# SECTION 7

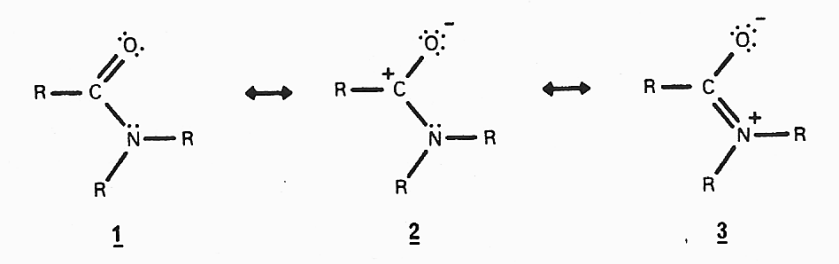
## Stereoelectronic Effects (S.E.)

## and Reactivity of Amides and Related Functions

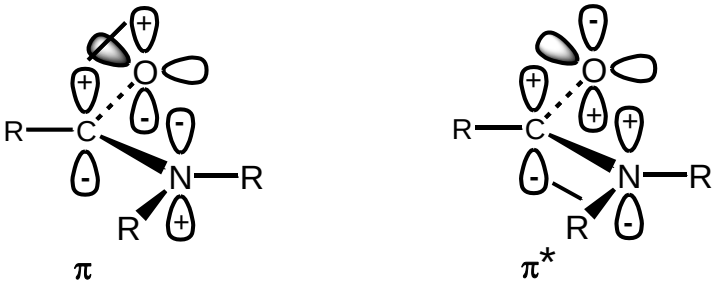
*(2018)*

# Amides and Stereoelectronic Effects

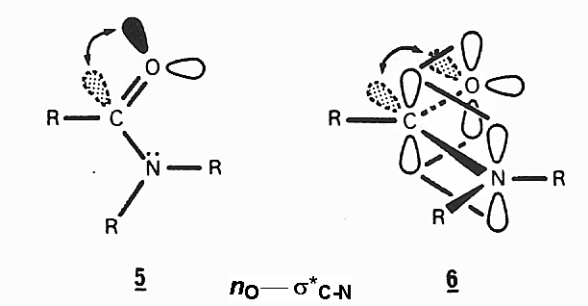
**Resonance Form** (a name which does not mean what it really means !)



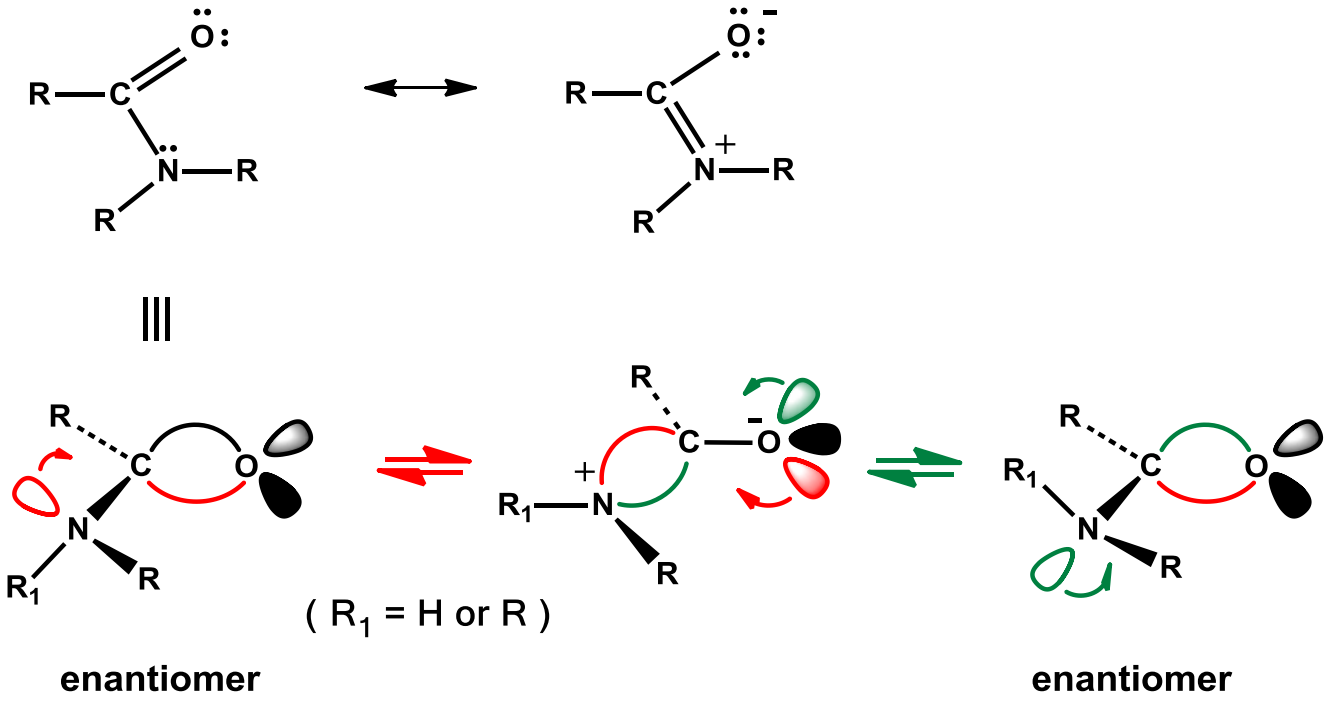

**Primary S.E.**




**Secondary S.E. (A.E.)**

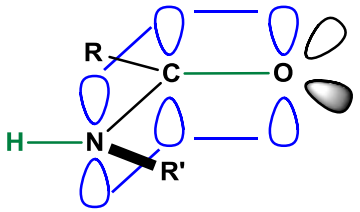


# τ Bond and Amides

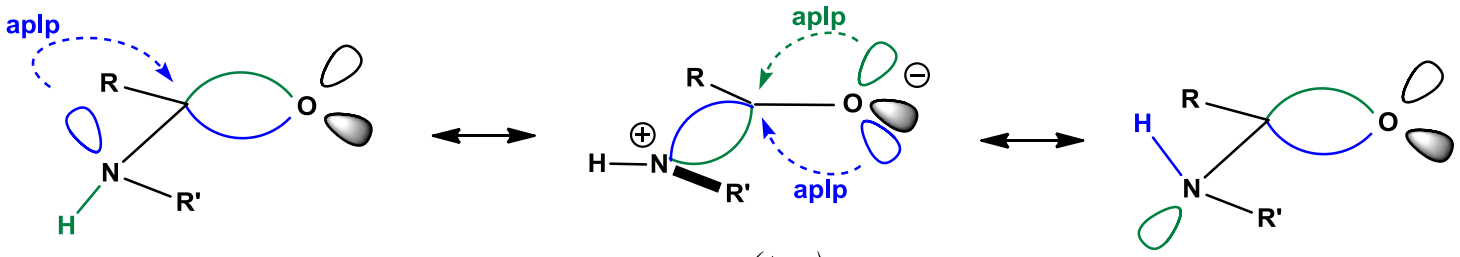



**Amide overall structure is planar**

# 2° amides *(s-trans)*

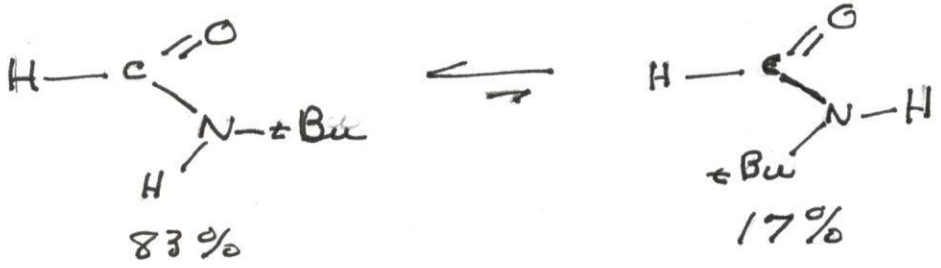


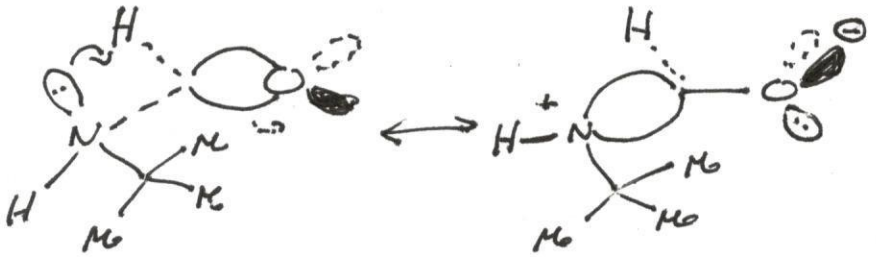

σ–π



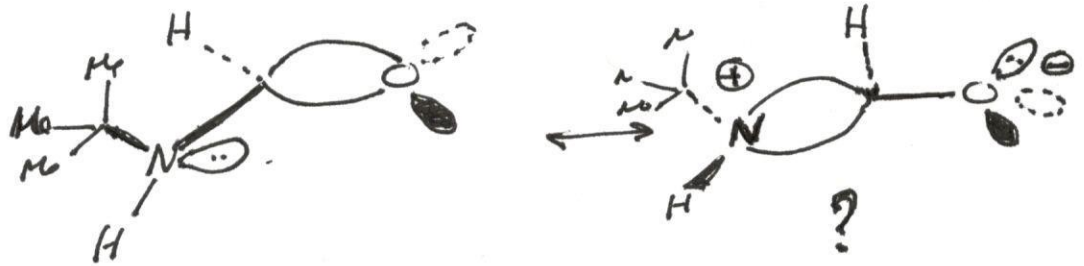

τ *(tau)*

Relative Stability of secondary amides.



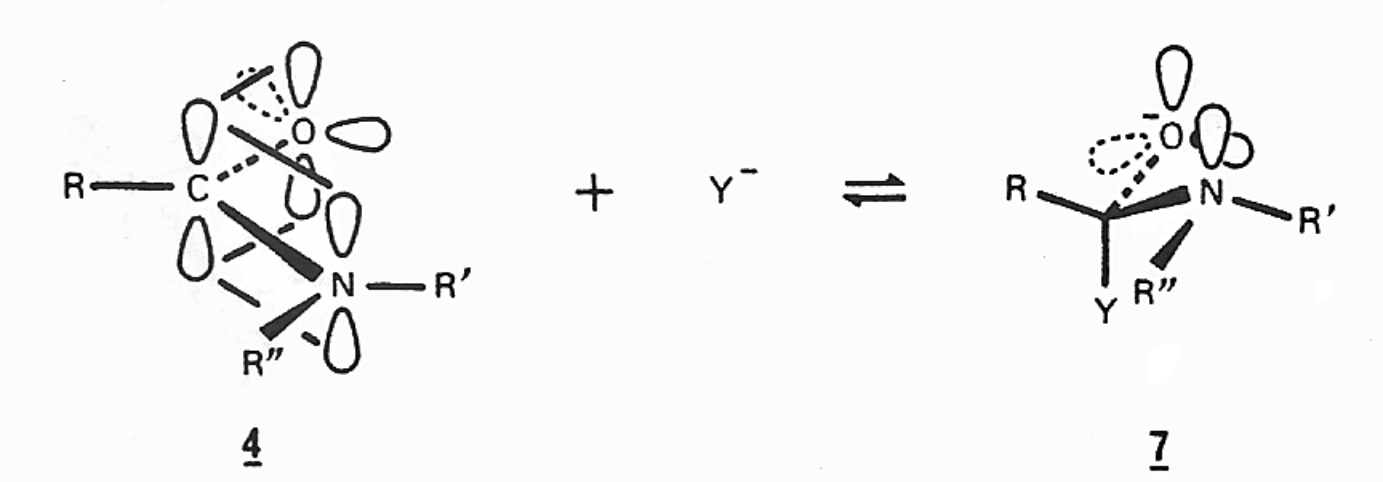



vs




J. Phys. Chem. A 2005, 109, 11878-11884

## Formation and Cleavage of Hemi-Orthoamide with Stereoelectronic Control

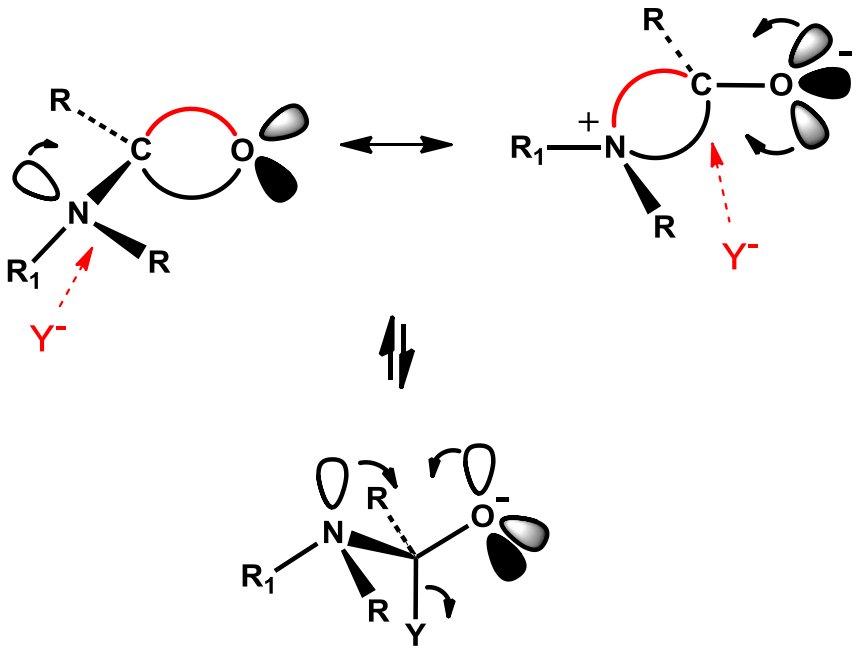



**4** **7**

$\pi$
$\pi^*$
$n_O — \sigma^*_{C\text{-}N}$

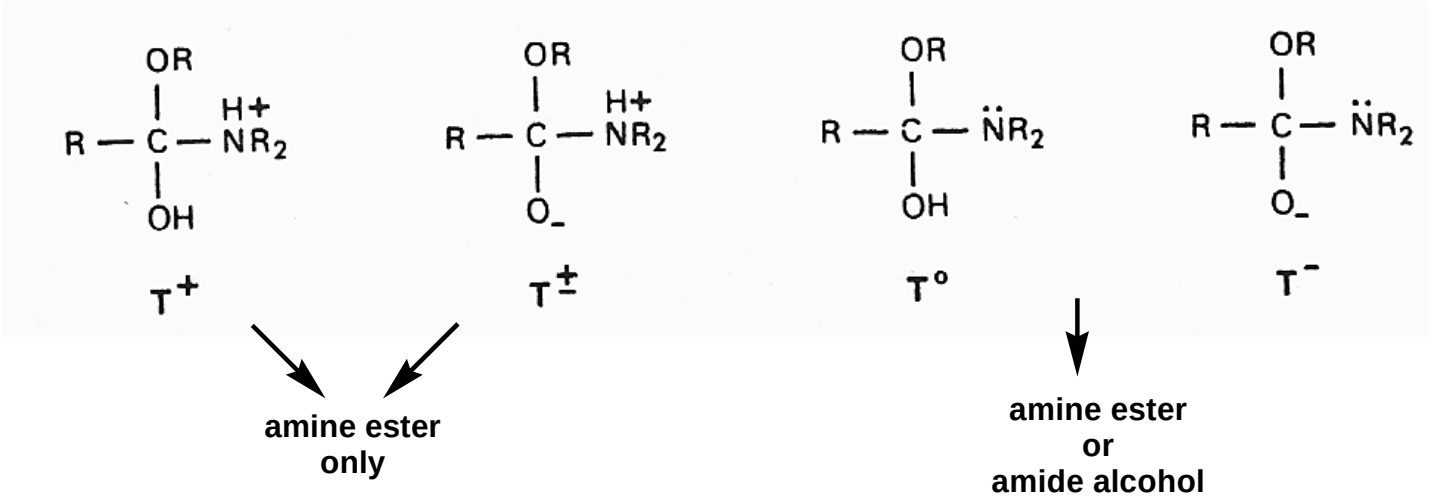
$n_O — \sigma^*_{C\text{-}N}$
$n_O — \sigma^*_{C\text{-}Y}$
$n_N — \sigma^*_{C\text{-}Y}$

# τ Bond and Amide Hydrolysis

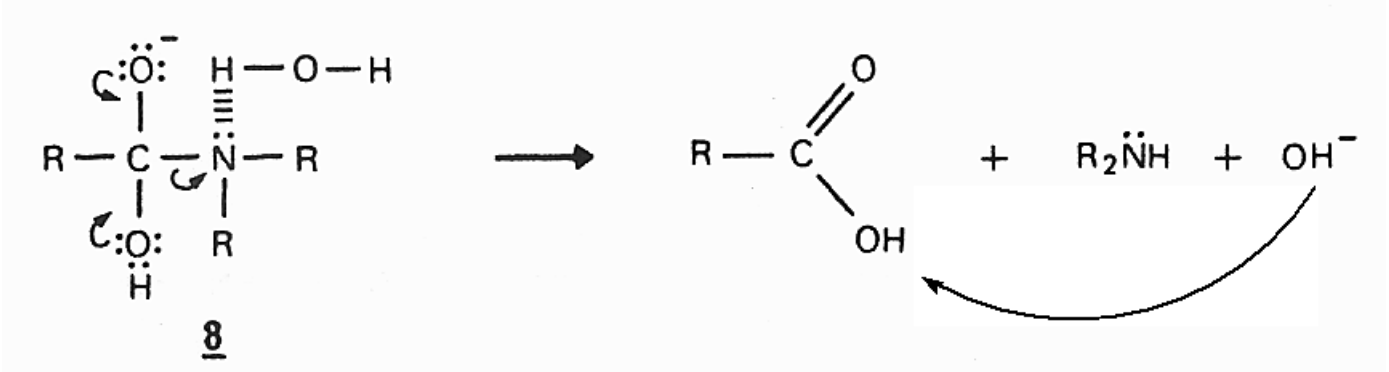



( $R_1$ = H or R )

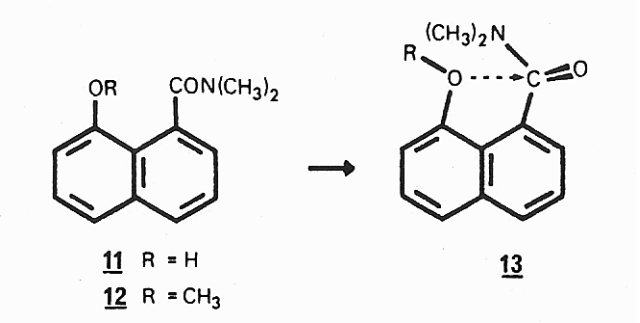
## Ionic Form of Tetrahedral Intermediate and Product Formation




**Also, cleavage of $T^-$ takes place with H-bond with water**

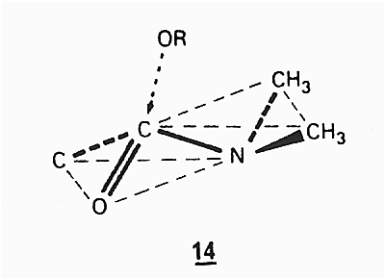


# X-Rays N,N-Dimethyl-8-Hydroxynaphtalene 1-Carboxamide




11 R = H
12 R = $CH_3$

13




14

*Dunitz et al.*

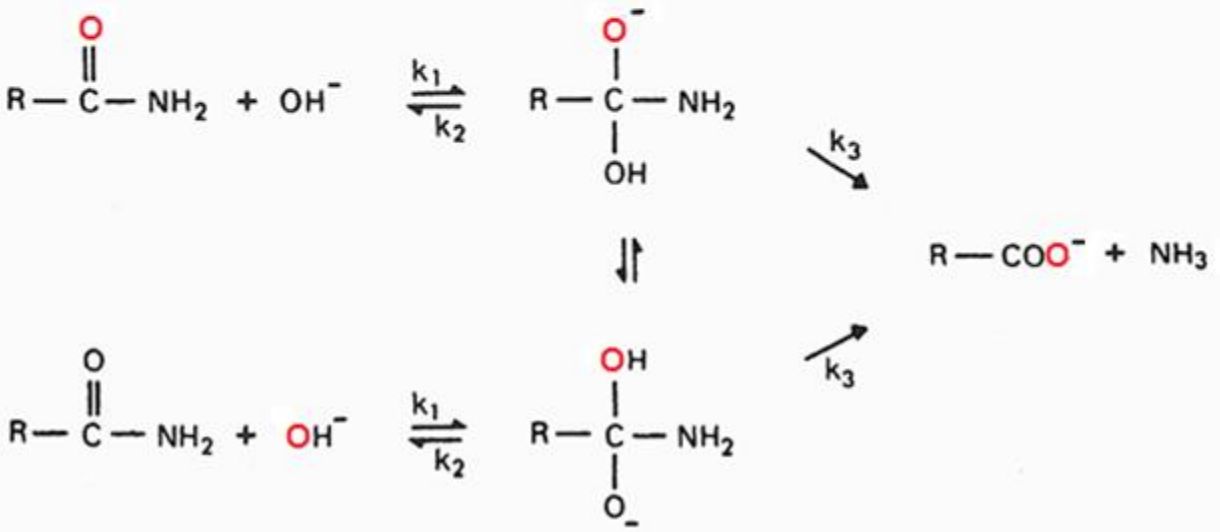
A very interesting observation was made by Dunitz and co-workers (22) in the crystal structure analyses of N,N-dimethyl-8-hydroxynaphthalene 1-carboxamide 11 and the corresponding methoxy derivative 12. The amide function is perpendicular to the aromatic ring, and is splayed outward while the C—OR bond is inward, i.e. toward the carbonyl group (cf. 13). The carbonyl naphthalene bond is bent in such a way to allow a better alignment of the oxygen nucleophile toward the carbonyl amide (5). There is also a small but significant pyramidalization of the carbonyl group carbon as well as the amide nitrogen but in the opposite direction; the carbonyl carbon atom is closest to the nucleophilic oxygen atom while the nitrogen atom displacement is away from it as illustrated in 14. This result is in complete agreement with the principle of stereoelectronic control in hydrolytic reactions.


Burgi, H.B.; Dunitz, J.D. *et al.* J. Am. Chem. Soc. **1973**, *95,* 5065;
Acc. Chem. Res. **1983**, *16*, 153.
Also, Raines, R.T. et al. Org. Lett. 2014, *16,* 3421-3423.

# Carbonyl-Oxygen Exchange Concurrent with Hydrolysis in Amides

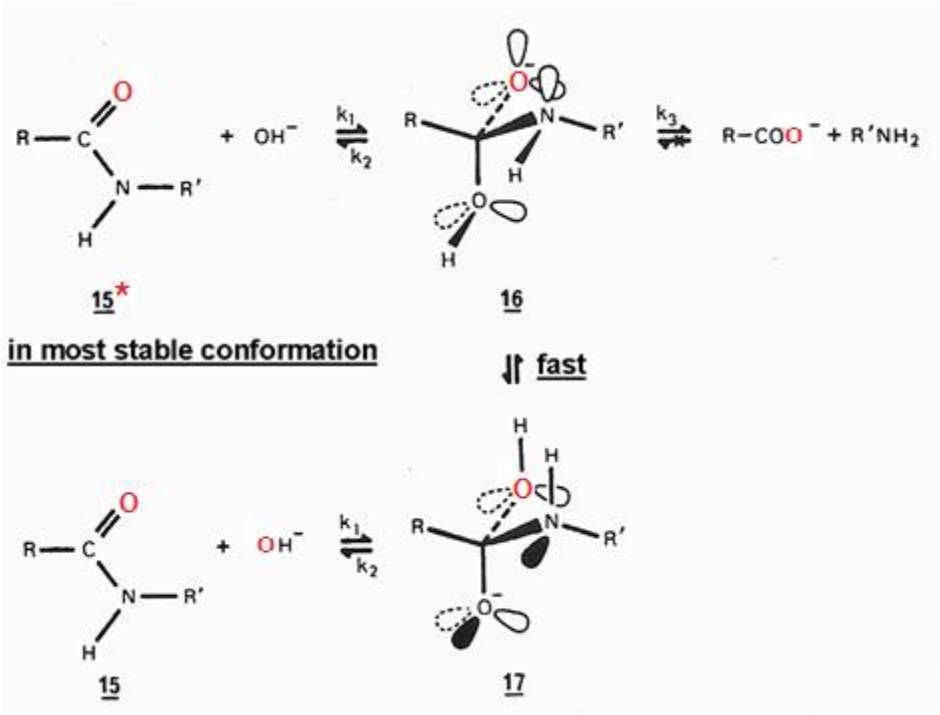
Carbonyl-oxygen exchange concurrent with hydrolysis in amides

Carbonyl-oxygen exchange has been observed in the course of the basic hydrolysis of primary amides (23, 24). The exchange, observed by using $^{18}O$-labeling ( O = $^{18}O$), occurs via a tetrahedral hemi-orthoamide intermediate and the extensive exchange observed was explained by the fact that $k_2$ is larger than $k_3$ because an OH group is a much better leaving group than an $NH_2$ group.




**This technique can be used to demonstrate the importance of the principle of stereoelectronic control in tetrahedal intermediates derived from amides.**

# Carbonyl-Oxygen Exchange in Primary and Secondary Amides and Hydrolysis

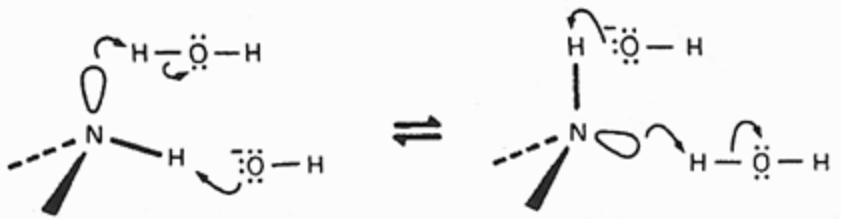



**Résumé:**

**Important $O^{18}$-exchange during hydrolysis because $k_2 >> k_3$**

**Proton-transfer on oxygen or on the nitrogen are allowed because:**

It is assumed that proton transfer on the two oxygens can take place prior to the breakdown of intermediate 16 (R'=H). The same assumption is also made for the proton transfer on the nitrogen. The conversion 16 (R'=H) → 17 (R'=H) is therefore allowed. The proton transfer on the nitrogen can occur with the solvent via the following process.



# Carbonyl-Oxygen Exchange in Tertiary Amides and Hydrolysis

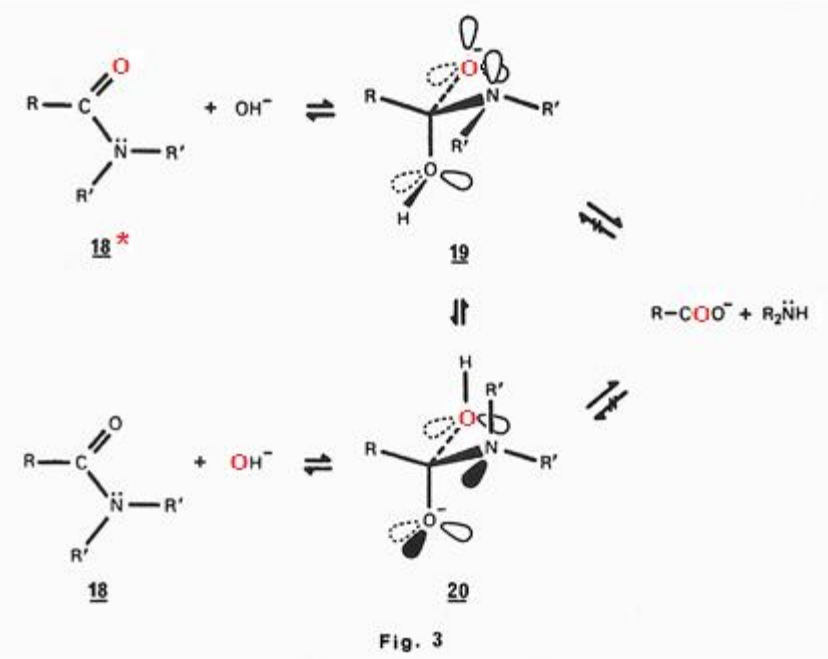
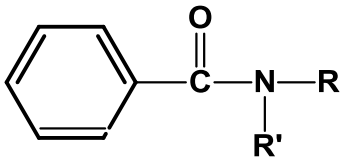



Fig. 3

The stereoelectronically controlled reaction of hydroxide ion with an $^{18}O$-labeled tertiary amide (18*) (Fig. 3) should give the intermediate 19 which can fragment in only two ways, yielding the starting labeled amide 18* or the hydrolysis products; direct cleavage of 19 to give unlabeled amide 18 cannot take place with the help of the primary electronic effect. In order to form the unlabeled amide 18 with stereoelectronic control, intermediate 19 must first be converted into another conformer such as 20. Oxygen exchange in tertiary amides depends therefore on the relative ease with which intermediate 19 can give either intermediate 20 or the hydrolysis products by direct fragmentation. Thus, the main difference between primary, secondary and tertiary amides, is that the first two can undergo $^{18}O$-exchange without invoking a conformational change at the nitrogen in the corresponding tetrahedral intermediate, whereas in the case of tertiary amide, $^{18}O$-exchange will take place only if conformational change at the nitrogen is allowed.

**Résumé: $O^{18}$ Exchange can take place only if conformational change occurs between 19 and 20.**

# $O^{18}$ Exchange and Hydrolysis in Amides (Experimental Results)

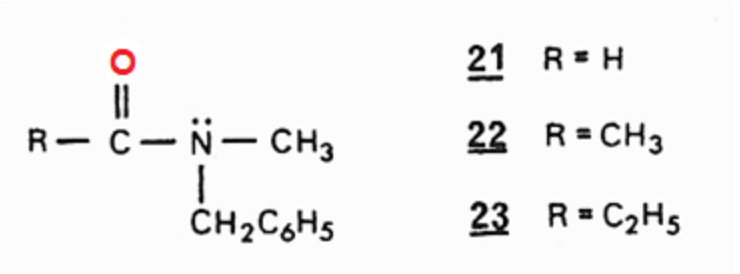



| | Exchange | Hydrolysis |
|---|---|---|
| R = R' = H | yes | yes |
| R = $CH_3$, R' = H | yes | yes |
| R = R' = $CH_3$ | no | yes |

Bunton, Nayak, and O'Connor (27) have studied carbonyl-oxygen exchange during the hydrolysis of a primary, a secondary and a tertiary amide. They have observed that the alkaline hydrolysis of benzamide and N-methylbenzamide but not of N',N-dimethylbenzamide, is accompanied by extensive oxygen exchange between water and the amide. Thus, the tetrahedral intermediate (19, R'=$CH_3$ and R=$C_6H_5$) derived from N,N-dimethylbenzamide fragments more easily than it can undergo conformational change. The fact that there is no carbonyl-oxygen exchange in N,N-dimethylbenzamide constitutes a strong support for the principle of stereoelectronic control because this result can be rationalyzed only if that principle is taken into consideration.

**BUNTON, C.A. *et al.* *J. Org. Chem.* 1968, *33,* 572.**

# Formamide, Acetamide, and Propionamide $O^{18}$ Exchange during Hydrolysis



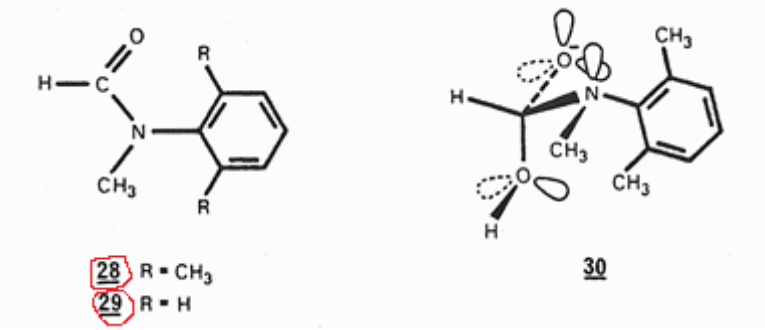
| | | |
|---|---|---|
| **21** | R = H | significant |
| **22** | R = $CH_3$ | little |
| **23** | R = $C_2H_5$ | none |

**The rates of hydrolysis and carbonyl-oxygen exchange was carried out at 27°C with potassium hydroxide (1.5 N).**

It was found that there is significant carbonyl-oxygen exchange in the formamide, very little in the acetamide and apparently none in the propionamide. Thus, as the R group increases in size (R=H, $CH_3$, $C_2H_5$), carbonyl-oxygen exchange is less favored. This observation can be readily explained. In intermediate 19, the barrier for internal rotation or inversion of the amino group should be lower when R is small and higher when R is large. At the same time, the energy barrier for the breakdown of 19 should be higher when R is small and lower when R is large. When R is a large group, it should favor the breakdown of the intermediate due to steric decompression. The reverse of this steric decompression effect is the classical steric hindrance caused by the size of the R group in esters (R−COOR') and amides ($R-CONR'_2$) which influences the rate of hydrolysis. For instance, formamides are hydrolyzed more rapidly than acetamides.

**DESLONGCHAMPS, P. *et al.* *Nouv. J. Chim.* 1978, *2,* 631.**

# Importance of H-bond (from Water) to Nitrogen in the Hydrolysis of Amide



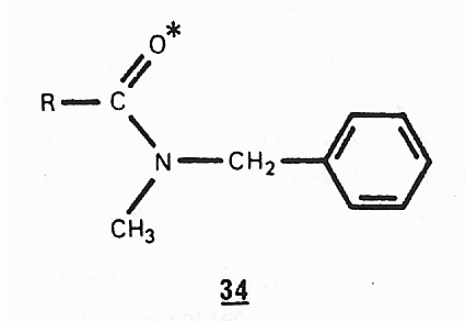

A clear demonstration of the importance of a hydrogen bond to the nitrogen was obtained by studying N-2,6-dimethylphenyl-N-methylformamide (28) (14) and N-methyl-N-phenylformamide (29). The essential difference between these two formamides is believed to be that in 28, contrasting to 29, the benzene ring is not conjugated with the amide function. The benzene ring in 28 is perpendicular to the plane of the amide function. X-Ray analysis of an imidate salt derived from 28 supports this assignment (vide infra, p. 121). Interestingly, formamide 28 does not hydrolyze (0.15 N, KOH, 90°C, 70 h) but undergoes considerable carbonyl-oxygen exchange (>90%). This is in contrast with N-methyl-N-phenylformamide (29) where the hydrolysis as well as the carbonyl-oxygen exchange proceeded with ease. Formamide 28 must form the tetrahedral intermediate 30 as it undergoes carbonyl-exchange.

| Résumé | $O^{18}$-Exchange | Hydrolysis |
|---|---|---|
| 28 | yes | no |
| 29 | yes | yes |

DESLONGCHAMPS, P. *et al.* *Nouv. J. Chim.* 1978, *2*, 631.

## Rate of Hydrolysis and Carbonyl-Oxygen Exchange in N-benzyl N-methylated Amides

**(R = H, R = $CH_3$ and R = $CH_2C_6H_5$) were carefully measured at several temperatures**

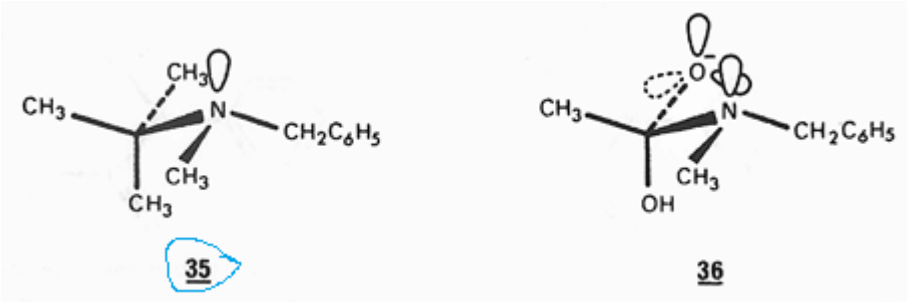



34

| R | $\Delta G^{\#}$cleav | $\Delta G^{\#}$exch (kcal) | |
|---|---|---|---|
| H (formamide) | **5.2** | **5.8** | |
| $CH_3$ (acetamide) | **6.2** | **8.0** | no exchange |
| $C_2H_5$ (propionamide) | **6.5** | **8.2** | no exchange |

**In formamide, the rate of exchange is only slightly lower than that for hydrolysis whereas in the case of acetamide and propionamide, the exchange occurs at a significantly lower rate.**

**Thus, rate of exchanges is directly related to rate of conformational change.**



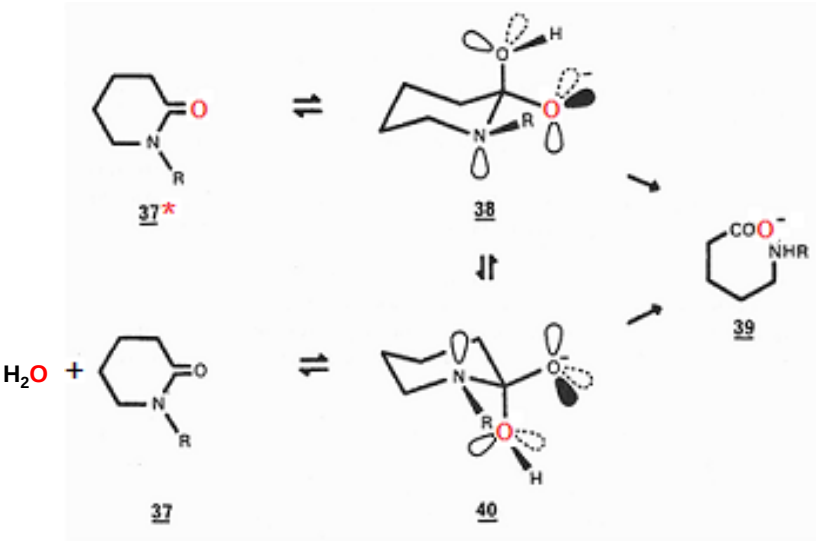

35 36

**In 35, rotation barrier and nitrogen inversion barrier are identical and estimated at 6.2 kcal/mol.**

**In 36 (i.e., acetamide 34), the higher value of 8.0 kcal/mol is a consequence of an anomeric effect (double bond character in the C-N bond ($n_N$ — $\sigma^*_{C\text{-}O}$).**

**DESLONGCHAMPS, P. *et al.* *Can. J. Chem.* 1980, *58,* 2167.**

# $O^{18}$-Exchange and Basic Hydrolysis in Lactams




Lactam (R = alkyl or H) cannot undergo $O^{18}$-exchange concurrent with hydrolysis because conformational change between 38 and 40 is too high in energy. Indeed, basic hydrolysis (NaOH, N) occurs at room temperature but no $O^{18}$ -exchange.

**N.B. Thus, contrary to secondary amide (*Z*-amide), there is no $O^{18}$-exchange in secondary lactam (*E*-amide).**

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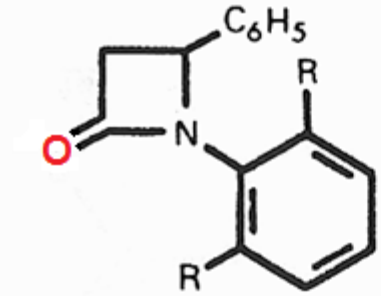
**DESLONGCHAMPS, P. *et al.* *Nouv. J. Chim.* 1977, *1,* 235.**

# Concurrent $O^{18}$-Exchange and Hydrolysis in β-Lactam




| | | $O^{18}$- Exchange | Hydrolysis |
|---|---|---|---|
| 41 | R = H | no | *fast* |
| 42 | R = $CH_3$ | yes | *very slow* |

42 is hydrolyzed at a much lower rate (hindrance to H-bond with $H_2O$)

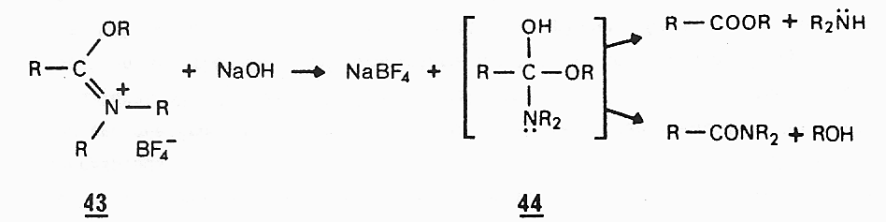
42 undergoes $O^{18}$-exchange ($K_2 >> K_3$) (cannot form amino acid)

41 does not undergo $O^{18}$-exchange ($K_3 >> K_2$) (β-lactam steric strain)

DESLONGCHAMPS, P. *et al. Can. J. Chem.* 1980, *58,* 2061.

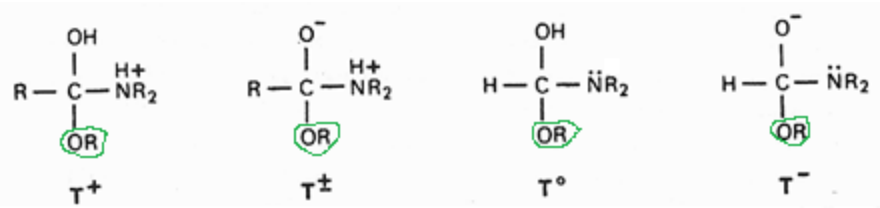
# Hydrolysis of Imidate Salts

Imidate salts are O-alkyl derivatives of tertiary amides. Being activated tertiary amides, they are extremely reactive towards nucleophiles. There is instantaneous reaction with hydroxide ion; they also react rapidly at room temperature with water under acidic conditions. When an imidate fluoroborate salt such as **43** reacts with sodium hydroxide, it gives sodium fluoroborate and the tetrahedral intermediate **44** which breaks down in an irreversible manner to yield the products of the reaction which can be either the corresponding ester and amine or amide and alcohol. The formation of **44** has been verified with $^{18}O$-labeling experiments.




**43** **44**

## Ionic form of tetrahedral intermediates

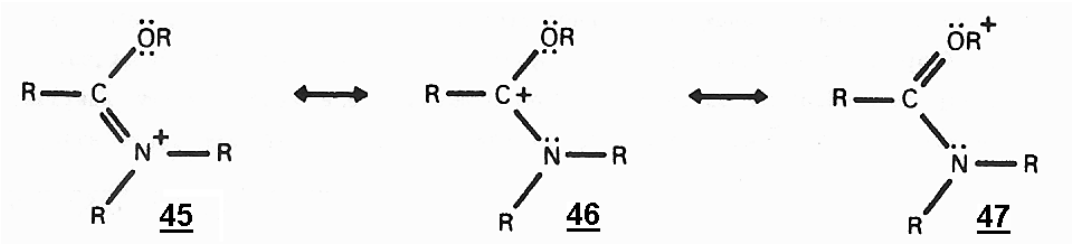


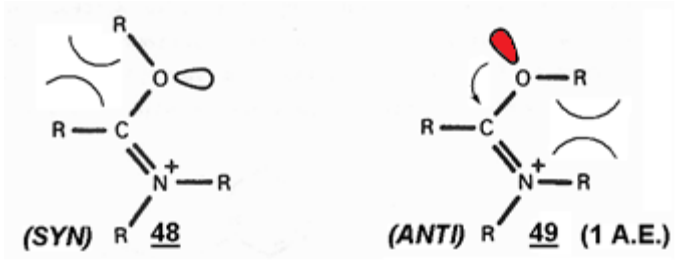

**amine ester**

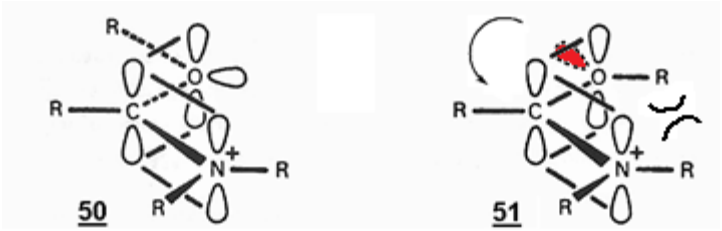
**amine ester or amide alcohol**

# Stereoelectronic Effects in Imidate Salts

**Resonance form**




**Stereoelectronic effects**

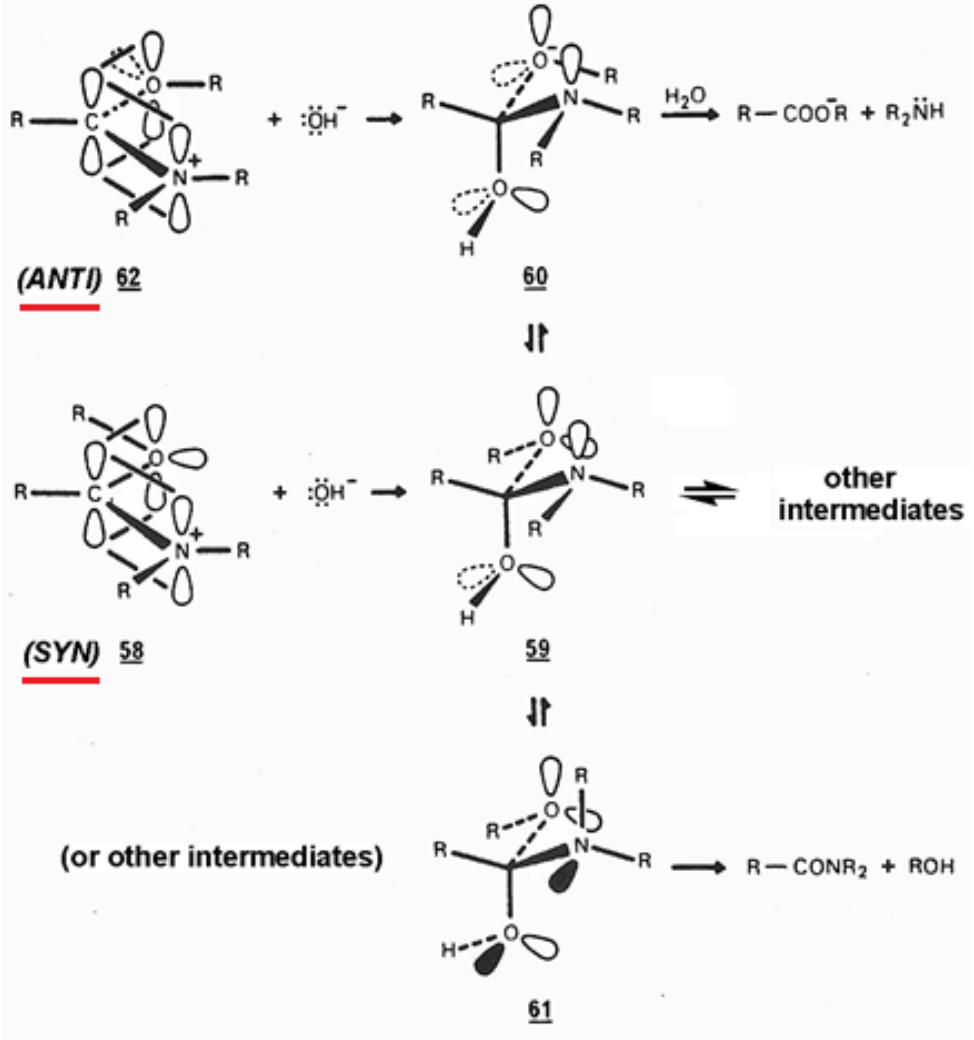
$\pi$
$\pi^*$

$\pi$
$\pi^*$
$n_O \text{—} \sigma^*_{C\text{-}N}$

**Steric effects**

**In the *anti* form, there is a severe steric interaction between the R group on the oxygen and one of the R groups on the nitrogen atom. In the *syn* form, there is a steric interaction between the R group of the oxygen and the R group on the carbon atom.**

# Hydrolysis of Imidate Salts in Basic Medium



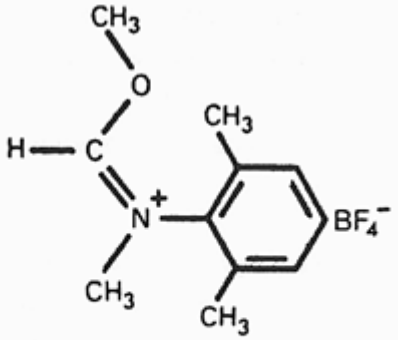

The stereoelectronically controlled reaction of the syn imidate salt 58 (Fig. 5) with hydroxide ion must give specifically conformer 59, in which the nitrogen and the oxygen of the OR group have each an electron pair antiperiplanar to the C—OH bond; also, the R groups on the central carbon and on the oxygen atom which were syn in 58 are gauche in 59.

Intermediate 59 cannot eject the OR or the $NR_2$ group with stereoelectronic control. It is therefore assumed that the energy barrier for the fragmentation of 59 is too high and this process cannot compete with internal molecular rotation. Thus, 59 would undergo conformational changes either at the OR or $NR_2$ groups yielding in principle a mixture of the nine conformers described in Fig. 1 (p. 104, where 59 corresponds to conformer G). Thus, a syn imidate salt would first form intermediate 59 which is then converted into a mixture of several conformers some of which give the ester and amine, others the amide and alcohol products. For example, intermediate 59 would give intermediate 60 by rotation of the OR group and intermediate 61 by rotation of the $NR_2$ group. A stereoelectronically controlled fragmentation of the $T^-$ ionic form of 60 can only give the ester and amine products whereas that of 61 can only yield the amide and alcohol products. Thus, the basic hydrolysis of syn imidate salts should give ester and amine plus amide and alcohol as products.

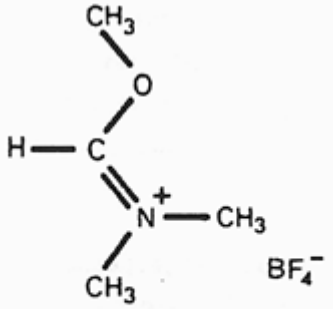
The stereoelectronically controlled reaction of hydroxide ion with an anti imidate salt (62) must give the hemi-orthoamide conformer 60 where the nitrogen and the oxygen of the OR group have each an electron pair antiperiplanar to the C—OH bond; also, the O—R bond and the N—R bond which were antiperiplanar to the C—R bond in anti imidate salt 62 remain in the same relative orientation in intermediate 60.

# Relative Stability of *Syn* and *Anti* Conformation in Imidate Salts

When the R group on the carbon atom is small (R=H), the steric interaction in the syn form is minimized and this form predominates. X-Ray analysis (32) of imidate salt 52 of N-2,6-dimethylphenyl-N-methylformamide confirms this conclusion and further shows that the 2,6-dimethylphenyl group is orthogonal to the imidate function. It was also shown (11, 15, 33) by a nuclear Overhauser effect study that the formamide imidate salt 53 exists in the syn form in solution.




52 X-rays

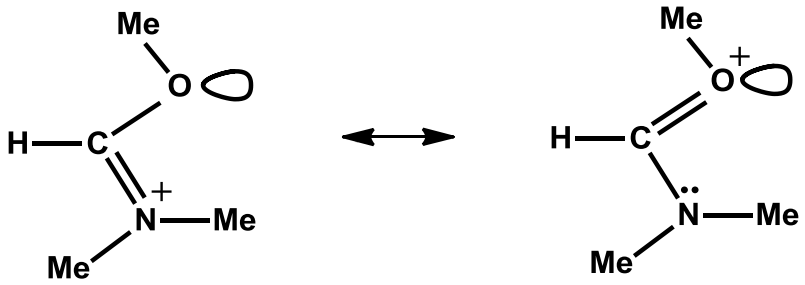



53 NMR (NOE)

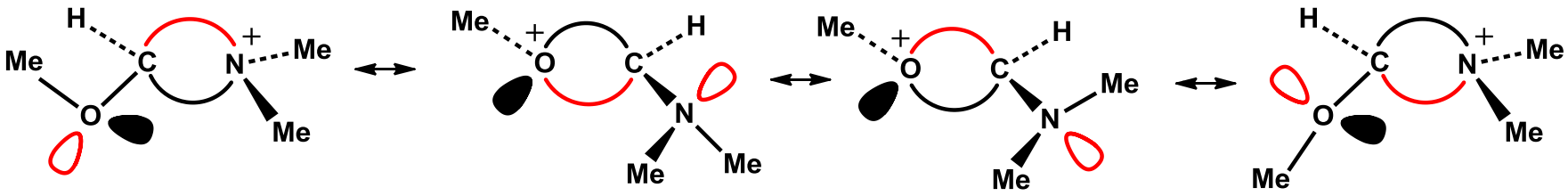
When the R group linked to the carbon atom is a large group (such as a t-butyl or a phenyl group conjugated with the imidate function), it is assumed that the anti form predominates. When that R group is of an intermediate size ($R=CH_3$ or cyclohexyl), it is assumed that there is a mixture.

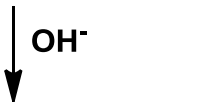
**DESLONGCHAMPS, P. *et al.* *Nouv. J. Chim.* 1979, *3,* 343.**

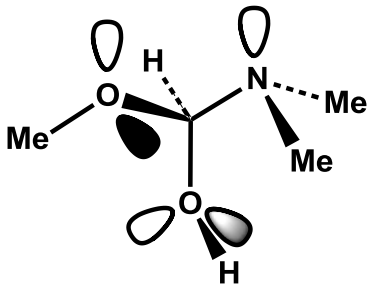
# τ Bond, Syn Imidate Salts and Hydrolysis




more important



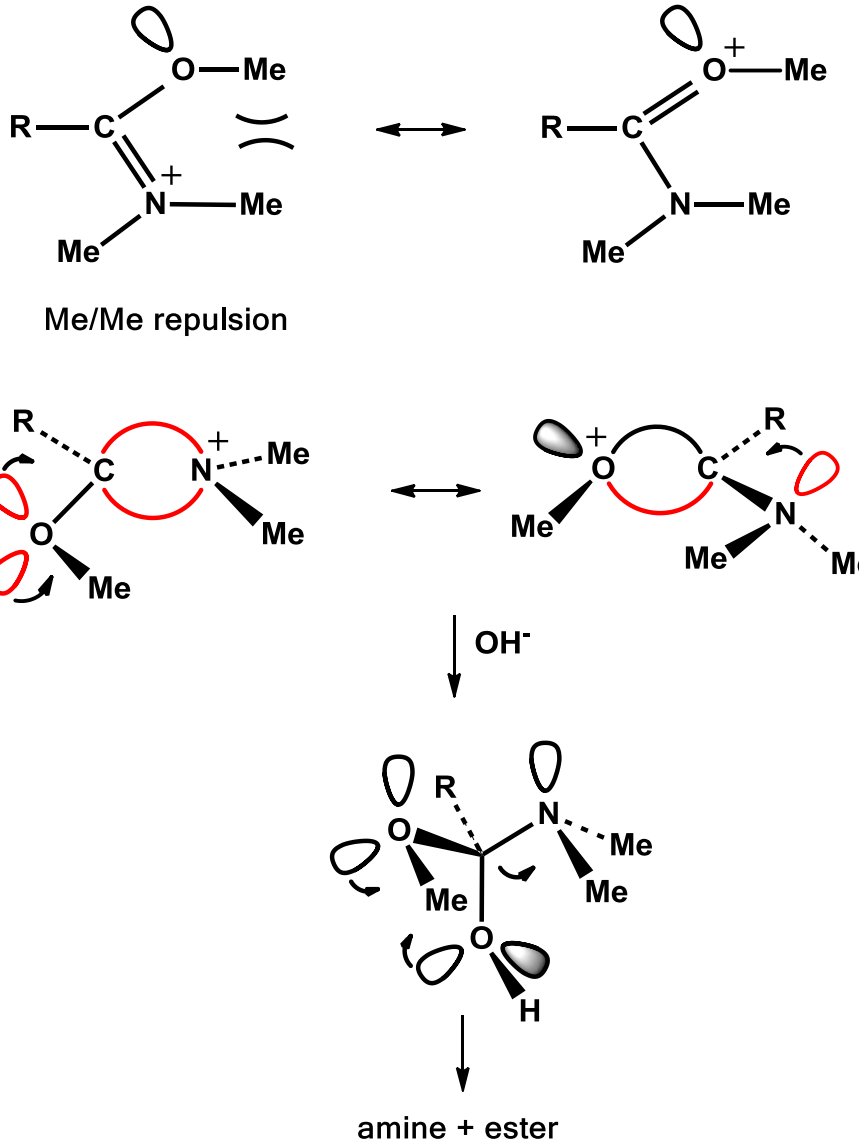



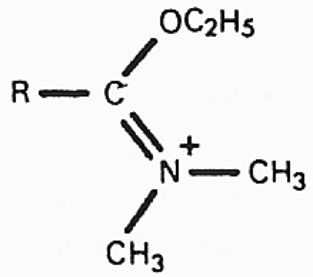

cannot breakdown

rotation & cleavage

## τ Bond, Anti Imidate Salts and Hydrolysis



# Hydrolysis of Imidate Salts at pH 11




| | | Products | |
|---|---|---|---|
| | | amide alcohol | ester amine |
| 63 | R = H | 50 | 50 |
| 54 | R = $CH_3$ | 20 | 80 |
| 55 | R = $C_6H_{11}$ | 25 | 75 |
| 56 | R = $C_6H_5$ | - | 100 |
| 57 | R = $(CH_3)_3C$ | - | 100 |

The results of hydrolysis of these imidate salts as a function of pH are the following: at pH 8.5 or lower, the imidate salts 54 and 55 yield the ester and amine products exclusively. At pH greater than 8.5, they start to produce the amide and alcohol products which reach a maximum yield at pH 11 (20% for 54 and 25% for 55), and this yield remains unchanged at higher pH. The imidate salts 56 and 57 behaved completely differently as they give exclusively the ester and amine products over the entire range of pH values.

**Thus, 56 and 57 are assumed to be 100% *anti* imidates.**

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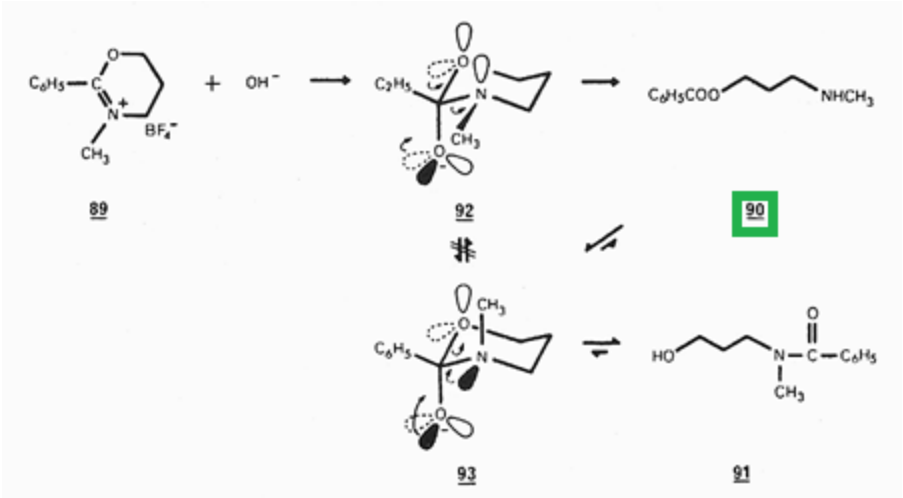
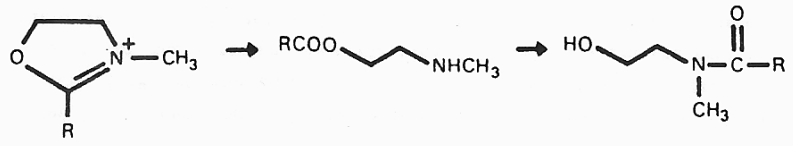
**DESLONGCHAMPS, P. *et al.* *Can. J. Chem.* 1975, *53,* 3029.**

# Hydrolysis of Cyclic *Anti* Imidate Salts




The six-membered imidate salt 89 where the anti conformation is assured by its cyclic structure, gave first under basic conditions, only the aminoester 90. The aminoester 90 was then slowly converted into the thermodynamic product of the reaction, i.e. the benzamido-alcohol 91. The reaction of imidate salt 89 with hydroxide ion must first give intermediate 92 following the principle of stereoelectronic control. It can also be seen that 92 can only give the aminoester 90 by following the same principle. Thus, the nitrogen inversion process to give 93 which can then yield the benzamidoalcohol 91 cannot compete with the breakdown of 92. The slow appearance of benzamidoalcohol 91 would be due to the slow formation of intermediate 93 from aminoester 90.

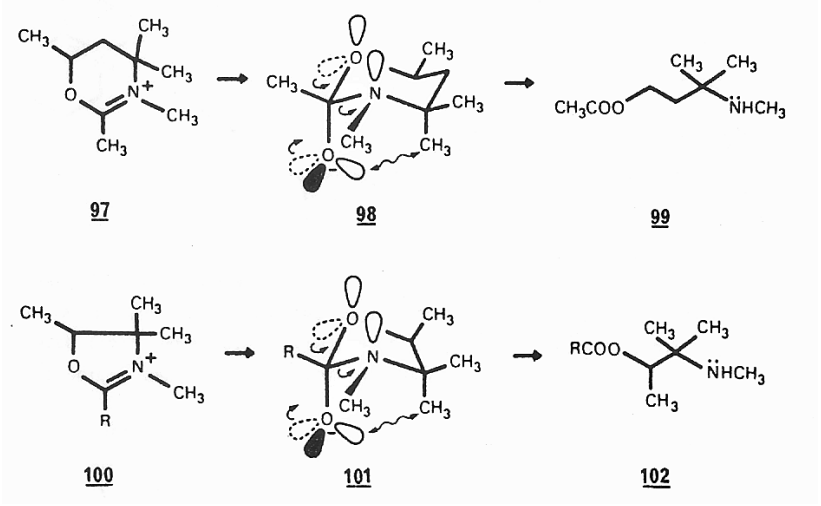
Similar studies were carried out (33) with cyclic imidate salts 94 (R=$C_6H_5$ or $CH_3$). They behaved like imidate salt 89, yielding first the aminoester 95 followed by the slow formation of the thermodynamic product, i.e. the corresponding amidoalcohol 96.





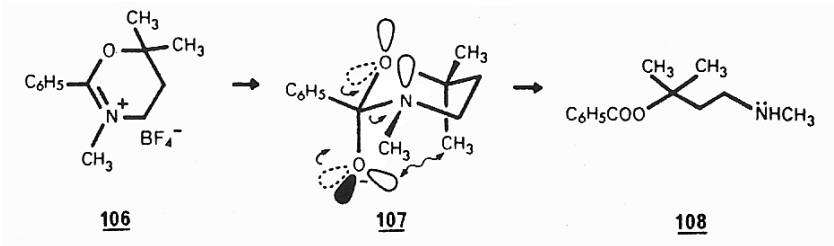

DESLONGCHAMPS, P. *et al. Can. J. Chem.* 1973, *51,* 1665; 1975, *53,* 2791.

# Other Examples of *Anti* Imidate Salts Hydrolysis




Imidate salt 97 also gave the aminoester 99 (33). Allen and Ginos (34) have reported that the basic hydrolysis of imidate salts 100 (R=$CH_3$, $C_2H_5$ or $(CH_3)_3C$) yielded only the corresponding aminoester 102.

There are two factors which help the cleavage of the C — N bond in the hydrolysis of imidate salts 97 and 100. Imidate salt 97 should form the intermediate 98 which has proper electron pair alignment to yield the aminoester 99. Also, in 98 there is a 1,3-diaxial steric interaction between the OH group and one of the methyl groups which should promote the cleavage of the carbon-nitrogen bond. Similarly, compound 100 should give intermediate 101 in which there is again a strong steric interaction. This, combined with the stereoelectronic effect, favors the carbon-nitrogen bond cleavage.

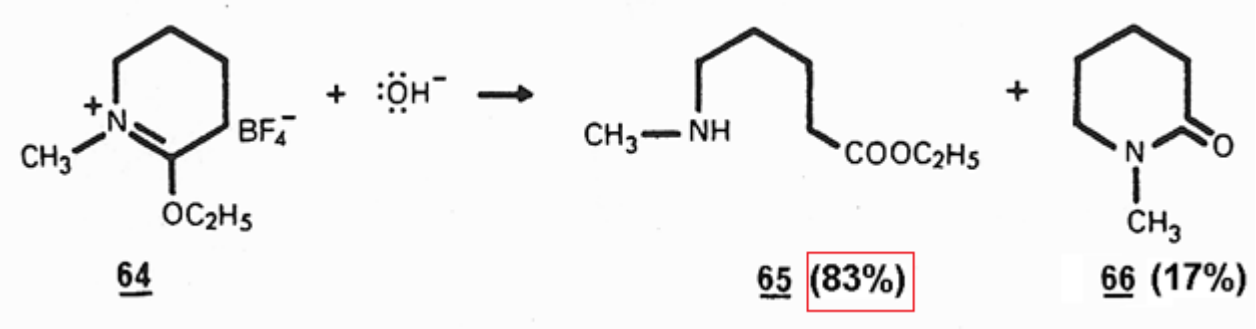



The reaction of hydroxide ion with imidate 106 should give the intermediate 107 in which stereoelectronic control promotes the cleavage of the C — N bond, while the 1,3-diaxial methyl-hydroxyl steric interaction favors the cleavage of the C — O bond. Hydrolysis of 106 gave exclusively the aminoester 108 (33); thus, stereoelectronic effects still control this reaction despite an important steric effect which favors the C — O bond cleavage.


**ALLEN and GINOS.** ***J. Org. Chem.*** **1963, *28,* 2759.**

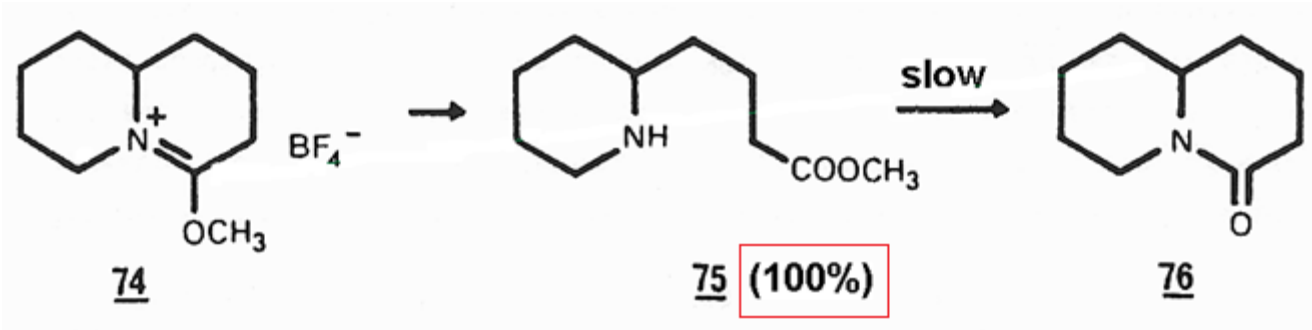
**DESLONGCHAMPS, P. *et al.* *Can. J. Chem.* 1975, *53,* 2791.**

# Basic Hydrolysis of Imidates 64 and 74




64 65 (83%) 66 (17%)

**Whereas:**

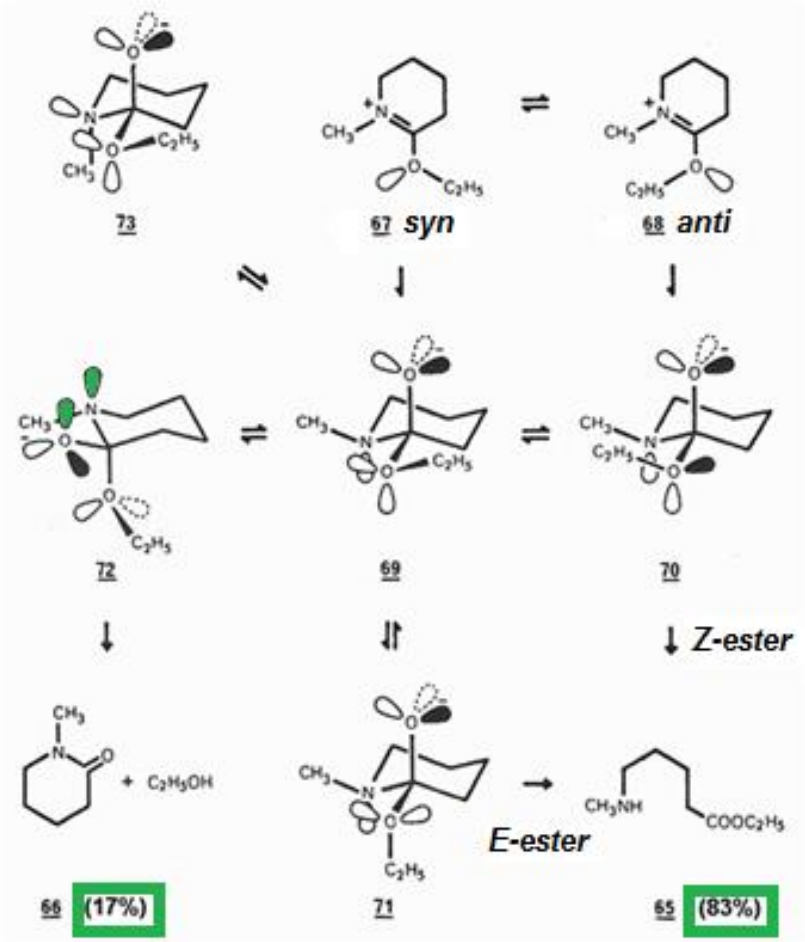



74 75 (100%) 76

**74 is a bicyclic version of 64. Why is there a difference !**

**DESLONGCHAMPS, P. *et al.* *Can. J. Chem.* 1975, *53,* 2791.**

# Imidate 64 can Exist as a Mixture of *Syn* (67) and *Anti* (68) Conformers



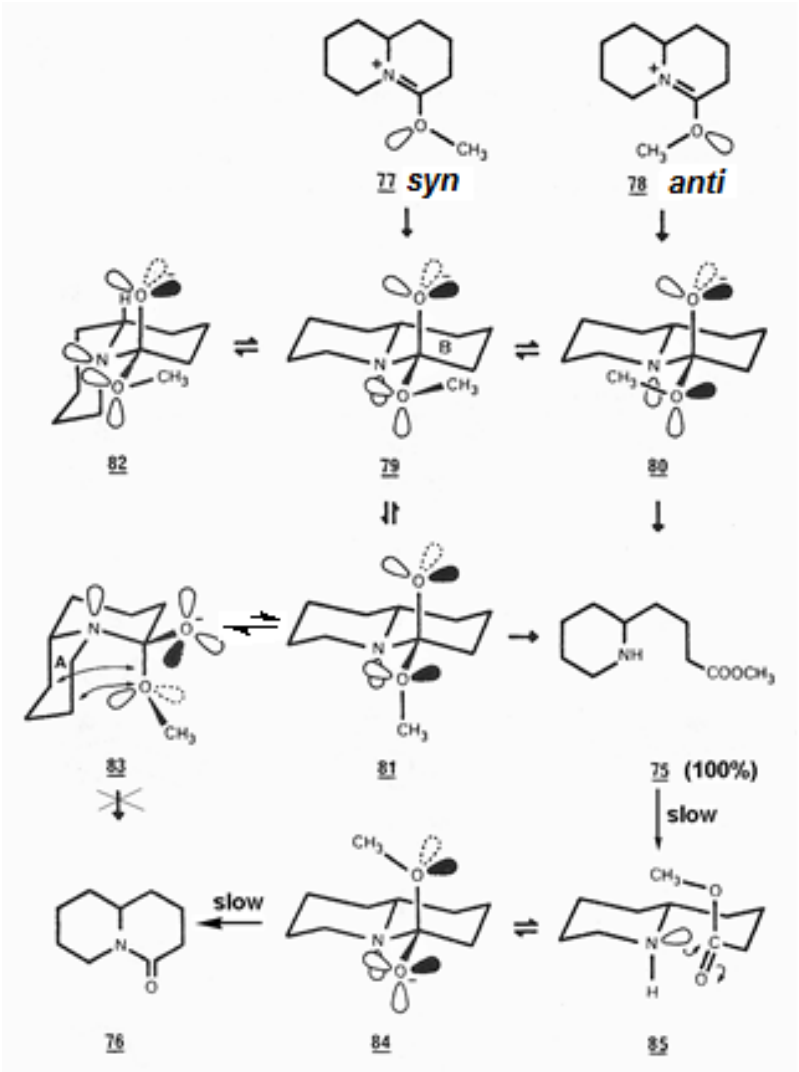

The basic hydrolysis of imidate salt 64 was carried out (33), and it gave a mixture of aminoester 65 (83%) and N-methylpiperidone (66) (17%). This result can be explained in the following way. Assuming that this salt exists as a mixture of the syn and anti forms 67 and 68 (Fig. 6), these two isomeric forms would give the tetrahedral conformers 69 and 70 respectively. Conformer 70 can yield the aminoester 65 with stereoelectronic control whereas conformer 69 cannot break down. Thus, 69 would either be converted into 70 and 71 by rotation of the ethoxy group or undergo a chair inversion to conformer 72. Interestingly, 71 as well as 70 which come from the rotation of the ethoxy group can only give the aminoester 65, whereas conformer 72 which comes from the chair inversion can give N-methylpiperidone (66). The chair inversion should be a higher energy process than the ethoxy group rotation and on that basis a large percentage of aminoester is expected. Note that a simple nitrogen inversion in 69 yields the intermediate 73 which cannot break down with stereoelectronic control.

**Résumé:**

**Lactam 66 can be produced only from intermediate 72 which must be obtained from a chair inversion of intermediate 69.**

**DESLONGCHAMPS, P. *et al.* *Can. J. Chem.* 1979, *57,* 3262.**

# Imidate 74 can Exist as a Mixture of *Syn* (78) and *Anti* (78) imidates

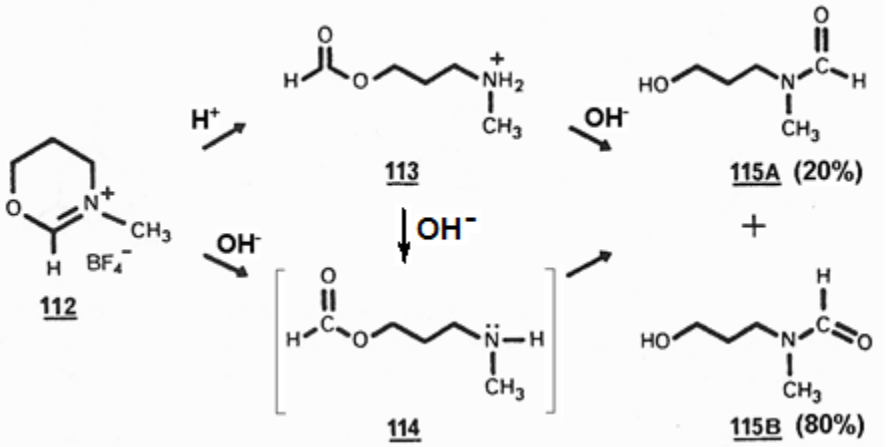



Contrary to 64, bicyclic imidate salt 74 gave first only the aminoester 75 (33). The bicyclic lactam 76 appeared only after a certain time in the reaction mixture, indicating that the aminoester 75 is clearly the exclusive kinetic product of the rotation. As in the case of imidate salt 64, the bicyclic imidate salt must exist as a mixture of the syn and anti isomeric forms 77 and 78 (Fig. 7). The reaction of hydroxide ion with 77 and 78 must give the intermediates 79 and 80 respectively. Intermediate 80 can yield the aminoester 75. Intermediate 79 cannot break down with stereoelectronic control; it will therefore be converted into 80 or 81 which can also fragment to give the aminoester 75. Intermediate 79 can also undergo a nitrogen inversion by inverting ring A or ring B giving respectively intermediate 82 or 83. Intermediate 82 cannot undergo a C—N bond cleavage with stereoelectronic control. Intermediate 83 can yield the bicyclic lactam 76 with stereoelectronic control, but this intermediate has a severe steric interaction between the axial methoxy group and ring A. The formation of 80 or 81 from 79 should be a much easier process than that of 83, and on that basis, imidate salt 74 should give exclusively the aminoester 75, in agreement with the experimental result.

**Résumé:**

**Lactam 76 can first be produced only from the sterically hindered 83, so, it is not observed. It can be slowly produced only from amino-ester 75 (85 to 84 to 76).**

# Peculiar Behavior of Hydrolysis of Imidate Salt 112




Under basic conditions, the hydrolysis of imidate salt 112 at 0°C gave a mixture (2:8) of the amidoalcohol rotamers 115A and 115B as the kinetic products of the reaction. Isomerization followed to yield the equilibrium ratio (4:6) of 115A and 115B. Imidate 112 is the first anti imidate salt which does not give the anticipated product, i.e. the aminoester 114. However, being a formate, thus a reactive ester, it is possible that under the reaction conditions, 114 recyclizes rapidly to give new tetrahedral intermediates which then yield a 2:8 mixture of amide rotamers 115A and 115B. This was proven by showing that the treatment of ester ammonium salt 113 under the same basic conditions led directly to a 2:8 mixture of 115A and 115B.

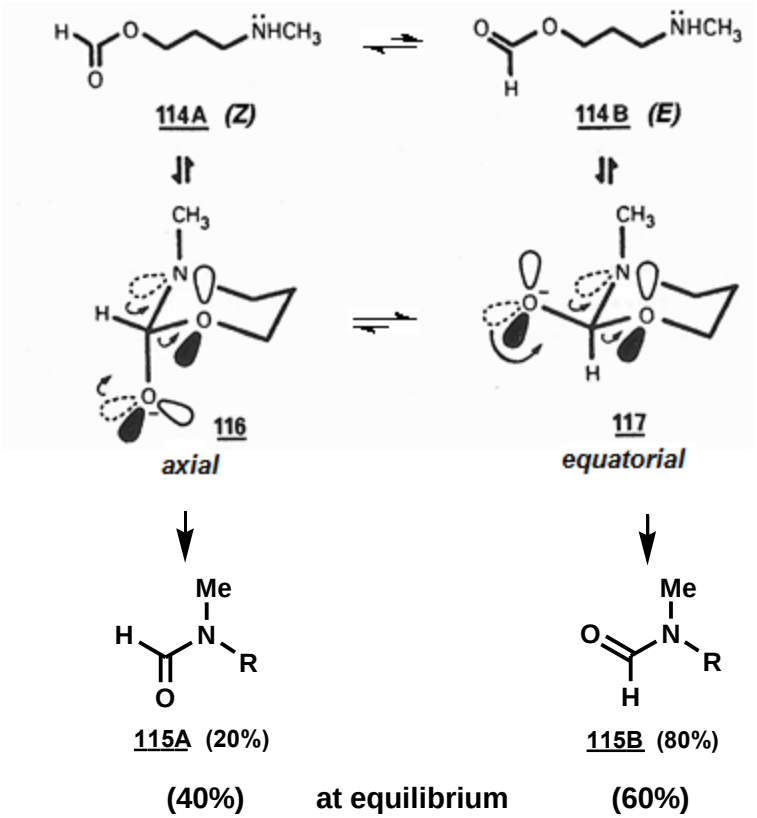
**Résumé:**

**112 gives directly amide alcohol 115 under basic conditions because it gives first amino ester 114 which then yields 115A and B in 2:8 ratio.**

# Specific Formation of Rotamers 115A and 115B

**Why aminoester 114 yields a 2:8 mixture of amide rotamers**

**114A and 114B which then slowly isomerizes to produce the equilibrium mixture (4:6) ?**

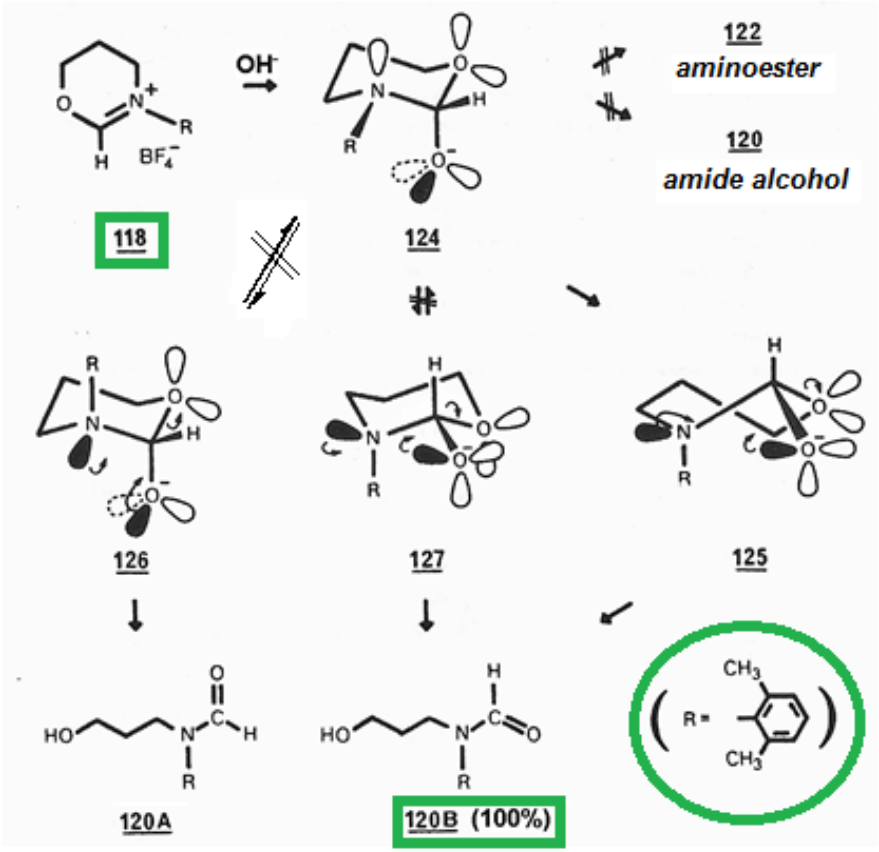



**N.B.** ***Z*** **ester 114A is more stable than** ***E*** **ester 114B.**

**However,** ***E*** **esters are more reactive.**

**This does explain why the amide rotamer 115B is preferentially formed under kinetically controlled conditions.**

# …Peculiar Behavior of 118 Under Basic Conditions




The basic hydrolysis of imidate salt 118 takes a different course from that of imidate salt 112, yielding first only the amide rotamer 120B which is then slowly isomerized to the equilibrium mixture (ratio 3:1) of 120A and 120B. Treatment of the ester ammonium salt 119 under the same basic conditions gave directly the aminoalcohol 123. This result shows that the aminoester 122 is not an intermediate in the basic hydrolysis of imidate 118. The formation of the amide rotamer 120B is therefore the result of the direct fragmentation of a tetrahedral intermediate which is formed from 118.

The two methyl groups on the phenyl ring of imidate salt 118 are responsible for its different reactivity by comparison with the other anti imidate salts. These two groups create enough steric hindrance in the resulting tetrahedral intermediate that the tertiary nitrogen cannot be hydrogen-bonded with the solvent and the cleavage of the C — N bond is prohibited. Thus, the reaction of hydroxide ion on imidate 118 must give intermediate 124 (Fig. 8). Intermediate 124 cannot break down with stereoelectronic control to yield the amidoalcohol 120, and it cannot give the aminoester 122 because the nitrogen cannot form a hydrogen-bond with the solvent.

Intermediate 124 will have to undergo a conformational change to cleave with stereoelectronic control. In 124, there is a very severe steric interaction between the hydroxyl and the 2,6-dimethylphenyl groups which can be lessened on going from 124 to the half boat 125. This steric interaction would be the main driving force for the specific conversion of 124 into 125 which has proper electron pair orientation to cleave the C — O bond and to produce exclusively the amide rotamer 120B. The half boat 125 would be formed in preference to intermediate 126 (via nitrogen inversion) or 127 (via a chair inversion) because these intermediates have the bulky R group on the nitrogen axially oriented. Note also that 126 and 127 lead to amide rotamers 120A and 120B respectively. The chair inversion process which leads to 127 with an axial R group cannot be a lower energy process than the nitrogen inversion which gives 126 also with an axial R group. Thus, because the amide rotamer 120B is the only product observed experimentally, intermediates 126 and 127 must be eliminated.

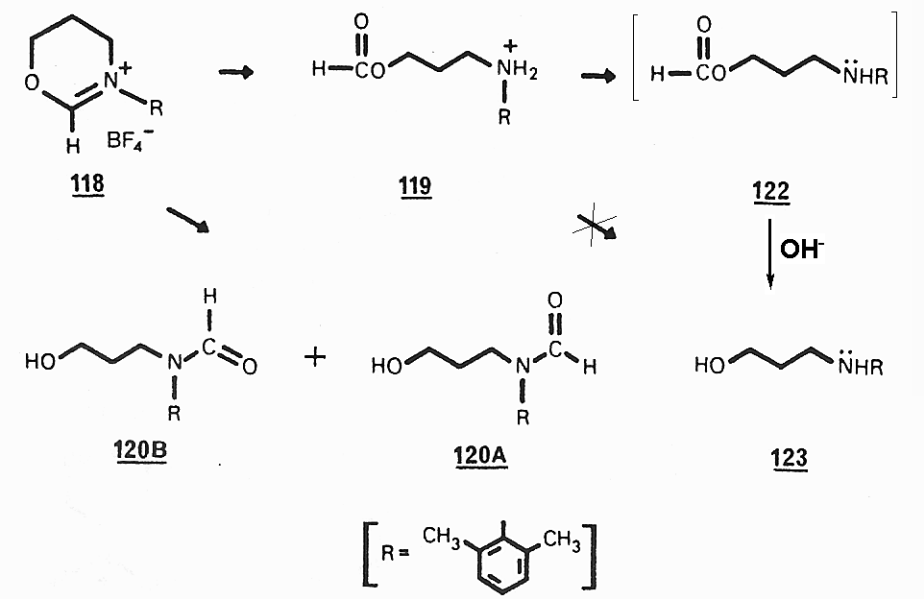
**Résumé:**

**118 gives 120B (100%) via 125.**

**120B then slowly equilibrates to 120A and 120B (3:1).**

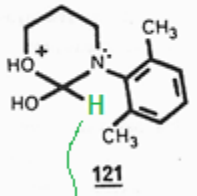
**Amino-ester cannot be formed due to steric hindrance to hydrogen bond formation with nitrogen.**

# Even More Peculiar Behavior of Imidate Salt 118 in Acidic Conditions




The imidate salt 118 (R=$(CH_3)_2C_6H_3$–) behaved in a completely different manner from the salt 112. Under acidic conditions, it yielded a ≈1:1 mixture of ester ammonium salt 119 and the amidoalcohol 120. Again, the hydrolysis is a slow process, and it could be observed (at the beginning of the reaction) that the amidoalcohol was first formed as the least stable rotamer 120B only. Rotamer 120B was then slowly isomerized to give an equilibrium mixture of 120A (67%) and 120B (33%).

The behavior of imidate 118 under acidic conditions can be readily explained by the presence of the two methyl groups on the phenyl ring which create an important steric hindrance to protonation of the nitrogen atom in the resulting tetrahedral intermediate. The salt 118 reacts with water to give first a tetrahedral intermediate in the neutral T° form. However, the conversion of T° into the $T^{\pm}$ or $T^{+}$ ionic form does not occur readily. So, the intermediate gives in part the ester ammonium salt 119 via $T^{+}$ or $T^{\pm}$ and in part the amidoalcohol 120 via T° or more likely via T° protonated on the OR group as in 121. The specific production of rotamer 120B is discussed below.




due to the presence of small H, there is less steric hindrance to protonation of nitrogen

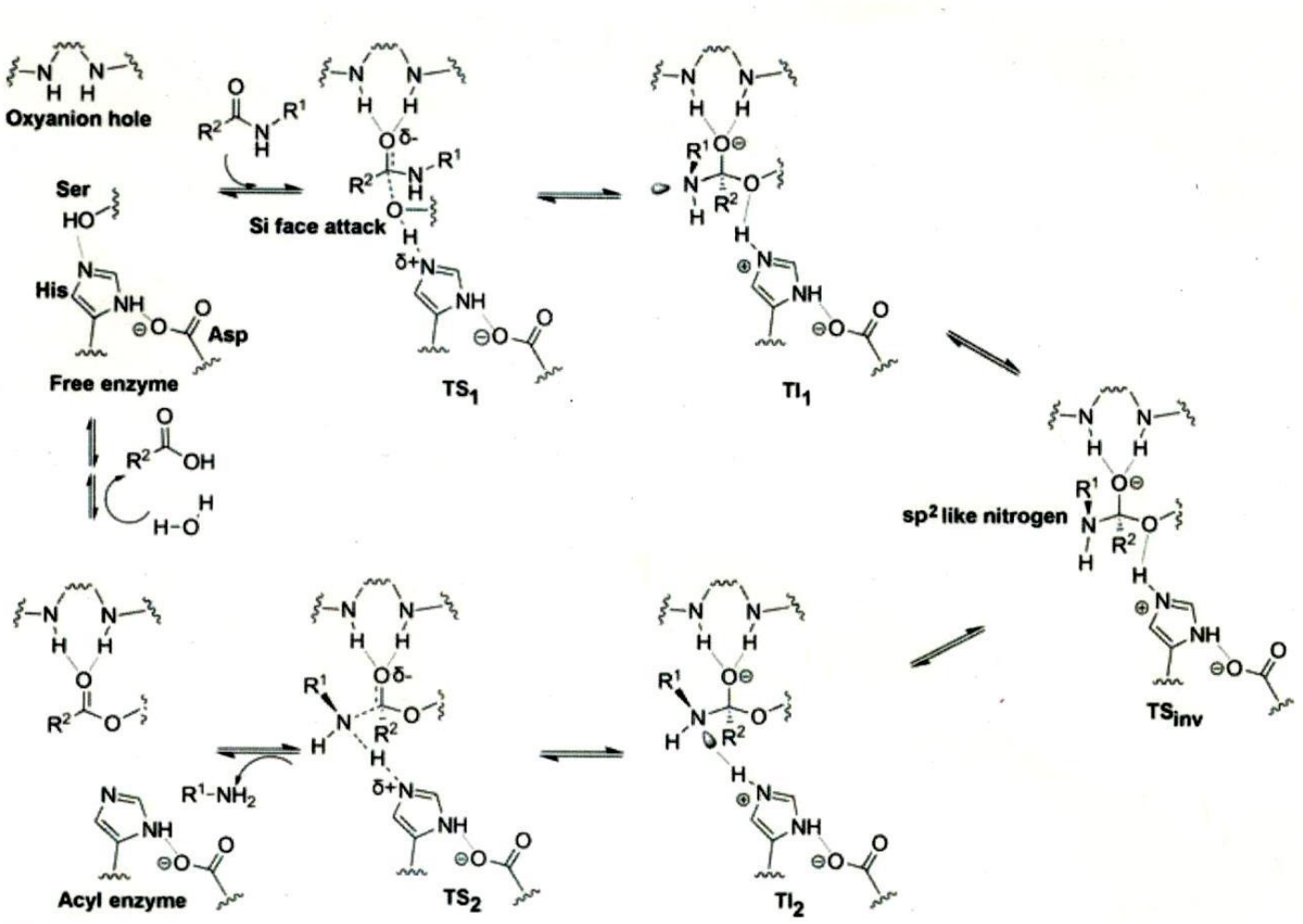
**Résumé:**

**Due to hindrance to protonation, a mixture of amide-alcohol and amino-ester is produced in acidic conditions.**

**Also, amide-alcohol is first produced only as rotamer 120B.**

**DESLONGCHAMPS, P. *et al.* *Can. J. Chem.* 1979, *57,* 3262.**

# Nitrogen Inversion in Amidases. Formation of Acyl Enzyme.





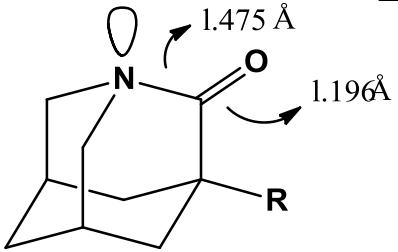
(1) P.-O. Syrén. *Febs Journal* 2013, *280,* 3069-3083.

(2) S. A. Bizzozero, H. Dutler. *Bioorg. Chem.* 1981, *10*, 46-62.

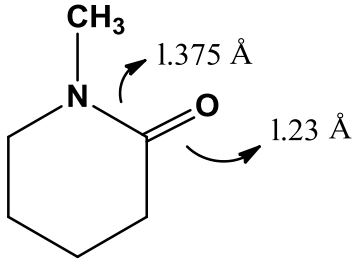
(3) P. Deslongchamps. *Tetrahedron* 1975, *31*, 2463-2490.

# Intermediate in *cis-trans* Amide Interconversion

**Comparison**



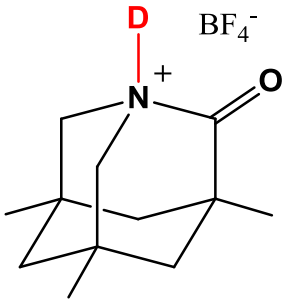

**1** R=H or $CH_3$



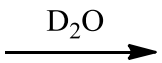

**2**

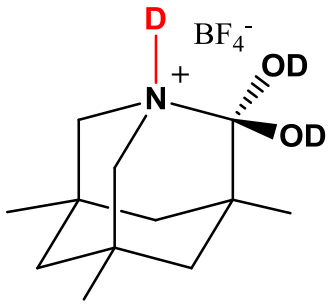
| | | |
|---|---|---|
| I.R. | 1732 $cm^{-1}$ | 1653 $cm^{-1}$ |
| NMR $C^{13}=O$ | 199.5 | 165 |

**also**




**3** (salt)




**4** (half-like 53.6 min)


**(1) A. J. Kirby *et al.* *J.A.C.S.* 2015, 137, 926-930.**

**(2) A. J. Kirby *et al.* *Angew. Chem. Int. Ed. Engl.* 1998, 37, 785.**