CHAPTER II

HISTORY

Valproic acid (2-propylpentanoic acid) was introduced into the United States in 1978 as an anticonvulsant specifically for the treatment of absence seizures. The antiseizure properties of valproate were discovered serendipitously when it was employed as a vehicle for other compounds that were being screened for antiseizure activity. Valproic acid is not only able to protect against pentylenetetrazole-induced seizures, but also effective in a variety of chemostimulant models including bicuculline, picrotoxin, 3-mercaptopropionic acid, isonicotinic acid semicarbazide, strychnine, penicillin, and aminophylline as well as in the kindling model. Valproate is currently effective in myoclonic seizures and generalized tonic-clonic seizures. (Edafiogho and Scott, 1996)

Valproic acid is a simple branched-chain carboxylic acid with differs markly from the substituted heterocyclic ring structure common to other anticonvulsants. It is a relatively strong carboxylic acid having a pK_a of 4.8 and is slightly soluble in water. (Levy and Lai, 1982) Valproic acid is absorbed rapidly and completely after oral administration, peak-concentration being attained in 1-2 hours. The apparent volume of distribution for valproate is about 0.2 litr / kg.

Its extent of binding to plasma proteins is usually about 90%. Although concentration of valproate in CNS suggests equilibration with free drug in the blood, there is evidence for carrier-mediated transport for valproate both into and out of the cerebrospinal fluid.

Almost no valproate is excreted unchanged in the urine or feces, most of the drug is converted to the conjugate ester of glucuronic acid, while mitochondrial metabolisms (both β-oxidation, and ω-oxidation) accounts for the remainder. Some of these metabolites, notably 2-propyl-2-pentenoic acid and 2-propyl-4-pentenoic acid, are nearly as potent antiseizure agents as the parent compound. The half-life of valproate is approximately 8 hours. (McNamara, 1996)

Valproic acid produces effects on isolated neurons similar to those of both phenytoin and ethosuccimide. At therapeutically relevant concentration, valproate inhibits sustained repetitive firing induced by depolarization of mouse cortical or spinal cord neurons. The action is similar to that of both phenytoin and carbamazepine and appears to be mediated by a prolonged recovery of voltage-activated Na^+ channels from inactivation. In neuron isolated from a distinct region, the nodose ganglion, valproate also produces small reduction of the low-threshold (T) Ca^{2+} current. This effect on T current is similar to that of ethosuccimide in thalamic neurons. Together, these actions of limiting sustained repetitive firing and reducing T currents may contribute to the effectiveness of valproic acid against partial and tonic-clonic seizures and absence seizures respectively.

Another potential mechanism that may contribute to valproate's antiseizure actions involves metabolism of GABA. Although valproate has no effect on responses to GABA, it does increase the amount of GABA *in vivo*. *In vitro*, valproate can stimulate the activity of the GABA synthetic enzyme, glutamic acid decarboxylase, and inhibit GABA degradative enzymes, GABA transaminase and succinic semialdehyde dehydrogenase. Thus far it has been difficult to relate the increased GABA levels to the antiseizure activity of valproate. (McNamara, 1996)

Adverse reactions generally appear early in the course of therapy and are mild and transient. These include hematologic and gastrointestinal reactions, sedation, minimal elevation in liver function tests and hyperammonemia. However, fatal hepatotoxicity has developed and is most common in children under 2 years who have congenital anomalies and metabolic and neurologic disorders and who are receiving polytherapy. Additionally, the use of valproate during pregnancy has been associated with an incidence of neural tube defects and other malformations. (Ambre, et al., 1995; Edafiogho and Scott, 1996)

Several derivatives and prodrugs of valproic acid have been synthesized in order to improve anticonvulsant activity, or improve bioavailability, or decrease undesired adverse reactions, for instance,

- the ester prodrugs of valproic acid e.g.,

  (2-Propylpentanoyl)-2-proylpentanoate (LX) (Badit, et al., 1991)

  Propyl-2-propylpentanoate (LXI) (Hadad et al, 1992)

  Glyceryl tri-2-propylpentanoate (LXII) (Hadad, et al, 1993)

- the amide derivatives of valproic acid e.g.,

  N,N′-bis-(2-propylpentanoyl)-1,2-ethylenediamine (LXIII) (Bechar and Astroug,1997),

  1-(2-Propylpentanoyl)-2-pyrrolidinone (LXIV) (Wicharn Janwitayanuchit and Chamnan Patarapanich, 1990)

- the N-(2-propylpentanoyl) derivatives of amino acids and their isomers e.g.,

  N-(2-propylpentanoyl) glycine (LXV)

  N-(2-propylpentanoyl) GABA (LXVI) (Hadad and Bialer, 1995; Hadad

and Bialer, 1997)

N-(2-propylpentanoyl) nipecotic acid (LXVII)

N-(2-propylpentanoyl) nipecotamide (LXVIII) (Bialer, et al., 1996)

- the cyclic analogues of valproic acid e.g.,

(±)-(E)-2,3-diethylcyclopropane carboxylic acid (LXIX)

Dicyclopropylpentanoic acid (LXX)

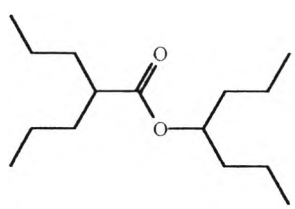
Spiro[4.6]undecane-2-carboxylic acid (LXXI) (Scott, et al., 1985)

- the unsaturated analogues of valproic acid e.g.,

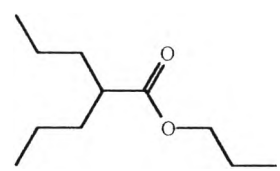
(E,E)-2-(1'-propenyl)-2-pentenoic acid (LXXII)

Cyclooctylideneacetic acid (LXXIII) (Palaty and Abbott, 1995)

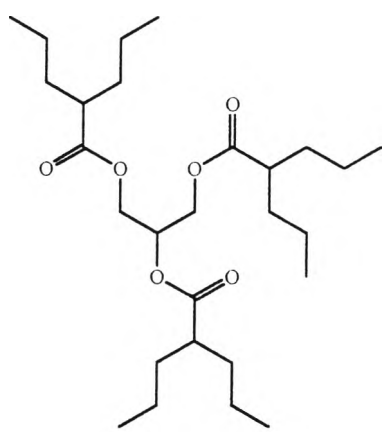
(±)-2-n-Propyl-4-pentenoic acid (LXXIV) (Elmazar, Hauck, and Nau, 1993) (See figure 12)



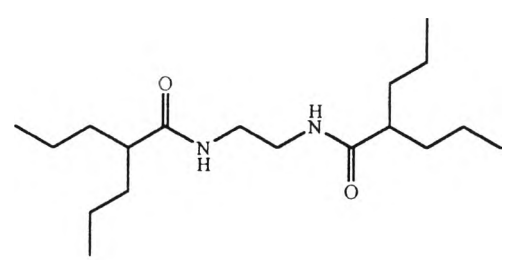
(LX)



(LXI)



(LXII)



(LXIII)

Figure 12. Chemical structures of some derivatives and prodrugs of valproic acid

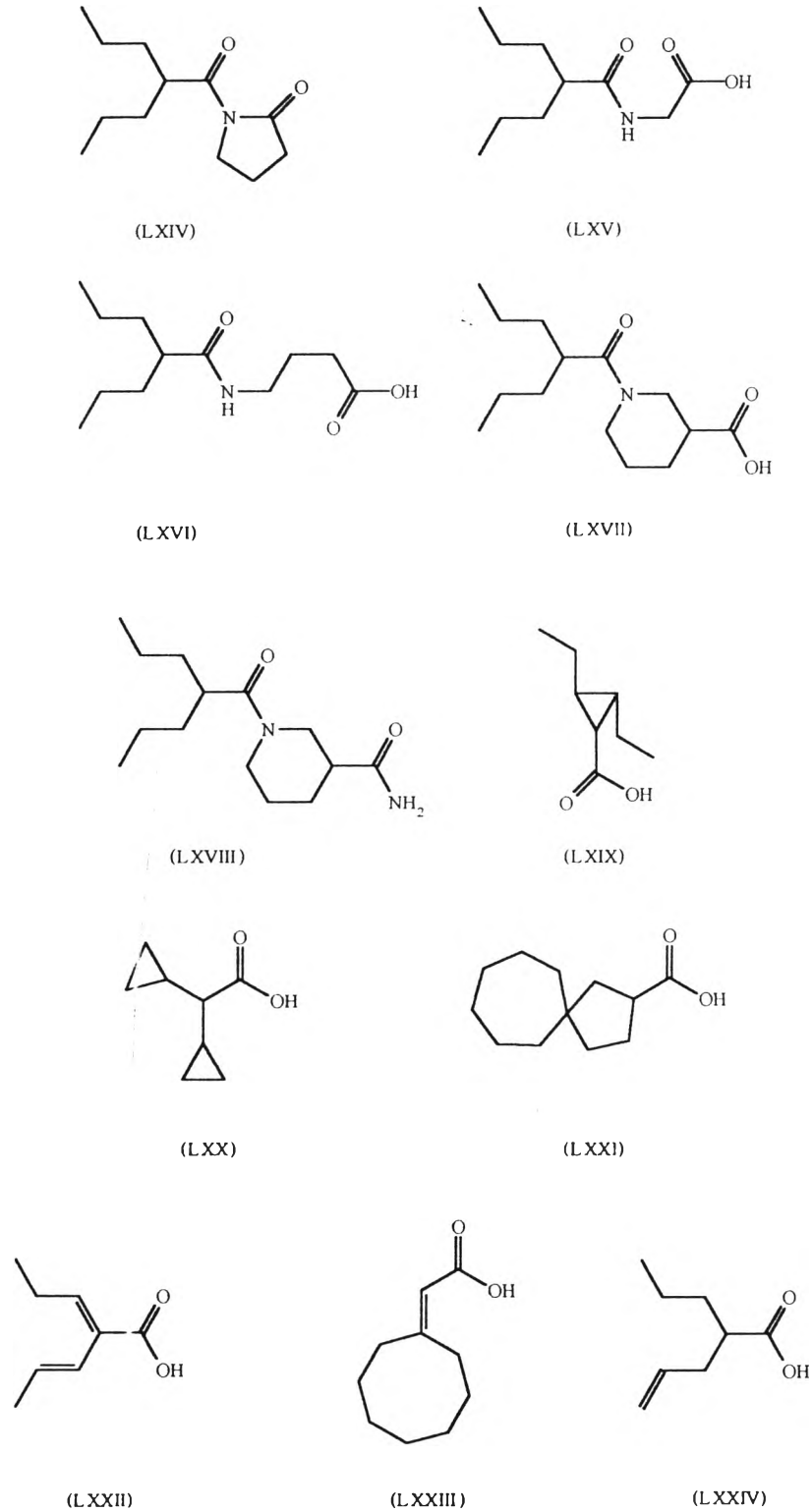
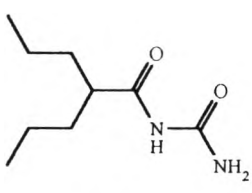


Figure 12.(continued) Chemical structures of some derivatives and prodrugs of valproic acid

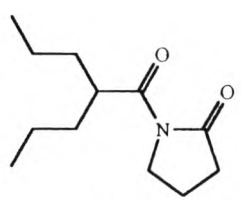
Structure-activity relationships of amide derivatives of valproic acid

In 1992, N-(2-propylpentanoyl) urea and N-(2-propylpentanoyl)-2-pyrrolidinone (LXIV) were synthesized and proven to possess good anticonvulsant activity in both maximal electroshock (MES) and pentylenetetrazole (PTZ) seizure models. (Wicharn Janwitayanuchit, 1992; Thongchai Sooksawate, 1995)

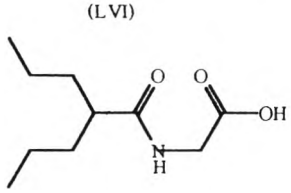
Considering the chemical structures, each compound possesses a carbonyl group adjacent to the amide nitrogen of 2-propylpentamide moiety, shifting of the carbonyl group by one carbon from the 2-propylpentamide nitrogen retains anticonvulsanrt activity, as shown in N-(2-propylpentanoyl) glycine (LXV) and its amide (LVII) (Hadad and Bialer, 1995). In contrast, if the carbonyl group is shifted more than one carbon atom, the anticonvulsant activity is abolished. For instance, in that of N-(2-propylpentanoyl) nipecotic acid (LXVII) and its amide (LXVIII), N-(2-propylpentanoyl) GABA (LXVI) and its amide (LXXV). (Hadad and Bialer, 1995; Bialer, et al, 1996)



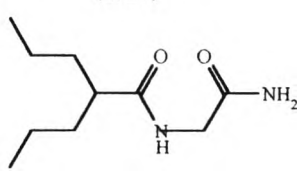
(LVI)



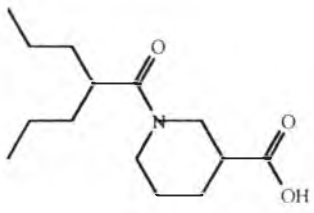
(LXIV)



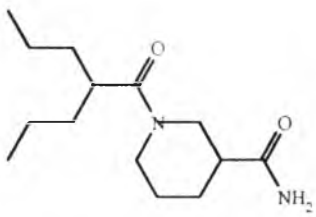
(LXV)



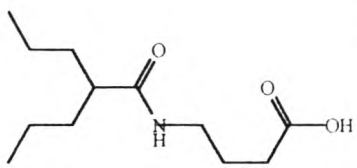
(LVII)



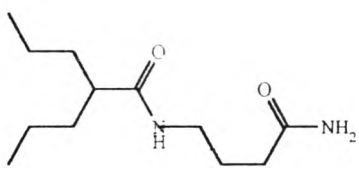
(LXVII)



(LXVIII)



(LXVI)



(LXXV)

Structure-activity relationships of 2-propylpentanohydroxamic acid derivatives

2-Propylpentanohydroxamic acid (LXXVI) exerted better anticonvulsant activity than that of valproic acid both in MES and PTZ models in mice and rats, although this compound was shown more neurotoxic than its parent molecule. In order to investigate the structure-activity relationships, some derivatives were prepared. (Levi, Yagen, and Bialer, 1997)

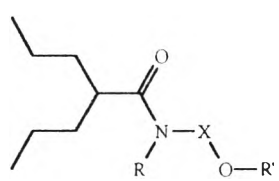
Shifting of the hydroxyl moiety from the nitrogen atom by one or two carbons does not affect the anticonvulsant activity of these compounds in mice, furthermore, the shifting by one carbon atom provides the high anticonvulsant potency as shown in the conpounds N-(hydroxymethyl)- and N-(hydroxyethyl)-2-propylpentamide. (LXXVII and LXXVIII, respectively)

Substitution of the hydroxylic hydrogen in 2-propylpentanohydroxamic acid results in N-methoxy-2-propylpentamide (LXXIX) and leads to improvement in anticonvulsant activity.

In contrast, substitution of the hydroxyl hydrogen in the active compound, N-hydroxyethyl-2-propylpentamide by a methyl group (LXXX) drastically decreases activity.

Branching on aliphatic chain connecting amide and hydroxyl moiety produce an inactive compound, N-(1,2-dihydroxyl propyl)-2-propylpentamide (LXXXI).

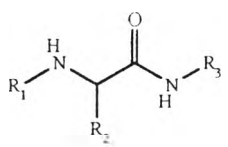
O-acylation and N-, O-acylation of 2-propylpentanohydroxamic acid (LXXXII, LXXXIII respectively) result in abolished anticonvulsant activity.



	R	X	R′
LXXVI	H	-	H
LXXVII	H	CH_2	H
LXXVIII	H	$-(CH_2)_2-$	H
LXXIX	H	-	CH_3
LXXX	H	$-(CH_2)_2-$	CH_3
LXXXI	H	$-CH_2CH(OH)CH_2-$	H
LXXXII	H	-	2-propylpentanoyl
LXXXIII	2-propylpentanoyl	-	2-propylpentanoyl

Structure-activity relationships of functionalized amino acids

Since 1985, excellent anticonvulsant activities of functionalized amino acid derivatives have been reported and these compounds have been claimed as a novel and important class of anticonvulsant agents. The general chemical structure of these compounds is as follow.



Potent protection against MES in mice is observed for the racemates containing an N-benzylamide moiety (R^1) and an acylated amino group (R^3). Systematic variation of the α-substituent (R^2) reveals that stringent steric and electronic requirements exist for optimal anticonvulsant activity.

A methyl or a phenyl substituent on the α-carbon gives potent anticonvulsant activities comparable to phenobarbital. (Conley and Kohn, 1987)

Addition of electron-releasing hydroxy or methoxy groups to the α-substituted phenyl group or expansion of the aromatic ring from the phenyl group to naphthyl residue lead to precipitous drop in anticonvulsant potency. (Kohn et al., 1990)

Substitution of the α-carbon with an electron-rich, five-membered heteroaromatic ring results in a substantial improvement in the potency of the compound in the MES test.

Placement of a methyl substituent on the five-membered heteroaromatic ring is accompanied by a decreased in the potency of the compound versus the unsubstituted compound.

The α-amino, α-alkylamino, and α-trimethylammonium derivatives all display anticonvulsant activities comparable to that observed for the α-methyl analogue.

Conversion of the α-amino derivative to the corresponding α-acylamino adducts leads to a decrease in activity.

Incorporation of a α-hydrazine derivative does not display significant anticonvulsant activity. This property has been attributed (in part) to the steric of these substituents.

The α-hydroxy and α-alkoxy adducts display activity comparable that reported for methyl adduct.

No enhancement of activity is noted for the α-sulfur dervative. (Kohn et al., 1991)

Overall reduction of the electron excessive character of the C (α) π-aromatic system by heteroatom incorporation leads to decreased biological activity.

Reduction of the furan to the tetrahydrofuran analogue leads to a decrease, but not abolition, of activity in MES test. The decreased activity can be attribute to the loss of the aromatic ring at the α-carbon site. (Kohn et al., 1993)

Placement of a small, substituted heteroatom moiety one atom from the α-carbon in this series of compounds leads to excellent anticonvulsant activities. (Bardel, Bolanos, and Kohn, 1994; Choi, Stables, and Kohn, 1996)

Significantly, for this class of compounds, anticonvulsant activity resides primarily in the R-stereoisomers.

General methods for the preparation of the amide derivatives of valproic acid

There are many intermediates included in the synthesis of valproic acid. These compounds represent many types of organic compounds e.g., acyl halide, amide, ester, N-hydroxyalkyl-, N-alkyloxyalkyl-, and N-acyloxyalkyl amide. General methods for the synthesis of these intermediates and products could be described as follows. (Vogel, Bodanszky, 1993; Bodanszky and Bodanszky, 1994; Fox and Foster, 1957; Bailey, 1967; Wade, 1991; March, 1968; and Carey and Sundberg, 1993)

Synthesis of acyl halides

Acyl chlorides are synthesized from the corresponding carboxylic acids using a variety of reagents. Usually, they can be prepared by heating the acid with phosphorus trichloride, or phosphorus pentachloride, or thionyl chloride.

$$3\,RCOOH + PCl_3 \longrightarrow 3\,RCOCl + H_3PO_3$$

$$RCOOH + PCl_5 \longrightarrow RCOCl + HCl + POCl_3$$

$$RCOOH + SOCl_2 \longrightarrow RCOCl + HCl + SO_2$$

Alternatively, the commercial method which allows the anhydrous sodium salt of the acid to be heated with phosphorus oxychloride gives very pure product.

$$2\ RCOONa + POCl_3 \longrightarrow 2\ RCOCl + NaCl + NaPO_3$$

Phosphorus pentachloride is preferably utilized in the preparation of aromatic acid chlorides, however, for aliphatic acid chlorides, thionyl chloride is the most convenient reagent since both by-products, HCl and SO_2 are volatile.

Synthesis of amides

(a) The synthesis of amides from acids

The most common industrial synthesis of amides involves heating an acid with an amine to drive off water and promote condensation.

$$RCOOH + R'NH_2 \xrightarrow{heat} RCONHR'$$

Primary aliphatic amides are obtained by heating the ammonium salt of the corresponding acid.

$$RCOO^-NH_4^+ \longrightarrow RCONH_2 + H_2O$$

For preparative purpose, it is best to heat the acid or its ammonium salt with urea. The reaction commences at about 120°C, the carbamic acid formed decomposes immediately into carbondioxide and ammonia. The latter may then interact with unreacted acid to yield the ammonium salt, which then yields the amide as formulated above.

In peptide synthesis, carbodiimides, particularly dicyclohexylcarbodiimide (DCC), are important reagents for the formation of peptide bond. These coupling reagents could be added to the mixture of the carboxylic component and the amine

component, thus, activation and coupling proceed concurrently. Addition of carboxylic acid to one of the double bonds of carbodiimide results O-acyl isourea of which the N=C group provides powerful activation in coupling with the amine.

It seems to be reasonable to attribute some basic character to O-acyl isourea and therefore general base catalysis can be invoked as the explanation of the surprisingly high reactivity observed in aminolysis.

A second and, at least equally in the peptide bond forming reaction proceeds via symmetrical anhydrides produced in the attack of a yet unreacted molecule of the carboxyl component on the O-acyl isourea intermediate.

The extremely rapid generation of symmetrical anhydrides can be rationalized by the assumption of a quasi-intramolecular attack of the carboxylate anion on the reactive carbonyl within the ion-pair of the two components.

The speedy execution of activation and coupling in a single operation and the simple removal of the insoluble by-product, N,N′-dicyclohexylurea (DCU), by filtration all contributed to the persistent popularity of the DCC method.

The mechanisms of coupling with N,N′-dicyclohexylcarbodiimide are shown in figure 13.

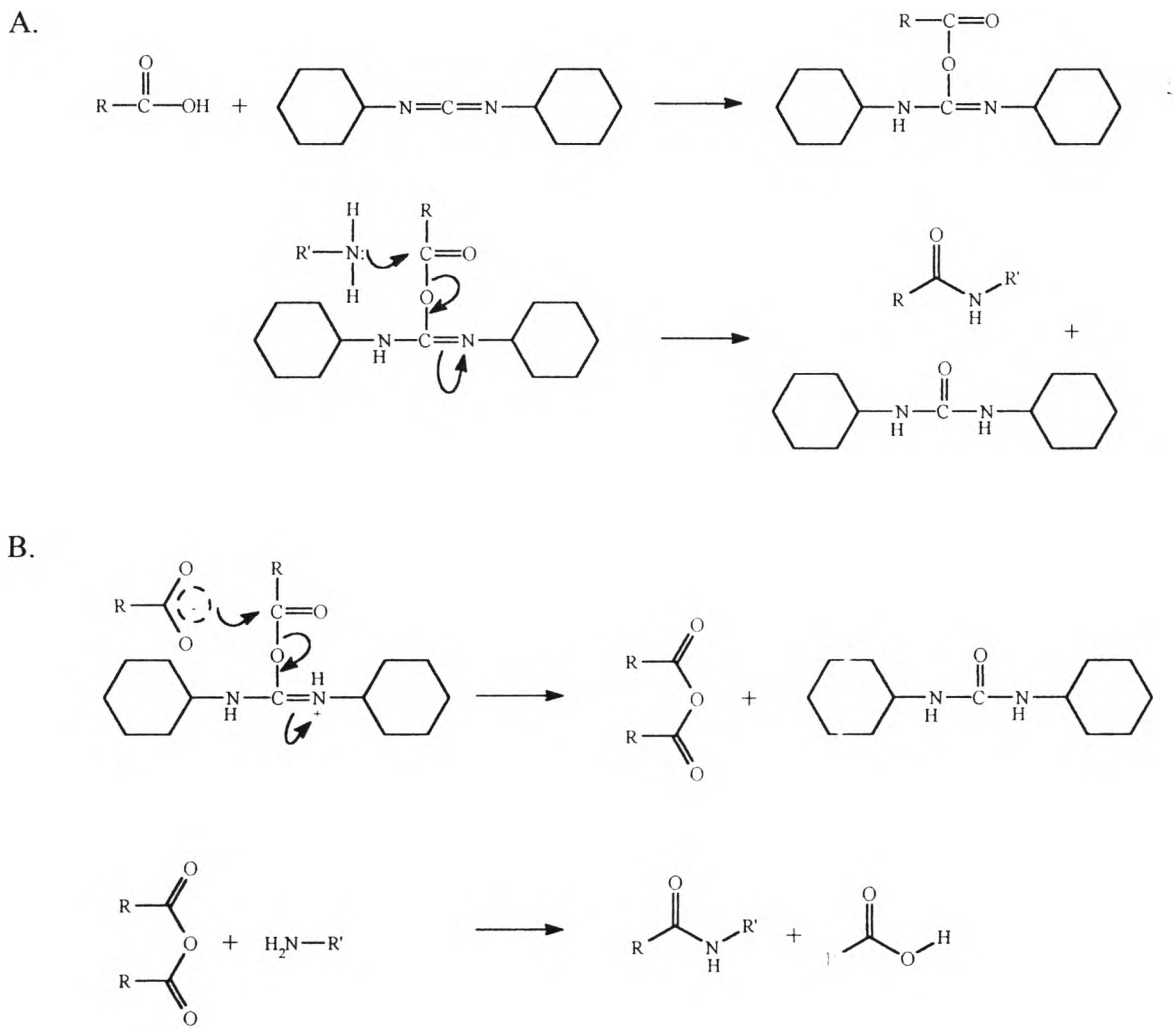


Figure 13. The mechanisms of coupling with N,N′-dicyclohexyl carbodiimide.

A. O-acylurea pathway

B. Acid anhydride pathway

(b) The synthesis of amides from the acyl halides

The reaction of an acyl chloride with an excess of ammonia represents one of best procedures for the preparation of primary amides.

The acyl chloride is added dropwise to well-stirred concentrated aqueous ammonia cooled in a freezing mixture. The amides of the higher carboxylic acids crystallized out on standing and need only to be filtered and recrystallized. Water-soluble amides are isolated by extraction with hot ethyl acetate following removal of water on a rotatory evaporator.

A milder procedure involves stirring a solution of the acyl chloride in acetone at room temperature with ammonium acetate. The filtered solution is evaporated to recover the required amide.

The use of primary or secondary amines in place of ammonia yields the corresponding secondary or tertiary amides in reaction with an acyl chloride. These compounds often serve as crystalline derivatives suitable for the characterization of either the acyl chloride (and hence of the carboxylic acid itself) or the amine.

$$RCOCl + R'NH_2 \longrightarrow RCONHR'$$

$$RCOCl + (R')_2NH \longrightarrow RCON(R')_2$$

The general mechanisms are well known. The nucleophilic species undergoes addition at the carbonyl group, followed by elimination of the halide group. Acyl halides are reactive reagents because of a combination of the inductive effect of the halogen substituent on the reactivity of the carbonyl group and the ease with which the tetrahedral intermediate can expel such relatively good leaving group.

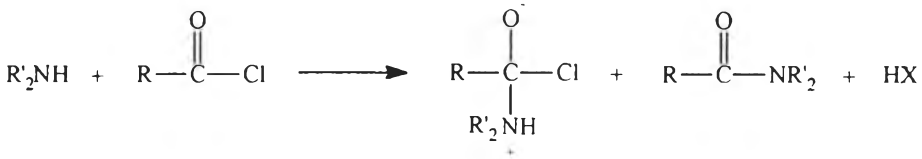
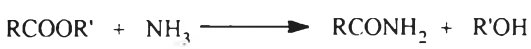


Figure 14. The mechanism of N-acylation of amine.

(c) The synthesis of amides from esters

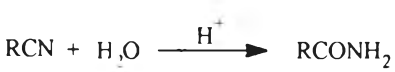
Amide are very easily prepared by the interaction of carboxylic esters with concentrated aqueous ammonia (ammonolysis).



The reaction usually proceeds readily in the cold, particularly when the methyl esters of the lower molecular weight carboxylic acids are involved. Sparingly soluble amides crystallize out from the reaction mixture upon standing.

(d) The synthesis of amides from nitrile

The interruption of the hydrolysis of nitrile at the amide stage can be achieved in a preparative manner where the nitrile is dissolved in concentrated hydrochloric acid at 40° C and subsequently poured into water. The use of hot polyphosphoric acid has also been recommended.

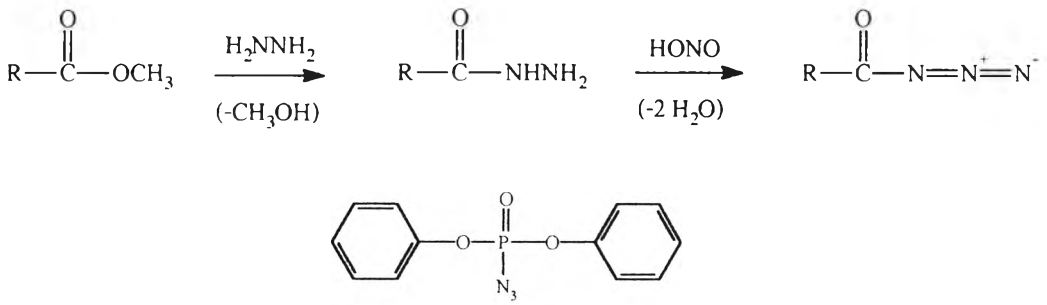


Reactions particularly applicable to aromatic nitriles involved the use of an aqueous solution of sodium hydroxide containing hydrogen peroxide, but alkyl cyanides do not always give good results.

(e) The acid azide method

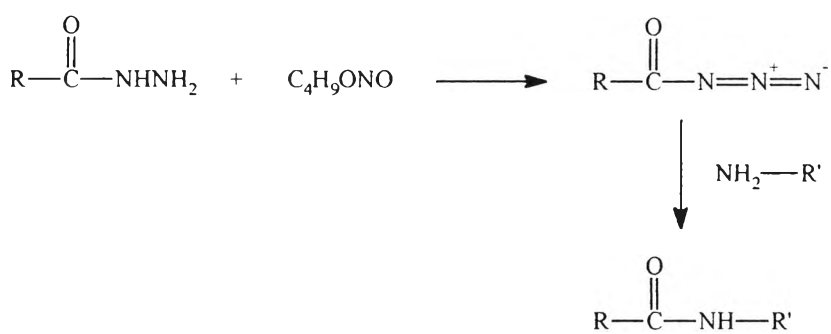
The activation of carboxylic acid in the form of acid azides has been a

powerful and practical approach for the synthesis of alkyl esters and conversion of the hydrazides to acid azides with the help of nitrous acid are still practiced, although direct conversion of carboxylic acids to acid azides with the help of diphenylphosphoryl azide (LXXVI) has become a viable alternative in recent years.



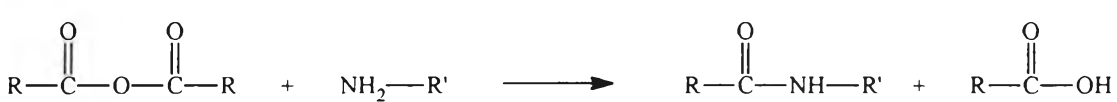
(LXXVI)

Also, instead of nitrous acid, alkyl nitriles can be used for the transformation of hydrazides to azides which is further acylated with amine to yield an amide.



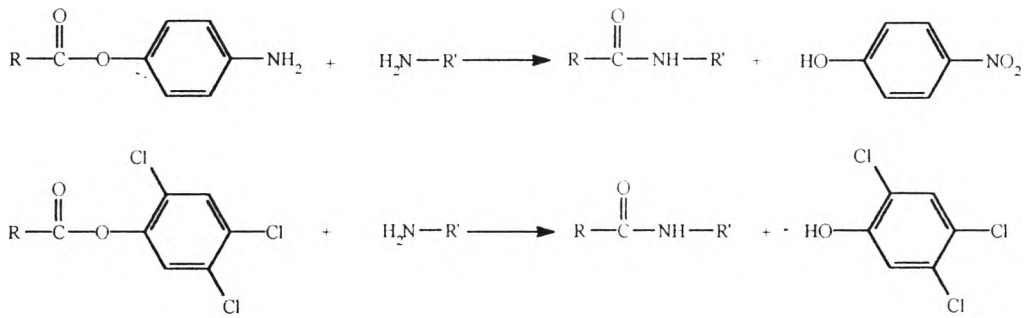
(f) The synthesis of amides from acid anhydrides

One of the simplest and most efficient methods of acylation is the treatment of amines with anhydrides of carboxylic acids. Anyway, the util zation of anhydrides is wasteful, of the two molecules of carboxylic acid comprised in the molecule of the anhydride only one is incorporated into the product while th : other is regenerated but usually not recovered:

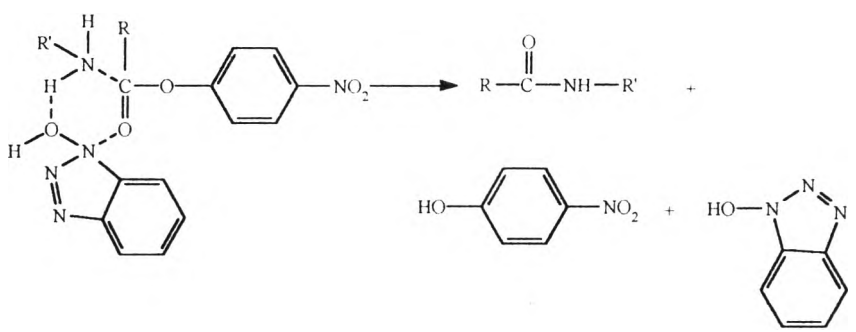


(g) The synthesis of amides from active esters

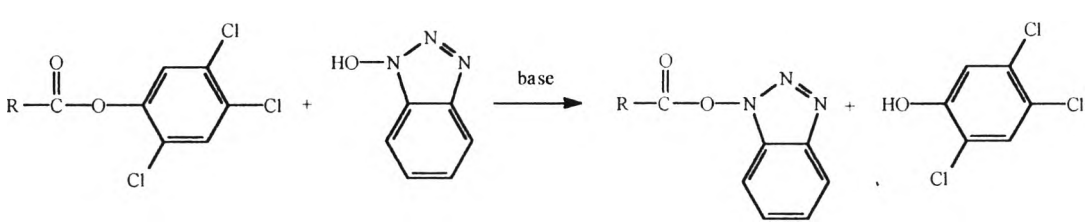
Aryl esters with electron-withdrawing substituents yielded a whole series of useful acylating agents which are among the tools of peptide chemists, for instance, p-nitrophenyl ester, 2,4,5-trichlorophenyl esters.



1-Hydroxybenzotriazole exerts catalytic effect on aminolysis of active esters. This effect could be rationalized by the assumption of a ternary complex between active ester, amine and catalyst



but further rate-enhancement on addition of tertiary amines suggests that, at least in part, base catalyzed transesterification take place.

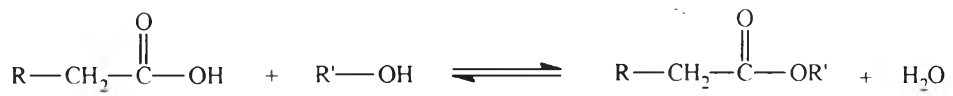


Similar catalysis is provided by several other N-hydroxy compounds, for instance, 1-hydroxy-2-pyridone and N-hydroxysuccinimide.

Synthesis of esters

(a) Direct esterification procedures

The interaction between a carboxylic acid and an alcohol is a reversible process and proceeds very slowly:



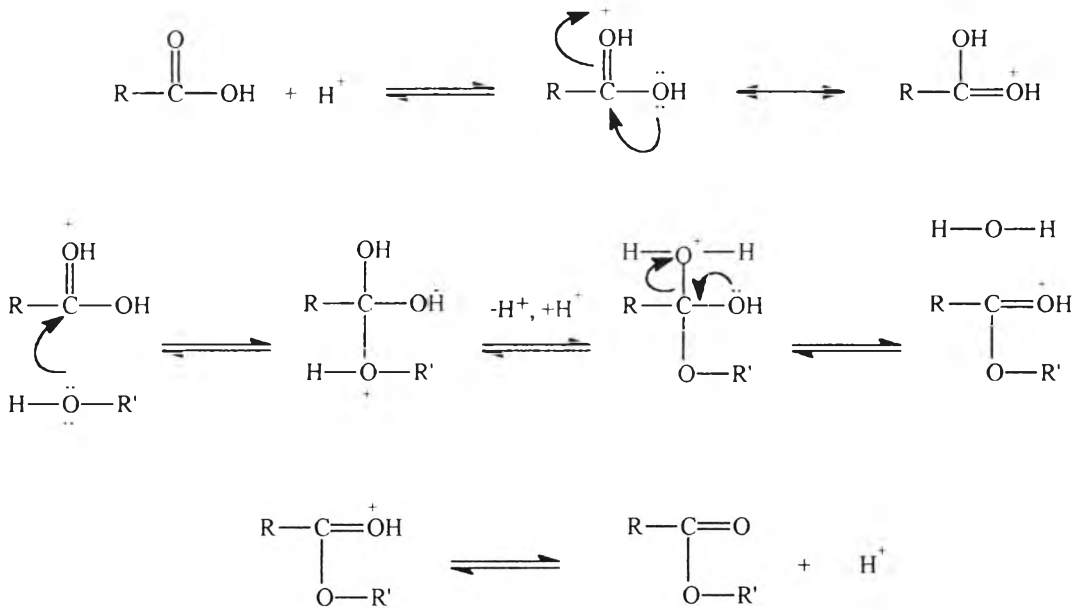
Addition of about 3% (of the weight of the alcohol) of either concentrated sulfuric acid or of dry hydrogen chloride accelerates the rate of reaction. It is frequently convenient to use an excess of the alcohol to promote ester formation. This method of esterification, in general, gives good yields with primary alcohols and fairly good yields with secondary alcohols. The method is unsatisfactory with tertiary alcohols.

Esterification with alicyclic alcohols proceeds best when the alcohol is saturated with hydrogen chloride and treated with an excess carboxylic acid (the Fischer-Speier method); a very impure ester results if sulfuric acid is used as the catalyst.

The acid-catalyzed esterification reaction usually proceeds via an acyl oxygen fission process. This involves the cleavage of the bond between the original carbonyl carbon atom and oxygen of hydroxyl group in the intermediate (II) arising from nucleophilic attack by an alcohol molecule on the protonated carboxylic acid group (I).

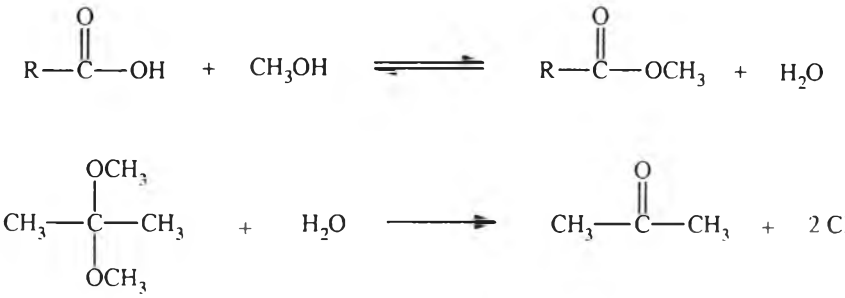
Several modifications of the simple direct esterification procedure described above have been developed. For example, it is sometimes convenient to prepare an ester by heating the organic acid, the alcohol, and sulfuric acid in a solvent such as

benzene. Upon the addition of water, followed by separation and distillation of the benzene layer (after washing and drying), benzene and alcohol pass over first, followed by the ester.



The process of acid catalyzed esterification in the present of benzene or toluene is greatly facilitated if the water produced in the reaction is removed by distillation as an azeotrope. When the reaction mixture is slowly fractionated a ternary azeotrope of the alcohol, toluene and water will pass over first, followed by a binary toluene-alcohol azeotrope. Continued distillation affords the required ester in good yield. Alternatively, the reaction mixture is subject to reflux under a Dean and Stark water separation unit. This allows the separation and removal of water from the azeotrope, the organic phase being returned continuously to the reaction flask.

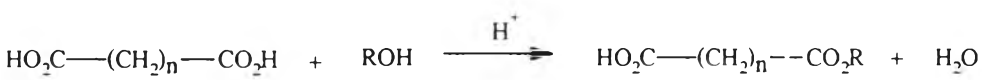
A recent procedure for the preparation of methyl esters involves refluxing the carboxylic acid with methanol and 2,2-dimethoxypropane in the presence of toluene-p-sulfonic acid as the catalyst. The water produced in the reaction process is effectively removed by acid-catalyzed reaction with the ketal to give acetone and methanol.



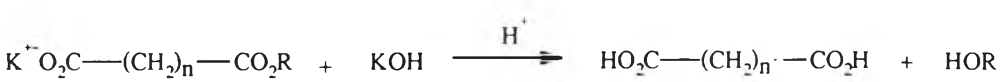
Methyl esters are conveniently prepared on the small scale using diazomethane.

(b) Preparation of acid esters of dicarboxylic acids

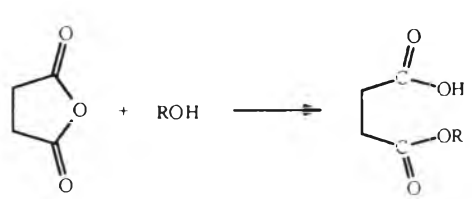
The acid-catalyzed reaction of dicarboxylic acid with an excess of alcohol yields a diester. However, the process may be adapted to prepare acid esters of dicarboxylic acids by using molar proportions of the diacid and alcohol.



Alternatively, the acid ester may be prepared by subjecting the diester to controlled partial hydrolysis with one molar proportion of potassium hydroxide.

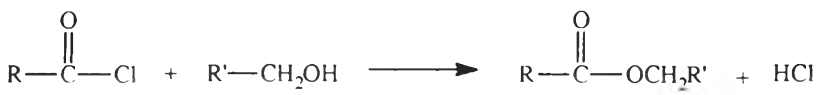


The acid esters of 1,2-dicarboxylic acids are conveniently prepared by heating the corresponding cyclic anhydride with one molar proportion of the a cohol.



(c) The use of acyl chlorides and acid anhydrides

Acyl chlorides react readily with primary and secondary alcohols to give esters in very good yields. With tertiary alcohols, the presence of a base (e.g., dimethylaniline) is essential to prevent acid catalyzed side reactions, such as dehydration or formation of the alkyl chloride.



Acylation may be carried out with acid anhydrides in the presence of a suitable catalyst; either an acidic catalyst, such as sulfuric acid or zinc chloride, or a basic catalyst such as pyridine, may be used.

The use of an acyl chloride or acid anhydride is the method of choice for the synthesis of phenyl esters which cannot prepared by the direct esterification method described above. The mechanism of O-acylation of alcohol is shown in figure 15.

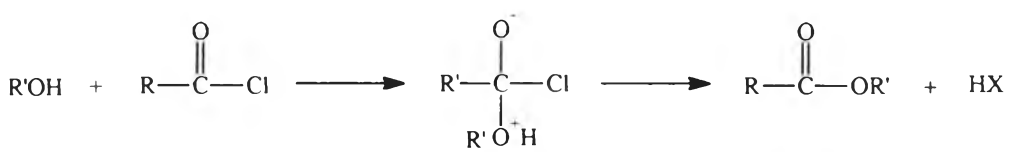


Figure 15. The mechanism of O-acylation of alcohol.

(d) Ortho-esters

These have the general formular $R^1C(OR^2)_3$ and are stable derivatives of the unstable ortho acids $RC(OH)_3$. Important examples are the esters of orthoformic acid (the orthoformates), which may be readily prepared by the interaction of the appropriate sodium alkoxide with chloroform.

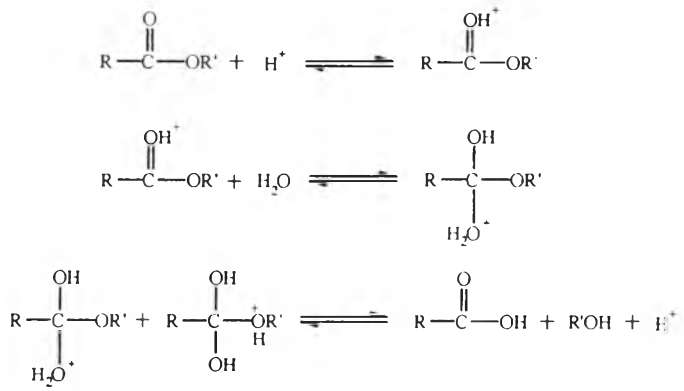
Ester Hydrolysis

Esters can be hydrolyzed in either basic or acidic solution. In acid solution, the reaction is reversible.

The position of the equilibrium depends on the relative concentration of water and the alcohol. In aqueous solution, hydrolysis occurs. In alcoholic solution, the equilibrium is shifted in favor of the ester. In alkaline aqueous solution, ester hydrolysis is essentially irreversible:

The carboxylic acid is converted to its anion under these conditions, and the position of the equilibrium lies far to the right. The mechanistic designations $A_{AC}2$ and $B_{AC}2$ are given to the acid-and base-catalyzed hydrolysis mechanisms, respectively. (See figure 16)

A. $A_{AC}2$ mechanism



B. $B_{AC}2$ mechanism

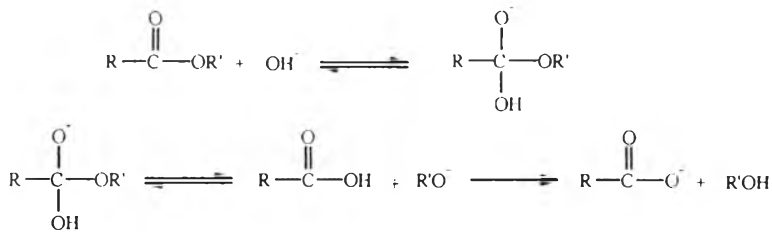


Figure 16. Mechanisms of ester hydrolysis.

A. $A_{AC}2$ mechanism

B. $B_{AC}2$ mechanism

Synthesis of N-hydroxymethyl amides

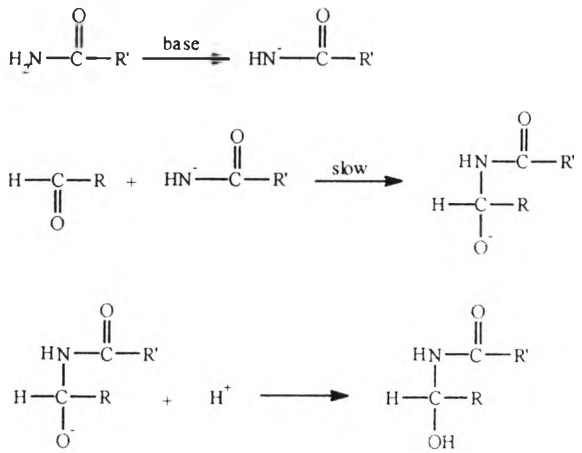
N-hydroxymethyl amides are generated by addition of the amides to aldehydes in the presence of bases or acids.

Bases can catalyze the reaction by converting the amide ($RCONH_2$) to the more powerful nucleophile ($RCONH^-$). The reaction then is regarded as nucleophilic addition resulting in tetrahedron intermediate.

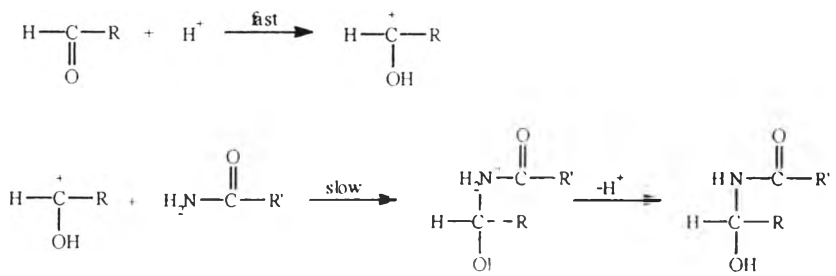
Acids may catalyzed it by converting the aldehyde to an cation in which the positive charge on the carbon is greatly increased, thus making it more attractive to nucleophilic attack. The latter type of catalysis may also take place with acids which are not so acidic that a problem is actually transferred to the substrate, but which are able to form a hydrogen bond with it resulting in a decreased electron density at the carbon. Mechanisms of catalysis are shown in figure 17.

In 1984, Varia, Schuller, Sloan, and Stella synthesized N-hydroxymethyl derivatives of hydantoins with very good yields in the presence of formaldehyde, potassium carbonate, and water at room temperature.

A.



B.



C.

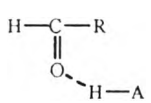


Figure 17. Mechanisms of addition of amide to aldehyde.

A. base catalysis

B. acid catalysis

C. hydrogen bond forming

Synthesis of N-alkoxymethyl amides

Several types of alkoxyalkyl amides have been reported. N-methoxymethyl acetamide was prepared by the base catalyzed reaction of of acetamide and formaldehyde followed by acid-catalyzed esterification with methanol. There was a report of the preparation of N-methoxymethylacetamide by the electrolysis of acetylglycine in methanol. (Finkelstein and Ross, 1972)

Treatment of 5-cyanouracil with methoxymethyl chloride gave N-methoxymethyl derivatives of uracil in high yield. The reaction takes place in polar solvent such as N,N-dimethylformamide in the presence of anhydrous potassium carbonate at the temperature lower than $0^{\circ}C$. (Su, Huang, Burchenal, Watanabe, and Fox, 1986)

Synthesis of N-acyloxyalkyl amides

Preparation of N-acyloxyalkyl amides utilizes esterification of N-hydroxyalkyl amides with acid anhydride in the presence of pyridine as a catalyst. (Barry, Mayeda, and Ross, 1977)