Synthesis and hydrolysis of an ester of the 'one ring open' hydrolysis product of the anticancer drug 1,2-bis(3,5-dioxopiperazin-l-yl)propane, 'Razoxane'

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(Received March 30, 1993)

Abstract

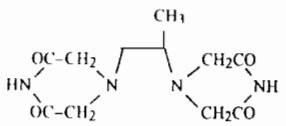
The reaction between the anticancer drug Razoxane (**I**) and $CuCl_2$ $2H_2O$ in methanol causes opening of one imide ring giving Cu-(**III**)$Cl_2 \cdot 1\frac{1}{2}H_2O$ which contains the ligand **III** resulting from methanolysis of one of the imide rings. The ester group in this complex undergoes a very rapid base promoted hydrolysis reaction to give the complex Cu-(**II**)$Cl_2 \cdot$ MeOH H_2O. The kinetics of this hydrolysis reaction at various temperatures have been studied and the very rapid rate of reaction, which is estimated to be 7.3×10^6 times faster than for the free ligand, was found to be due to a lowering in $\Delta H^{\neq}$ and an increase in $\Delta S^{\neq}$. The proposed reaction mechanism involves nucleophilic attack by OH^- ion on the ester group activated by coordination

Key words. Kinetics and mechanism, Hydrolysis; Copper complexes, Anticancer drug complexes

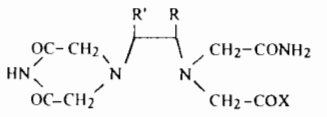
Introduction

The bis(dioxopiperazin-l-yl)alkane anticancer drugs of which the propane derivative 'Razoxane' (**I**) is the most widely used were originally designed on the basis that they would penetrate cell membranes and once inside the cell would undergo hydrolytic metabolism to produce chelating agents capable of interfering with metalloenzymes necessary for tumour cell growth [1]. The possible hydrolysis products of Razoxane, discounting subsequent amide hydrolysis, may involve the opening of one or both imide rings to give products **II** and **IV**, respectively. In experiments involving uptake of ^{14}C-labelled Razoxane by cultured cells three hydrolysis products were detected by thin layer chromatography, one of these being the diacid diamide, the other two which were unidentified may be the 'one ring' open isomers shown in **II** [2].

Aspects of the coordination chemistry of the diacid diamide (**IV**) have been reported previously [3]. The one ring open products (**II**), although not isolated, have been reported in solution following the copper(II) promoted hydrolysis of Razoxane [1]. Since these could act as tridentate 2N, O^- (from COO^-) chelating agents, or as tetradentate ligands if the amide oxygen is also involved in complexing, it is quite possible that the anticancer activity of Razoxane may be due to the formation of this one step hydrolysis product. The preparation and isolation of the one ring open hydrolysis products (**II**) have proved elusive. In this paper we report on the reaction between $CuCl_2 \cdot 2H_2O$ and Razoxane in refluxing methanol which causes opening of one imide ring and gives a copper(II) complex of the ester derivative (**III**). The ester group in this complex

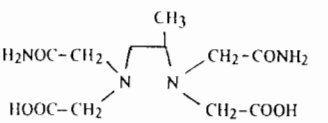


I



R=H, R'=Me or R=Me, R'=H

II: X = OH **III**: X = OCH_3



IV

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undergoes extremely rapid hydrolysis to give Cu-(**II**), the isolation, characterisation and kinetics of formation of which are also reported herein.

Experimental

*Preparation of 1,2-bis(3,5-dioxopiperazin-1-yl)propane (**I**) (Razoxane)*

Razoxane was prepared by a literature reported method [4]. Anal. Found: C, 49.30; H, 5.82; N, 20.59. Calc. for $C_{11}H_{16}N_4O_4$: C, 49.22; H, 6.03; N, 20.88%. Yield 62.5%; m.p. 228–230 °C.

*Preparation of Cu-(**III**)$Cl_2 \cdot 1\frac{1}{2}H_2O$*

A suspension of 1,2-bis(3,5-dioxopiperazin-1-yl)-propane (2 g, 7.5 mmol) and copper(II) chloride dihydrate (1.3 g, 7.5 mmol) in dry methanol (40 cm^3) was refluxed for a period of 30 min. During this time a green solution formed which was immediately followed by the formation of a green precipitate. After cooling to room temperature the product was filtered under suction and washed with methanol (20 cm^3). Finally the product was dried in an oven at 80 °C for 3 h *Anal.* Found: C, 31.24; H, 4.90, N, 12.15; Cl, 15.14. Calc. for $C_{12}H_{20}N_4O_5CuCl_2 \cdot 1\frac{1}{2}H_2O$: C, 31.19, H, 5.03; N, 12.13; Cl, 15.36%. Yield 3.0 g (6.5 mmol), 87%. Numerous attempts were made to obtain crystals of this complex suitable for X-ray analysis. These involved preparation of the complex by the above method but in the presence of an excess of $CuCl_2 \cdot 2H_2O$ (>3.1) in methanol under which conditions the complex did not precipitate from solution when it was formed. Attempts to obtain crystals on cooling and standing at room temperature or by layering a second solvent (ether, acetone, ethanol) over the methanol solution of the complex gave needle-like crystals which however were too thin for X-ray analysis.

*Preparation of Cu-(**II**)$Cl_2 \cdot MeOH \cdot H_2O$*

Since the complex Cu-(**III**)Cl_2 $1\frac{1}{2}H_2O$ was thought to contain an ester group as described later in the discussion, attempts were made to hydrolyse this and to isolate the hydrolysis product. Hence the complex Cu-(**III**)$Cl_2 \cdot 1\frac{1}{2}H_2O$ (1.3 g, 2.3 mmol) was suspended in hot methanol (50 cm^3) and the suspension stirred. Water (3.5 cm^3) was added dropwise to the hot, stirring suspension whereupon a green solution formed. This was left at room temperature for 2 days after which time a green crystalline complex formed. This was collected by suction filtration and dried in air. *Anal.*Found: C, 31.29; H, 5.19; N, 12.29; Cu, 13.93. Calc. for $C_{11}H_{18}N_4O_5CuCl_2 \cdot MeOH$ H_2O: C, 30.59; H, 5.14; N, 11.90; Cu, 13.50%. Several attempts to obtain crystals of this complex for X-ray analysis were made but without success.

In an attempt to isolate the ligand **II** the complex Cu-(**II**)$Cl_2 \cdot MeOH$ H_2O (2.5 g, 5.33 mmol) was dissolved in water (20 cm^3) and H_2S gas was passed through the solution for 5 min. The precipitated copper(II) sulfide was removed by gravity filtration and the yellow filtrate was evaporated to dryness on a rotary evaporator leaving a yellow oily residue. This was triturated by the addition of acetone followed by stirring for 2 days whereupon a white solid was obtained This was collected by suction filtration and dried over P_2O_5 in a desiccator. *Anal.* Found: C, 33.55; H, 5.80; N, 14.58; Cl, 15.5. Calc. for $C_{11}H_{20}N_4O_6 \cdot 1\frac{3}{4}HCl \cdot 1\frac{1}{2}H_2O \cdot$ C, 33.42; H, 6.32; N, 14.18; Cl, 15.71%. Yield 72% (1.5 g, 3.8 mmol); m.p. 150 °C (dec.). The IR spectrum of the product was found to be very similar to that of **IV** indicating that hydrolysis of both rings occurred during the isolation procedure

*Preparation of N,N'-dicarboxamidomethyl-N,N'-dicarboxymethyl-1,2-diaminopropane dihydrogen sulfide $(H_2NOCCH_2)(HOOCCH_2)NCH_2CH(CH_3)$-$N(CH_2COOH)(CH_2CONH_2)$ (**IV**)*

This compound was prepared via its copper(II) complex from Razoxane according to literature methods [5]. *Anal.* Found: C, 35.79; H, 6.35; N, 14.91. Calc for $C_{11}H_{20}N_4O_6 \cdot 2H_2S$: C, 35.48; H, 6.49; N, 15.05%. Yield 36%; m.p. 160 °C (dec.)

Kinetic measurements

The hydrolysis of the ester group in the complex Cu-(**III**)$Cl_2 \cdot 1\frac{1}{2}H_2O$, was studied at temperatures of 15, 25, 35 and 45 °C by the pH stat method using a Mettler DL25 automatic titrator fitted with a Mettler DG III combined electrode. The electrode assembly was buffered at the appropriate temperatures with citrate/hydrochloric acid (pH = 4.01 at 25 °C) and phosphate (pH = 6.98 at 25 °C) buffers. The reaction solution which was placed in a 50 cm^3 air tight reaction vessel fitted with a mechanical stirrer, nitrogen inlet and outlet tubes, a calibrated thermometer and a titrant inlet tube, contained Cu-(**III**)$Cl_2 \cdot 1\frac{1}{2}H_2O$ (0.19 g, 0.41 mmol) dissolved in H_2O (25.0 cm^3) with an appropriate quantity of $NaClO_4$ added in order to maintain ionic strength constant at 0.1 M. Reactions were followed for 2–3 half-lives in all cases For base hydrolysis of esters the rate expression given in eqn (1) is observed.

$$\text{rate} = k_2[\text{ester}][OH^-] \quad (1)$$

At constant pH eqn. (1) becomes

$$\text{rate} = k_{obs}[\text{ester}] \quad (2)$$

where k_{obs}, the pseudo first order rate constant, $= k_2[OH^-]$. Values of k_{obs} for the reaction were obtained by Guggenheim plots of $\ln[V_{t+2t(0.5)} - V_T]$ versus t where

$t(0.5)$ is the half life of the reaction [6]. Values of k_2 (the second order rate constant) were obtained from the expression $k_2 = k_{obs}/[OH^-]$. In order to obtain $[OH^-]$ values from the pH meter readings a standard acid solution (0.01 M), the ionic strength of which was adjusted to 0.1 M with $NaClO_4$, was titrated with standard base (0.1 M) at each temperature investigated and p(H) plotted against p[H]. At 15 °C the relationship $p(H) - p[H] = 0.04$ was observed while at temperatures 25, 35 and 45 °C the relationship $p(H) - p[H] = 0$ was observed [7]. Values of $[OH^-]$ were calculated using $pK_w (= p[H] + p[OH])$ values of 14.35 at 15 °C, 14.00 at 25 °C, 13.68 at 35 °C and 13.40 at 45 °C [8].

Activation parameters were obtained from the $\ln(k_2/T)$ versus $1/T$ Eyring plot, the slope of which is $\Delta H^*/R$ and the intercept of which is related to ΔS^* by eqn. (3) where K, h and R are the Boltzmann, Planck and gas constants, respectively [9].

$$\Delta S^* = [\text{intercept} - \ln(K/h)]R \quad (3)$$

Spectroscopic methods

The IR spectra of the ligands and complex were obtained on a Philips PU 9714 spectrophotometer. Proton NMR spectra were recorded on JEOL 60 and 250 MHz spectrometers.

Results and discussion

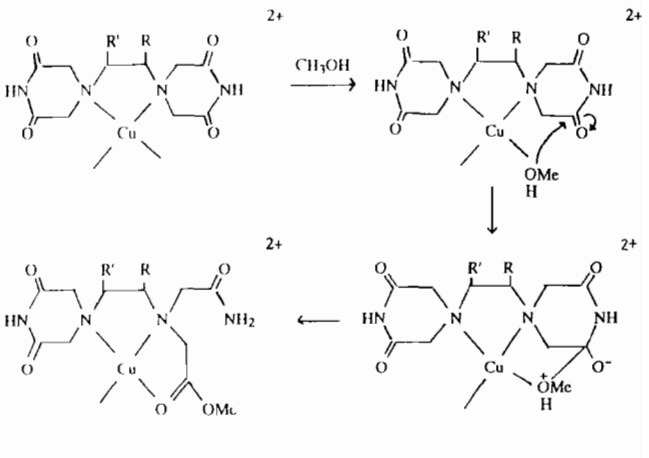
Reaction of $CuCl_2 \cdot 2H_2O$ with Razoxane

The addition of $CuCl_2 \cdot 2H_2O$ to a suspension of Razoxane in methanol followed by refluxing produced a temporary green solution from which a green product immediately precipitated. The product analysed correctly for the complex Cu-(**III**)$Cl_2 \cdot 1\frac{1}{2}H_2O$ where **III** is a monoamide, monoester obtained by methanolysis of one of the imide groups of Razoxane.

Despite exhaustive attempts the product of the above reaction could not be obtained in suitable crystalline form for X-ray analysis. However the products from several independent preparations gave a consistent IR spectrum which is quite different from that of free or coordinated Razoxane. In the carbonyl region there are three distinct absorptions, one at 1720 cm^{-1} (broad, intense) due to the C=O stretch of an imide group, another at 1655 cm^{-1} (broad, intense) due to the C=O stretch of an amide (either coordinated or uncoordinated, amide I band) and the third which is weak at 1580 cm^{-1} corresponding to the N–H bend (amide II band) of an amide group. There is a shoulder at ~1740 cm^{-1} on the 1720 cm^{-1} band which is due to the C=O stretch of an ester group. Additional absorption bands occur at 3605 cm^{-1} due to the OH stretch of coordinated or lattice water and at 3495, 3330 and 3270 cm^{-1} due to the NH stretch of the imide and amide groups. The coordination sites of the ligand are difficult to ascertain on the basis of the available information and possibilities include 2N (amino), O (ester) as shown in the product of the reaction in Scheme 1 or 2N (amino), O (amide) or N (amino), O (amide), O (ester).

The complex in aqueous solution even at $pH < 6$ undergoes an extremely rapid base promoted hydrolysis, the kinetics and mechanism of which are discussed below. This reaction proceeds with the consumption of one mole of base per mole of complex and therefore is most likely due to hydrolysis of the ester group since this should be more labile than the amide group and hydrolysis of the imide group would be much slower than the observed reaction as shown in a previous study on the metal promoted hydrolysis of Razoxane [1]. Although a number of possible structures may be suggested for the isolated product the analytical, spectroscopic and kinetic evidence strongly favours Cu-(**III**)$Cl_2 \cdot 1\frac{1}{2}H_2O$. However whether it is the imide ring adjacent to or remote from the central methyl substituent which undergoes methanolysis cannot be ascertained.

The proposed mechanism for the formation of the complex Cu-(**III**)$Cl_2 \cdot 1\frac{1}{2}H_2O$ is shown in Scheme 1. This involves methanolysis of the Cu(II)–Razoxane complex followed by intramolecular nucleophilic attack by coordinated methanol on the imide carbonyl group. The resulting tetrahedral intermediate decomposes by cleavage of the C–N bond to give the amide-ester. That the second imide ring does not undergo methanolysis by a similar mechanism may be due to the fact that in the product of the first reaction the coordination of the metal ion switches from that shown to a site involving amine N, ester O and amide O which would move the metal ion away from the second imide ring and would explain its unreactivity. A similar methanolysis reaction



Cu-(**III**)

R = H, R′ = Me or R = Me, R′ = H

Scheme 1.

which may or may not occur by the same mechanism has been observed for amides of *p*-nitrobenzoic acid [10].

The complex Cu-(III)$Cl_2 \cdot 1\frac{1}{2}H_2O$ was hydrolysed by dissolving in hot methanol/water solution as described in 'Experimental' and the product complex Cu-(II)Cl_2 MeOH H_2O was isolated The IR spectrum of this complex contains broad bands in the 3100–3400 cm^{-1} region. Its spectrum in the C=O stretching region differs from that of Cu-(III)$\cdot Cl_2$ $1\frac{1}{2}H_2O$ in that the band at 1715 cm^{-1} in the former is much broader than the band at ~1720 cm^{-1} in the spectrum of the latter. This complex does not undergo hydrolysis like Cu-(III)$Cl_2 \cdot 1\frac{1}{2}H_2O$ consistent with the absence of an ester group. Attempts were made to isolate the ligand **III** from this complex by addition of H_2S. The IR spectrum of the isolated product however was very similar to that of the diacid diamide, $HOOCCH_2(H_2NOC-CH_2)NCH_2CH(CH_3)N(CH_2CONH_2)CH_2COOH$ [5], suggesting that the second imide ring was hydrolysed during the isolation procedure

Base hydrolysis of the ester group in Cu-(III)Cl_2 $1\frac{1}{2}H_2O$

The pH of an aqueous solution of Cu-(III)Cl_2 $1\frac{1}{2}H_2O$ falls quickly with time and in the light of arguments presented in the last section this is due to hydrolysis of the ester group in the complex. The kinetics of this reaction were studied in aqueous solution at $I = 0.1$ M $NaClO_4$, by the pH stat method in the pH range 3.90 to 4.50 and over the temperature range 15–45 °C The rate of reaction was found to increase with increasing pH consistent with a base promoted hydrolysis

The reaction followed first order kinetics at each pH and at each temperature studied and the values of the pseudo first order rate constants are summarised in Table 1 Each reaction was repeated at least three times, excellent consistency between rate constants were obtained and the values quoted in Table 1 are mean values from these experiments. The effect of added copper concentrations on the rate of hydrolysis of the complex Cu-(III)Cl_2 $1\frac{1}{2}H_2O$ was investigated keeping the ionic strength constant but was found to be negligible indicating that complete complex formation occurred under the reaction conditions described in 'Experimental', Table 2. The visible spectrum of the solution changes very little during the hydrolysis. However when the pH of the product solution was raised from 4.4 to 10.7 a change in λ_{max} from 750 to 630 nm was observed. This change is consistent with hydrolysis of the imide ring as the pH is raised giving a bis acid amide product and the displacement of the two in-plane coordinated carboxylate groups by deprotonated amide groups at high pH, Scheme 2 (axial ligands not shown) [3].

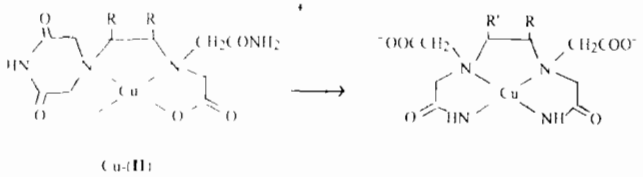
TABLE 1 Rate constants for the hydrolysis of the ester group in the complex Cu-(III)Cl_2 $1\frac{1}{2}H_2O$ at different temperatures and constant ionic strength 0.1 M $NaClO_4$

Temperature (°C)	p(H)	k_{obs}[a] (s^{-1})	$k_{obs}/[OH^-]$[b] (M^{-1} s^{-1})
15	3.90	2.33×10^{-4}	7.20×10^6
15	4.20	4.02×10^{-4}	6.23×10^6
15	4.50	8.65×10^{-4}	6.71×10^6
25	3.90	0.79×10^{-3}	9.94×10^6
25	4.20	1.45×10^{-3}	9.15×10^6
25	4.50	3.02×10^{-3}	9.55×10^6
35	3.90	2.37×10^{-3}	14.28×10^6
35	4.20	4.64×10^{-3}	14.01×10^6
35	4.50	8.95×10^{-3}	13.55×10^6
45	3.90	6.69×10^{-3}	21.16×10^6
45	4.20	12.87×10^{-3}	20.39×10^6

[a]Each value of k_{obs} is a mean of values calculated from the results of at least three independent kinetic runs All values were within ±4% of the mean value [b]In order to obtain $[OH^-]$ values from the pH meter readings standard acid (0.01 M) versus base (0.1 M) titrations were carried out at a constant ionic strength of 0.1 M and p(H) plotted versus p[H] At 15 °C, p(H)-p[H] = 0.04 while at the other temperatures p(H)-p[H] = 0 Values of $[OH^-]$ were calculated using pK_w values of 14.35 at 15 °C, 14.00 at 25 °C, 13.68 at 35 °C and 13.40 and 45 °C [8]

TABLE 2 The effect of added copper(II) on the rate of hydrolysis of the ester group in the complex Cu-(III)Cl_2 $1\frac{1}{2}H_2O$ at 25 °C, at a total ionic strength of 0.3 M

Added $[Cu^{2+}]$ (mol dm^{-3})	$[NaClO_4]$ (mol dm^{-3})	pH	k_{obs} (s^{-1})
0.1	0.0	3.90	7.51×10^{-4}
0.05	0.15	3.90	7.36×10^{-4}
0.00	0.30	3.90	7.77×10^{-4}

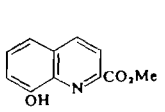


Cu-(II)

Scheme 2

The observed rate of hydrolysis of the ester group in Cu-(III)Cl_2 $1\frac{1}{2}H_2O$ is very fast Since attempts to isolate the free ester were unsuccessful its rate of hydrolysis is unknown. However the hydrolysis of methyl glycinate $NH_2CH_2COOCH_3$ may be taken as a suitable model and the reported k_2 value for this at 25 °C is 1.3 M^{-1} s^{-1} [11] The second order rate constant for the base hydrolysis of the ester group in the complex Cu-(III)$Cl_2 \cdot 1\frac{1}{2}H_2O$ at 25 °C is 9.5×10^6 M^{-1} s^{-1} which represents an acceleration of 7.3×10^6 over the estimated rate for the free ester. Previous systems which show greatly accelerated rates for ester hydrolysis include

the copper(II) complex of **V** which undergoes base hydrolysis 2×10^8 times faster than the free ligand [12], complexes of **VI** which undergo base hydrolysis 10^3–10^6 faster than the free ligand [13], the copper(II) complex of **VII** which undergoes base hydrolysis some 2.2×10^7 times faster than the free ligand [14] and the copper(II) complex of the tetramethylester of EDTA undergoes base hydrolysis some 1.6×10^5 times faster than the free ligand [15].



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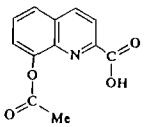

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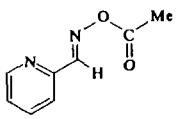
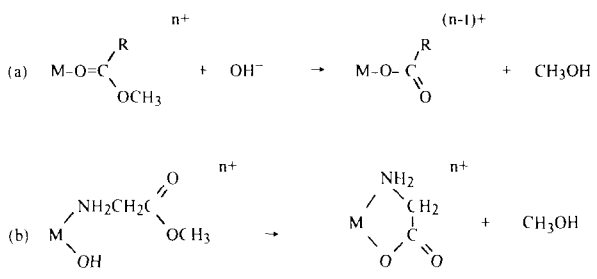


VII

Two general reactions account for metal ion promoted ester hydrolysis and these are shown in Scheme 3. The mechanism of the reaction in Scheme 3(a) leads to rapid hydrolysis because the metal ion by coordination increases the susceptibility of the ester carbonyl group to attack by nucleophiles. The rate acceleration in this case is reflected in the activation parameters with decreased $\Delta H^{\neq}$ and a more positive $\Delta S^{\neq}$, the latter due to charge neutralisation and desolvation in the transition state [16]. The mechanism in Scheme 3(b) leads to rapid hydrolysis because of the juxtapositioning of the reactants in the coordination sphere of the metal ion. For this mechanism there is desolvation of OH^- in the ground state hence $\Delta S^{\neq}$ is large and negative and the acceleration in rate is due totally to a lowering in $\Delta H^{\neq}$.

Mechanisms such as those described above are possible for the base hydrolysis of the ester group in the complex Cu-(**III**)$Cl_2\cdot1\frac{1}{2}H_2O$. In order to distinguish between these mechanisms activation parameters were determined using the Eyring plot of $\ln(k_2/T)$ versus $1/T$, Fig. 1, from which the values $\Delta H^{\neq}=26.0\pm1.1$ kJ mol^{-1}, $\Delta S^{\neq}=-23.9\pm2.0$ J K^{-1} mol^{-1} were calculated [9]. For the free ligand the expected values of $\Delta H^{\neq}$ would be ~44 kJ mol^{-1} and $\Delta S^{\neq}\sim-90$ J mol^{-1} K^{-1} based on the values for methyl glycinate [8]. The enhanced rate for the base promoted hydrolysis of the ester group in the complex Cu-(**III**)$Cl_2\cdot1\frac{1}{2}H_2O$ is therefore due to contributions from a decreased $\Delta H^{\neq}$ and an increased $\Delta S^{\neq}$. The large increase in $\Delta S^{\neq}$ implies desolvation between the ground and transition states and is indicative of a mechanism involving nucleophilic attack by external OH^- on the complexed ester group as in Scheme 3(a). By comparison the thermodynamic parameters for the copper(II) ion promoted hydrolysis of **V** are $\Delta H^{\neq}=33.1$ kJ mol^{-1} and $\Delta S^{\neq}=-22.6$ J K^{-1} mol^{-1} whereas for the copper(II) promoted hydrolysis of **IV** $\Delta H^{\neq}=33.9$ kJ mol^{-1} and $\Delta S^{\neq}=25$ J K^{-1} mol^{-1} at 298 K. Generally enthalpies of activation for base hydrolysis of copper(II) ester complexes lie in the range 20–35 kJ mol^{-1} [17].



Scheme 3.

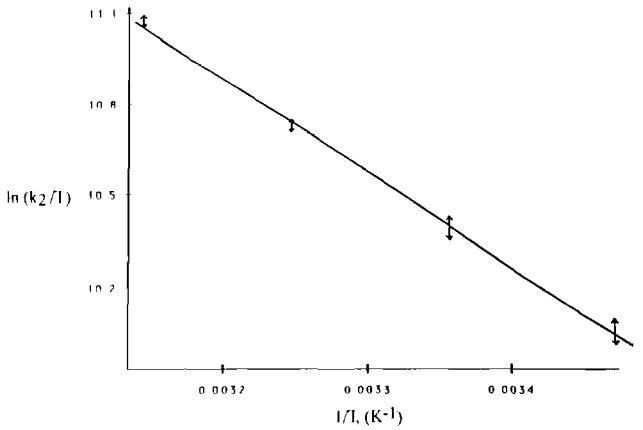


Fig 1 Eyring plot of $\ln(k_2/T)$ versus $1/T$ for the base hydrolysis of the ester group in the complex Cu-(**III**)Cl_2 $1\frac{1}{2}H_2O$

Acknowledgements

We thank the Xunta de Galicia, Spain for financial support for E.B.G. on leave from the Departmento de Quimica Inorganica, Universidad de Santiago de Compostela (Spain) and also the Research Committee of the Royal College of Surgeons in Ireland (L.P.R.). We thank the Department of Chemistry, University College Dublin for microanalytical results.

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