KINETICS AND MECHANISMS OF THE CATALYTIC HYDROLYSIS OF ACETAMIDE IN PRESENCE OF COPPER COMPLEX

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Abstract:

In this paper, we report combined theoretical and experimental effort aimed at providing an understanding of the kinetic and mechanisms and surface process involved in the catalytic hydrolysis of acetamide with copper complex as a catalysts. The kinetics expermental was carried out at different temperetre (25, 35 and 45 ^{o}C) and at different amount of catalyst (0.1, 0.3, 0.5 and 0.7 gm) also at different concentration of acetamide (0.84, 1.69, 2.54 and 3.39 M) and we calculated the thermodynamic parametrs (ΔH, ΔS, ΔG and E_a).

Keywords: kinetics, acetamide, mechanism, metal complexes.

Introduction:

A mild protocol for the alkaline hydrolysis of secondary and tertiary amides in non-aqueous conditions, by the use of NaOH in methanol / dichloromethane or methanol/ dioxane (1:9) at room temp-erature or under reflux, has been developed and a plausible reaction mechanism is discussed. Primary amides are hydrolyzed much slower than with the classical procedure, while nitriles are converted selectively to primary amides.[1]

Amide derivatives constitute important moieties in many pharmaceutical and biologically active molecules. Hydrolysis of an amide, a nitrile or an ester functional group is a very common trans-formation in organic synthesis with many applications and a common way to prepare carboxylic acids. In general, nitriles and amides are exceptionally stable to acid and basic hydrolysis and classically they are hydrolyzed under vigorous reaction conditions and long reaction times by heating in the presence of mineral acids or concentrated solutions of alkali hydroxides

(10-40%), which can sometimes cause undesirable side reactions and low yield. Tertiary amides are very difficult to be cleaved and in most cases stronger conditions are required than for primary and secondary amides.[1]

Amides and nitriles are very stable to basic hydrolysis in aqueous solutions and forcing reaction conditions are often needed. Primary amides are hydrolyzed more easily than secondary, tertiary amides are very difficult to be cleaved, while nitriles are hydrolyzed first to amides and further to carboxylates and amines with even more strong reaction conditions. With our methodology, in non aqueous conditions, the rank is reversed. As the lipophilicity of the amide increases, going from the primary to the tertiary amides, the rate of the alkaline hydrolysis increases, depending also on the acyl group and the amide leaving anion. This simple methodology offers an attractive alternative, available for the alkaline hydrolysis of *sec*- and *tert*-amides and for the selective hydrolysis of nitriles to primary amides. Furthermore, it may allow the protection of both, secondary amines and carboxylic acids, *via* their conversion to *tert*-amides.[1]

Nitriles are hydrolyzed first to amides and further to carboxylic acids and ammonia with even more strong reaction conditions. The hydrolysis of amides and nitriles is a well studied reaction and numerous methods have been developed.[2] Among them, the use of sodium peroxide and of phthalic anhydride5 for the amide hydrolysis have been described, while nitriles can also be converted to amides by catalyzed hydration,[3] enzymatically and on unactivated alumina. Ames and Islip in their work, described the use of *N*,*N*-dimethylamide as a protecting group for long-chain ω-acetylenic acids. The amide achieved by the reaction of the appropriate acid chloride and dimethyl amine, was hydrolyzed under vigorous alkaline conditions, with KOH / H_2O in refluxing 2-methoxyethanol.[3]

The total synthesis of biotin in the presence of more active sites, protected the carboxylic group as its piperidide, for the removal of which vigorous hydrolysis conditions were required. Some author succeeded to hydrolyze tertiary amides using two equivalents of the strong base t-BuOK in diethyl ether and one equivalent of water at room temperature, while primary and secondary amides were extremely resistant under the same conditions. The mechanism of the alkaline amide hydrolysis has been intensively investigated.[4] It is similar to that of the esters, with the exception that the tetrahedral intermediate, formed after the addition of the hydroxide, could regenerate the amide than give the hydrolysis products. The loss of the hydroxide anion is the

thermodynamically preferred route and the accompanying oxygen exchange is generally faster than hydrolysis .[5]

The hydrolysis of small amides has garnered major attention due to its relevance to peptide hydrolysis, one of the most fundamental reactions of biology. Both experimental and theoretical research efforts have studied the reaction in different media, and a consensus has been reached regarding the specific acid- and base catalyzed reaction pathways. Nevertheless, for the water reaction, large discrepancies between theoretical and experimental results are found in the literature. Herein, we report the results of theoretical calculations of formamide and urea hydrolysis at different pH values. Model systems have been built clustering one and two water molecules with the reactive amide.[6]

Experimental :

The acetamide used was a product of (BDH) and was further purified by succesive crystalization from alcohol and benzene [7]

Preparation of copper complex catalysed hydrolysis of acetamide

A. Preparation of the ligand (1)

4-Chlorophenol (1mol, 1.28 g) was added to 30 cm^3 of mthyl alcohol containing sodium salt of methyl 4-hydroxy benzoate (1mol, 1.74 g). Stirring the suspension at 70 ^oC for one hour, The product obtained is filtered off to remove sodium chloride then take solution (a starting material). Ethylene diamine (1mol, 0.6 g) was added to above solution, heating to 60 ^oC with stirring for an hour. The product obtained reacted with salicyaldehyde (1 mol, 1.22 g) by heating to 60 ^oC with stirring for an hour was filtered off to give crude product which was crystallized in water to yield pure yellow ligand (1) as shown below:

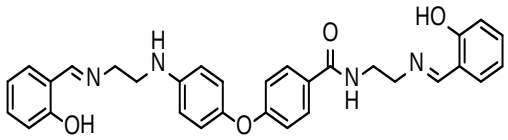


Figure (1): Ligand (1)

B. PREPARATION OF COPPER COMPLEX AS ACATALYST

Copper(II) chloride dihydrate (2 mol, 3.4g) dissolved in ethanol 30 cm^3 was added to (L1) (1 mol, 5.22 g) dissolved in ethanol 25 cm^3. The mixture was warmed at 60 C^o with stirring for 1 hour, then the solution was cooled at room temperature filtered off and green precipitate was obtained.

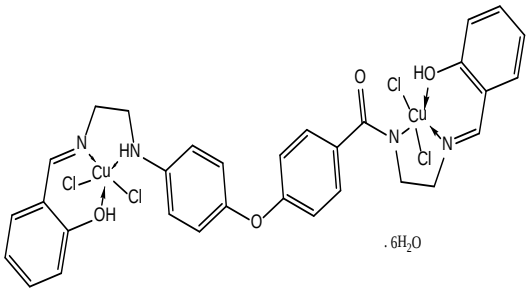
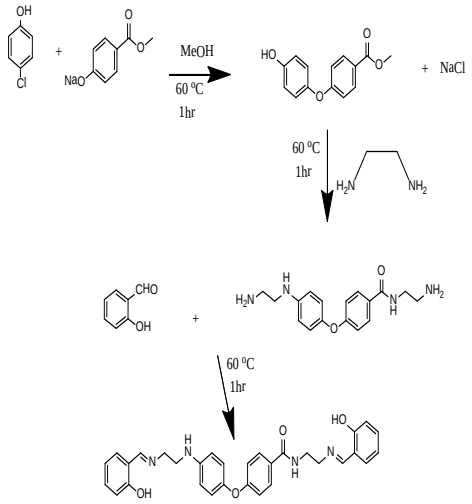


Figure (2): Structure of copper complex



Scheme (1). Preparation of Ligands 1

C. CATALYTIC HYDROLYSIS OF ACETAMIDE:

All chemicals were of analytical reagent grade and were employed without further purification. The experimental set up is given in **Figure (3)**. It contains: (1) 1. Thermostatic water bath. (2) Sort ball neck (reactor) borosilicate glass 500 ml volume. (3) A syringe to take samples (4) Thermometer. (5) Motor stirrer (6) A condenser to prevent evaporation of the reaction medium and maintaining constant the content of acetamide. (7) iron support.

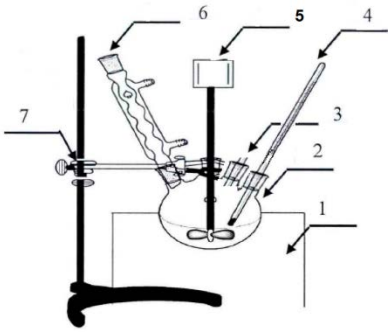


Figure (3): Experimental setup

The hydrolysis of acetamide catalyzed by copper complex can be kinetically monitored by prepare 10 gm of acetamide interduced in 100 ml flask and the weight of catalyst was added. The flask was stirred by a motor stirrer which was immersed in thermostated water at 0.05 °C. the rate of the reaction with drawing 5 ml sample (using a certified pipette) of th reaction mixture at different time intervals and analysed by titration against NaOH. The amount of alkali consumed is a measure of the amide decomposed. The hydrolysis of acetamide was carried out in a thermostated water at different temperatures 25, 35 and 45 °C.

Results and discussion

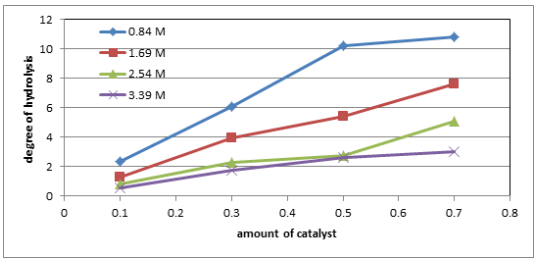
1. Kinetic studies of catalytic hydrolysis of acetamide in presence of copper complexs A. Effect of copper complexs catalyst:

For studing the effect of copper complexs catalyst on the rate percent conversion (degree of hydrolysis) of acetamide catalytic hydrolysis reaction, four different quantity of copper complex catalyst (catalyst (0.1, 0.3, 0.5 and 0.7 gm) have been used at constant different temperature (25, 35 and 45 °C). The observation can be drown from the results given in figour (1, 2 and 3) represent the catalytic hydrolysis curves obtained under the formentioned experimental conditions. It is clear from these figures that the degree of hydrolysis

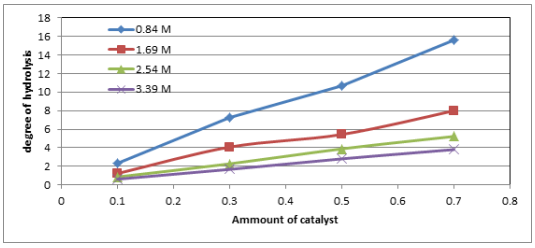
increases with increasing the amount of copper complex catalyst .

In general increasing the temperature of the catalytic hydrolysis reaction leads to an increase on the reaction rate. The slow rate of acetamide catalytic hydrolysis observed at the initial stage of the reaction indicated the presence of an induction period at the beginning of the reaction due to the formation of some active centers which will be accumulated on the surface of copper complex catalyst. Since after acertain period (induction period). The number of active centeres on the copper complex catalyst surface increased. The rate of acetamide catalytic hydrolysis after this period would take place more faster.

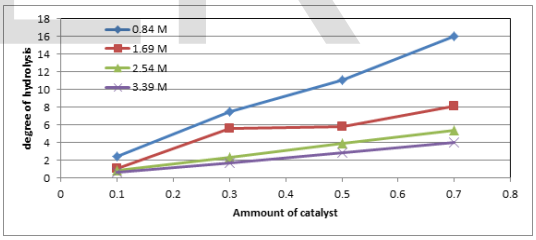
On the other hand the induction period observed in the present study was found to be decreased by increasing the amount of copper complex catalyst and the temperature of reaction. These results can be explained on the basis that increase of amount of copper complex catalyst may be accompanied by increase in the number of active centers and the increase of temperature may active the side reaction involved the formation of these active centers.



Figour (4):Effect of the amount of Complex on the catalytic hydrolysis of acetamide (At various initial concentration of acetamide , T 25 °C).



Figour (5):Effect of the amount of Complex on the catalytic hydrolysis of acetamide (At various initial concentration of acetamide , T 35 °C).

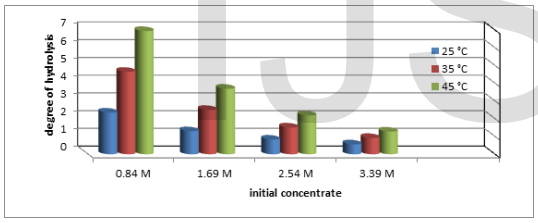


Figour (6):Effect of the amount of Complex on the catalytic hydrolysis of acetamide (At various initial concentration of acetamide , T 45 °C).

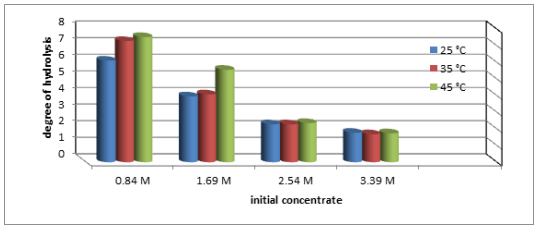
B. Effect of initial concentration of acetamide:

The heterogeneous catalytic hydrolysis of acetamide in presence of copper complex catalyst was carried out at different conc-entration of acetamide (0.84, 1.69, 2.54 and 3.39 M) with different weights of copper complex

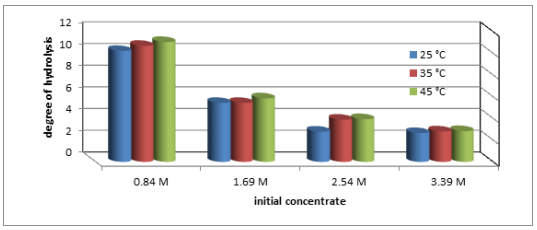
catalyst (0.1, 0.3, 0.5 and 0.7 gm) the degree of catalytic hydrolysis – initial concntration of acetamide curves obtained under these experimental conditions are represented in **Figour (7-10)**. It is clear that the degree of catalytic hydrolysis of acetamide decrease with increasing the concentration of acetamide. As mentioned before, the slow rate of acetamide catalytic hydrolysis observed at the initial stage of the reaction indicated the presence of an induction period at the start of the reaction due to the formation of some active centers on the surface of the copper complex catalyst. The induction period decreases by increasing both the amount of catalyst and temperature.



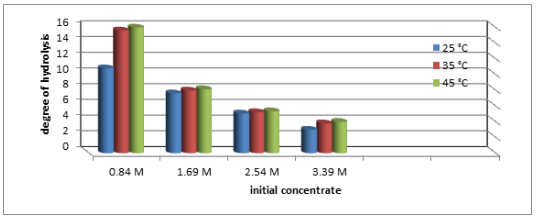
Figour (7):Effect of initial concentration of acetamide on the catalytic hydrolysis of acetamide ,at 0.1g of Complex as a catalyst).



Figour (8):Effect of initial concentration of acetamide on the catalytic hydrolysis of acetamide ,at 0.3g of Complex as a catalyst).



Figour (9):Effect of initial concentration of acetamide on the catalytic hydrolysis of acetamide , at 0.5g of Complex as a catalyst).



Figour (10):Effect of initial concentration of acetamide on the catalytic hydrolysis of acetamide , at 0.7g of Complex as a catalyst).

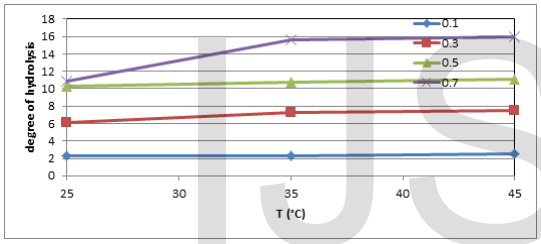
C. Effect of temperature:

The catalytic hydrolysis of acetamide on copper complex catalyst was carried out at different temperature (25, 35 and 45 °C) and the results given in **Figour (11-14)**. The increase in the degree of hydrolysis with increase in temperature due to endothermic nature of the reaction. The specific rate constant increased with temperature raised as shown in **Table (1)** results obtained are shown to be obyed the arrhenious equation of E_a (Arrhenious energy of activation in Kcal) derived from equation :

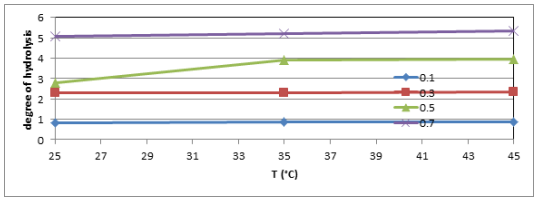
$$E_a = 2.303\ R\ \frac{T_1 - T_2}{T_2 - T_1}\ \log\ \frac{k_1}{k_2}$$

Table (1): Rate constant for catalytic hydrolysis of acetamide (S^{-1}) by copper complex catalyst at different temperature.

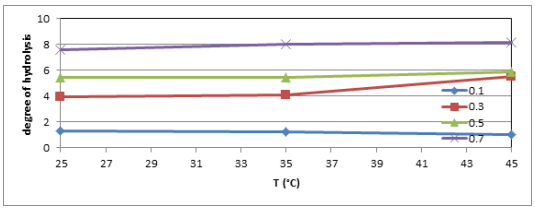
Temp. (^oC)	*1/T*	*k*	*Log k*
25	0.00335	0.0019	-2.72
35	0.00324	0.0020	-2.69
45	0.00314	0.0021	-2.67



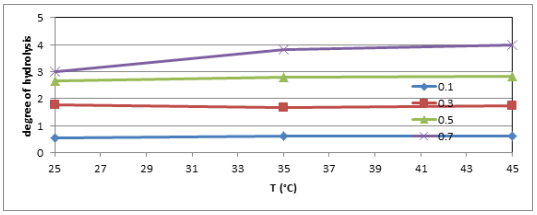
Figour (11):Effect of temperature on the hydrolysis of acetamide (at [acetamide]$_o$ = 0.84 M , at various amount of complex as a catalyst).



Figour (12):Effect of temperature on the hydrolysis of acetamide (at [acetamide]$_o$ = 1.69 M , at various amount of complex as a catalyst).



Figour (13):Effect of temperature on the hydrolysis of acetamide (at [acetamide]$_o$ = 2.54 M , at various amount of complex as a catalyst ^oC).



Figour (14):Effect of temperature on the hydrolysis of acetamide (at [acetamide]$_o$ = 3.39 M , at various amount of complex as a catalyst).

Table (2) calculated the Arrhenious energy of activation and thermodynamic parameter for catalytic hydrolysis of acetamide by copper complex catalyst (ΔH, ΔS, ΔG and E_a) as the following :

Table (2): Thermodynamic parameter for catalytic hydrolysis of acetamide by copper complex catalyst

Temp. (K)	*ΔG* (KJ/mol)	*ΔS* (J/mol k)	*ΔH* (KJ/mol)	*E_a* (KJ/mol)
298	88.5	-292.45	1.368	4.569
308	91.44			
318	94.36			

The enthalpy of reaction ΔH in all temperature are positive indicating the endothermic nature of reaction, entropy of reaction ΔS show negative value indicating the spontaneous nature of the reaction. Equation used for calculation all thermo-dynamic parameter are :

The enthalpy of reaction ΔH from equation:

$$Ln\ k/k298 = \Delta H/1.99\ (\ 1/T - 1/298\ )$$

The free energy of reaction from equation :

$$Ea\ (\Delta G) = -RT\ ln\ K_{aq}$$

The entropy of reaction from equation :

$$\Delta G = \Delta H - T\Delta S$$

Table(3) summary the kinetic studies for the catalytic hydrolysis of acetamide by copper complex

amount of catalyst					
	0.7g	0.5g	0.3g	0.1g	temp.	concentration of acetamide
degree of hydrolysis (%)						
	10.82	10.23	6.11	2.35	25 °C	0.84 M
	15.64	10.7	7.29	2.35	35 °C	
	16	11.06	7.53	2.47	45 °C	
	7.63	5.44	3.96	1.3	25 °C	1.89 M
	7.99	5.44	4.08	1.24	35 °C	
	8.16	5.86	5.56	1.06	45 °C	
	5.07	2.79	2.28	0.83	25 °C	2.54 M
	5.23	3.89	2.28	0.87	35 °C	
	5.35	3.94	2.36	0.87	45 °C	
	3	2.66	1.77	0.56	25 °C	3.39 M
	3.81	2.81	1.65	0.62	35 °C	
	4	2.84	1.74	0.62	45 °C	

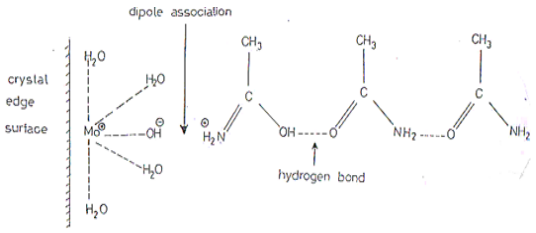
2. Adsorption mechanisms of acetamide

The study of adsorption of acetamide into copper complex catalyst allowed clasification to the number of points. Under our working conditions, i.e.at low aqueous concentration and without imposing a pH on the solution :

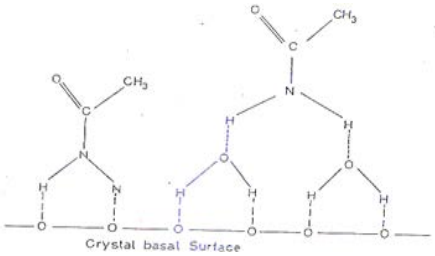
I. The acetamide is irreversible adsorbed at the external surface of copper complex catalyst particles.
II. The adsorption involves the existence of neutral and charged (protonated) molecules.
III. These two types of molecules lead to kinds of adsorption; chemisorption for protenated molecules and physical adsorption for neutral molecules.
IV. The quantity chemisorbed depends on the poiarizing power of exchangeable cation.
V. The amount retained through physical adsorption is more substantial one, it decreases strongly as temperatre increases.

The experimental results showed that a physical adsorption of netural molecules must be superimposed on the intense adsorption which has been described. This physical adsorption takes place through the formation of hydrogen bonds between the neutral acetamide molecules on the one hand, and the protonated molecules on the srface of copper complex catalyst, on the other hand the following schemes are possible:

a) Adsorption on the edge as in Figour (15).
b) Adsorption on the basal planes as in Figour (16)

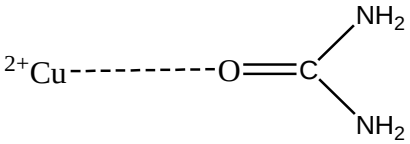


Figour(15): Adsorption mechanism of acetamide molecules on the edge surface of copper complex catalyst particales



Figour(16): Adsorption mechanism of acetamide molecules on to the basal surface of copper complex catalyst particales

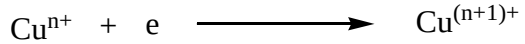
The presence of water bridges between the acetamide molecule and the copper complex catalyst accounts for the decrease of physical adsorption due to drying of the copper complex catalyst and as the adsorption temperatre increases. The mobility of the water molecules is enhanced to such an extent that no bridge linkages may be created. The low hydration capacity of the copper complex cation allows adirect coordination of acetamide molecule with cation located on the edge surface as the following :



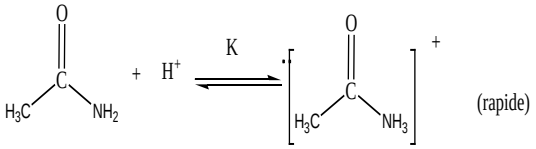
3. Mechanism of acetamide hydrolysis over copper complex catayst :

Various mechanisms have been proposed for the heterogeneous catalytic hydrolysis of acetamide over metal complexs catalysts containing metal ions of variable valences. However most of them are based on the oxidation reduction of the catalysts. On this basis, the dissociation of acetamide may take place either by donating an electron from the copper complexs catalyst to the solution as:

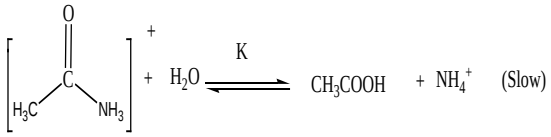
Or vice verse



A modified mechanism in presence of heterogeneous catalysts as copper complexs cold be sggested as follows :



(1)



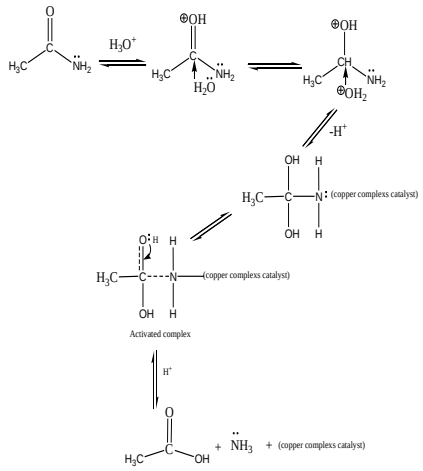
(2)

The protonation pre-equilibrium (1) is evident from the fact that a maximum rate is obtained at some high amount of the copper complexs catalyst in the hydrolysis of acetamide, the maximum corresponding to the complete protonation of the acetamide present in the system. Under the condition, [CH_3-CO-NH_2 $\gg$ H^+]. The mechanistic paths (1) and (2) would lead to thr rate low as the following :

$$\frac{-d\,[H^+]}{dt} = \frac{k\,K[H^+][CH_3\text{-}CO\text{-}NH_2]}{1+K\,[CH_3\text{-}CO\text{-}NH_2]}$$

$$\text{rate} = k\,[CH_3\text{-}CO\text{-}NH_2][H^+]$$

Possible scheme of catalytic hydrolysis of acetamide on copper complexs catalyst could be represented as in the following :



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