M^+ - H_2O$).

Anal. Calcd. for $C_9H_{17}NO_2$: C, 63.13; H, 10.01. Found: C, 63.07; H, 10.48.

Hydroxy lactam **87** (12 mg, 0.07 mmol) was dissolved in a mixture of acetic anhydride (2 ml) and dry pyridine (1 ml). This solution was stirred at room temperature, under nitrogen, for 3 h. Solvent was removed *in vacuo* to leave a clear oil (13 mg). After preparative t.l.c. (silica gel, $CHCl_3$ – 6% (v/v) CH_3OH, R_f 0.8) this oil gave pure lactam acetate **88** (6 mg, 40%) as a clear oil; i.r. (CCl_4): 1740 and 1640 cm^{-1}; n.m.r. ($CDCl_3$): δ 4.18 (2H, triplet, J = 6 Hz, CH_2O), 3.6–3.2 (2H, multiplet), 3.00 (3H, singlet, CH_3N), 2.5–1.4 (9H, multiplet), and 2.10 (3H, singlet, CH_3CO); m.s.: *m/e* 213 (M^+).

Acidic Conditions—Imidate tetrafluoroborate salt **86** (100 mg, 0.434 mmol) was dissolved in deuterium oxide (300 μl) along with aqueous tetrafluoroboric acid (86 mg of 48% HBF_4–H_2O, 0.5 mmol HBF_4). The progress of the reaction was followed by n.m.r. After 1 month at room temperature, solvent was removed *in vacuo* to leave a clear oil (148 mg). This oil was dissolved in acetonitrile and the solution dried over sodium sulfate. Solvent was removed *in vacuo* to leave a waxy semisolid (142 mg). This was triturated extensively first with dichloromethane, then with acetonitrile. The dichloromethane was evaporated *in vacuo* to leave a clear oil (29 mg) which consisted for the most part of unreacted imidate **86**. The acetonitrile solution was diluted with diethyl ether. Upon cooling in the refrigerator, the desired lactone ammonium salt **89** (79 mg, 100%) precipitated as a waxy semisolid; i.r. (CH_3CN): 1730 cm^{-1}; n.m.r. (CD_3CN): δ 7.3–6.3 (1H, multiplet), 4.5–4.25 (2H, multiplet), 3.8–3.4 (1H, multiplet), 3.3–2.9 (2H, multiplet), 2.72 (3H, triplet, J = 5 Hz), and 2.2–1.3 (partially obscured by solvent).

Ammonium lactone salt **89** (113 mg, 0.455 mmol) was dissolved in acetic anhydride (5 ml) under nitrogen. Dry pyridine (1 ml) was added with vigorous stirring. This was stirred for 3 h at room temperature, then solvent was removed *in vacuo*. The residue was triturated with dichloromethane. Evaporation of the dichloromethane *in vacuo* left crude **90** (54 mg) as an oil. Preparative t.l.c. (silica gel, $CHCl_3$ – 6% (v/v) CH_3OH, R_f 0.6) gave pure **90** (10 mg, 10%) as a clear oil (the crude yield is reasonable but the recovery off the t.l.c. plate is inexplicably poor); i.r. (CCl_4): 1740 and 1650 cm^{-1}; n.m.r. ($CDCl_3$): δ 4.40 (1H, triplet, J = 5 Hz), 4.3–4.00 (1H, multiplet), 3.8–3.20 (2H, multiplet), 3.2–2.95 (3H, singlet, CH_3NCO), 2.7–1.10 (9H, multiplet), and 2.18 (3H, singlet, CH_3CO); m.s.: *m/e* 213 (M^+), 170 ($M^+ - CH_3CO$).

Basic Hydrolysis of Lactone Ammonium Salt 89

Lactone ammonium salt **89** (10 mg) was dissolved in deuterium oxide in an n.m.r. tube. One drop of sodium hydroxide in deuterium oxide (4 *N*) was added, then the n.m.r. spectrum of this solution was run immediately. The spectrum showed no resonance due to starting material, and the spectrum did not change during 30 min. Solvent was removed *in vacuo* to leave a clear oil whose t.l.c. retention time and spectral characteristics (i.r. and n.m.r.) were identical to those of a sample of hydroxy lactam **87**.

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1. P. DESLONGCHAMPS, P. ATLANI, D. FRÉHEL, and A. MALAVAL. Can. J. Chem. **50**, 3405 (1972); P. DESLONGCHAMPS, R. CHÊNEVERT, R. J. TAILLEFER, C. MOREAU, and J. K. SAUNDERS. Can. J. Chem. **53**, 1601 (1975); P. DESLONGCHAMPS, R. J. TAILLEFER, C. MOREAU, and R. CHÊNEVERT. In preparation.
2. P. DESLONGCHAMPS. Pure Appl. Chem. In press.
3. P. DESLONGCHAMPS, C. LEBREUX, and R. J. TAILLEFER. Can. J. Chem. **51**, 1665 (1973).
4. J. F. KING and A. D. ALLBUTT. Tetrahedron Lett. 49, (1967); Can. J. Chem. **48**, 1754 (1970).
5. E. L. ELIEL and F. W. NADER. J. Am. Chem. Soc. **91**, 536 (1969); **92**, 584 (1970).
6. H. B. BÜRGI, J. D. DUNITZ, and E. SHEFTER. J. Am. Chem. Soc. **95**, 5065 (1973); H. B. BÜRGI, J. D. DUNITZ, and E. SHEFTER. Acta Crystallogr. B, **30**, 1517 (1974); J. M. LEHN, G. WIPFF, and H. B. BÜRGI. Helv. Chim. Acta, **57**, 493 (1974); H. B. BÜRGI, J. M. LEHN, and G. WIPFF. J. Am. Chem. Soc. **96**, 1956 (1974); H. B. BÜRGI, J. D. DUNITZ, J. M. LEHN, and G. WIPFF. Tetrahedron, **30**, 1563 (1974); J. M. LEHN and G. WIPFF. J. Am. Chem. Soc. **96**, 4048 (1974).
7. G. L. SCHMIR and B. A. CUNNINGHAM. J. Am. Chem. Soc. **87**, 5692 (1965); B. A. CUNNINGHAM and G. L. SCHMIR. J. Am. Chem. Soc. **88**, 551 (1966); B. A. CUNNINGHAM and G. L. SCHMIR. J. Am. Chem. Soc. **89**, 917 (1967); W. P. JENCKS and M. GILCHRIST. J. Am. Chem. Soc. **90**, 2622 (1968); G. M. BLACKBURN and W. P. JENCKS. J. Am. Chem. Soc. **90**, 2638 (1968); G. L. SCHMIR. J. Am. Chem. Soc. **90**, 3478 (1968); R. K. CHATURVEDI and G. L. SCHMIR. J. Am. Chem. Soc. **90**, 4413 (1968); T. C. PLETCHER, S. KOEHLER, and E. H. CORDES. J. Am. Chem. Soc. **90**, 7072 (1968); T. OKUYAMA and G. L. SCHMIR. J. Am. Chem. Soc. **94**, 8805 (1972); T. OKUYAMA, T. C. PLETCHER, D. J. SAHN, and G. L. SCHMIR. J. Am. Chem. Soc. **95**, 1253 (1973); T. OKUYAMA, D. J. SAHN, and G. L. SCHMIR. J. Am. Chem. Soc. **95**, 2345 (1973).
8. M. EIGEN. Angew. Chem. Int. Ed. Engl. **3**, 1 (1964).
9. P. ALLEN and J. GINOS. J. Org. Chem. **28**, 2759 (1963).
10. A. I. MEYERS and N. NAZARENKO. J. Am. Chem. Soc. **94**, 3243 (1972).
11. P. DESLONGCHAMPS and C. MOREAU. Can. J. Chem. **49**, 2465 (1971); P. DESLONGCHAMPS, C. MOREAU, D. FRÉHEL, and P. ATLANI. Can. J. Chem. **50**, 3402 (1972); P. DESLONGCHAMPS, P. ATLANI, D. FRÉHEL, A. MALAVAL, and C. MOREAU. Can. J. Chem. **52**, 3651 (1974); P. DESLONGCHAMPS, C. MOREAU, D. FRÉHEL, and R. CHÊNEVERT. Can. J. Chem. **53**, 1204 (1975).
12. H. HANACK. *In* Conformation theory Vol. 3. *Edited by* A. T. Blomquist. Academic Press, New York and London. 1965. p. 116.
13. E. L. ELIEL and H. HAUBENSTOCK. J. Org. Chem. **26**, 3504 (1961).
14. R. HUISGEN and H. OTT. Tetrahedron, **6**, 253 (1959).
15. R. U. LEMIEUX. Pure Appl. Chem. **25**, 527 (1971); H. BOOTH and R. U. LEMIEUX. Can. J. Chem. **49**, 777 (1971); E. L. ELIEL. Angew. Chem. **84**, 779 (1972) and Angew. Chem. Int. Ed. Engl. **11**, 739 (1972).
16. H. MEERWEIN. Org. Synth. **46**, 113, 120 (1966).
17. P. DESLONGCHAMPS, U. O. CHERIYAN, and D. R. PATTERSON. Can. J. Chem. **53**, 1682 (1975).
18. W. SCHNEIDER, H. MOEHRLE, V. WEDE, and E. KAEMERER. Arch. Pharm. (Weinheim), **300**, 540 (1967).