Physiochemical Properties and Kinetics of the Decomposition of N-Hydroxymethylated Ethionamide in Aqueous Solution and Assessment of its Solubility as Possible Pro-Drug

by

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ABSTRACT:

The physiochemical properties and Kinetics of the decomposition of N-hydroxymethyl ethionamide in aqueous solution was studied to assess its suitability as pro-drug of ethionamide. The N-hydroxymethyl derivative was found to possess higher water solubility and higher intrinsic dissolution rate than the parent compound. The derivative also exhibited lower lipophilicity than the parent compound, and showed an apparent hydroxide ion catalysed decomposition in the pH range of 5 - 8.8. The N-hydroxymethyl ethionamide was very rapidly cleaved to formaldehyde and the parent compound at pH 7.4 and 37°C and it is therefore suggested that N-hydroxymethylation may be considered as a potential means of obtaining pro-drug of ethionamide.

INTRODUCTION

Previous studies (1,2), have shown N-hydroxymethylation as a potential means of obtaining pro-drug forms of amides and imides. Ethionamide possessing thioamide functional group was considered amenable to this type of reaction. Ethionamide is an anti-tubercular agent used mainly for pulmonary tuberculosis resistant to isoniazid or when the patient is intolerant to other drugs. The drug is insoluble in water readily absorbed from the gastro-intestinal tract and is extensively matabolised, that less than one percent of it is excreted as active form in urine (3). The drug has also been reported to produce adverse effects, like hypersensitisation, psychotic reaction and gastro intestinal disturbances etc., of which the latter is the most common (3).

The purpose of this investigation, was to study the feasibility of utilising this pro-drug approach to improve the water solubility, so that bioavailability of the drug may have to depend both on solubility and partition co-efficient rather than mainly on the latter. Also increased water solubility may improve the parenteral administration of the drug which is seriously hampered by its low aqueous solubility.

In this paper, the synthesis, physiochemical properties and the kinetics of breakdown of N-hydroxymethyl ethionamide are described.

EXPERIMENTAL

Materials: Ethionamide was of pharmaceutical grade (sigma product), and all other reagents were BOH/Merck products. Ultra-voilet, Visible and Infra-red measurements were done with Sp8 - 4000 UV/visible spectrophotometer and Unicam Sp - 1000 respectively. The pH measurements were carried out at the temperature of study with Eil Ph - meter. Melting points were taken on a capillary melting point apparatus and uncorrected. The N.M.R analysis was done using 60MHz apparatus.

SYNTHESIS AND CHARACTERISATION OF N-HYDROMETHYL ETHIONAMIDE

To a solution of 5g (30 mmol) of ethionamide in 30 ml of ethanol was added 4.86g (162.5 mmol) of 37% formaldehyde and the mixture was refluxed for 45 minutes. The solvent was removed under reduced pressure and the reaction mixture was allowed to cool and then left overnight in a refrigerator. The product was recrystallised from benzene, m.p 121 - 124 °C. It was characterised by elemental analysis (4), U.V, I.R, N.M.R. and by molecular weight determination (5). The purity was checked by thin layeor chromatography and melting point.

Solubility Determination: was determined in a water at 30°C after shaking for 24hrs. The supernatant was filtered and the concentration of the filtrate was determined spectrophotometrically at 289 nm by reference to the calibration graph of ethionamide. The result are shown in table 1

Intrinsic Dissolution Rate: was determined using Wood's apparatus (6) A portion of the powder (700mg) was compressed in a hydraulic press at about 1000kg. The apparatus was placed in a disso-

lution medium (500ml), that was agitated with magnetic stirrer. Analysis of the samples withdrawn at intervals was determined spectrophotometrically at 289nm. Intrinsic dissolution rates in $mgml^{-1}min^{-1}cm^{-2}$ was calculated from the slopes of amount dissolved against the time divided by the surface area of the opening in the die of the apparatus. The result are Shown in table 1.

Apparent Partition co-efficient was determined in 1 - octanol - water systems. The aqueous phase was 0.1M phosphate buffer (pH 7.4) and the organic phase was 1-octalnol. Exactly weighed compounds (50 mg each) were dissolved in a mixture of 20ml of the aqueous phase and 30ml of organic phase, each system being previously saturated with the other. The system was agitated at 30°C for 1.5 hours to achieve complete equilibration. Analysis of the concentration in each phase was done spectrophotometrically at 289 nm and the apparent partition co-efficient calculated. The result are shown in table 1.

Kinetics of Decomposition: was determined in aqueous buffer solutions at pH of 5.00 7.40, 8.40 and 8.80 at 37°C ± 0.1 and constant ionic strength (u = 0.4_ using potassium chloride. The buffer solutions used were acetate, phosphate and borate. Measurement of formaldehyde released was utilised to follow the reaction progress colorimetrically (6). The initial concentration of N-hydroxymethyl ethionamide was 5.09×10^{-4}M, and at suitable intervals, 1ml aliquot was diluted to 10ml and 0.5 ml of the dilute solution was used for analysis. In the analysis, 0.4 ml of 0.1M acetate buffer (pH 4.0) and 0.1 ml of a 0.5% aqueous solution of 3-methyl-benzothiazol-2-one hydrazone hydrochloride were added to each of the aliquot. After 30 minutes standing at room temperature (30°C), 1ml of a 0.25% ferric chloride hexahydrate solution was added, 10 minutes later, 1.5ml of distilled water was added and the absorbance read at 626nm against a reagent blank. First - order rate constants were determined from plots of log (A - At) against time, where A and At are the absorbance readings at infinity and at time, t respectively. Results are shown in table 11

RESULTS AND DISCUSSION

The water solubility of the N-hydroxymethyl ethionamide was measure and compared to that of ethionamide. The result in table 1, showed a 2.3 - fold increase in solubility of the derivative when compared to the parent compound. The intrinsic dissolution rate of the derivative in water is higher than the parent compound, and the determined logarithm of the apparent partition co-efficient of the derivative showed it to be of lower lipohilicity than ethionamide. The hydrolysis of derivative in aqueous solution at 37°C was subject to specific base catalysis. At constant temperature and pH, the reactions were of first-order rate Kinetics. In the pH range studied, the observed pseudo -first- order rate constants were found to be directly proportional to the hydroxide ion activity as the plot of log Kobs against pH gave a linear graph with slope of 0.93. Second - order rate constants were calculated from $Kobs = K_1 aoH^{-1}$ where aoH refers to the hydroxide ion activity, Kobs = first order rate constant and K_1 = second order rate constant. The aoH activity was calculated from the measured pH (at 37°C) according to the equation (7), $aoH = 10^{(pH - 13.62)}$ -2 Applying logarithm, equation 2 becomes

$\log aoH = pH - 13.62$

As the result of this study, showed that there was improved water solubility of the derivative and also the conversion of the derivative into formaldehyde and the parent compound at pH 7.4 (37°C), N-hydroxymethyl ethionamide may be considered a pro-drug form of ethionamide

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SOLUBILITY, DISSOLUTION RATE AND PARTITION CO-EFFICIENT OF ETHIONAMIDE AND N-HYDROXYMETHYL ETHIONAMIDE AT 30 ± 1°C

Compound	Solubility ($Mgml^{-1}$)	Dissolution Rate ($Mgml^{-1}min^{-1}cm^{-2}$)	Log of Partition Co-efficient
Ethionamide	4.10×10^{-2}	2.65×10^{-4}	1.61
N-hydroxymethyl Ethionamide	9.20×10^{-2}	4.42×10^{-4}	1.57

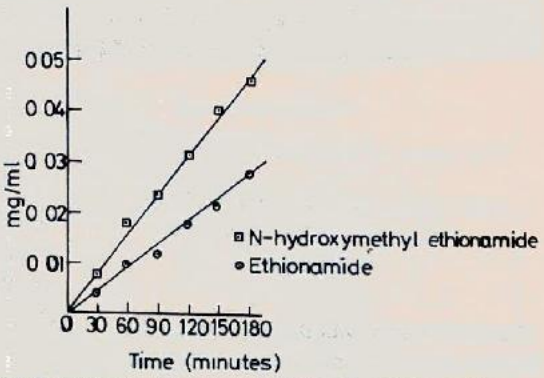

Fig. 2: Intrinsic dissolution rate of ethionamide and N-hydroxymethyl ethionamide in water at 30 ± 1°C

TABLE II

FIRST-ORDER AND SECOND-ORDER RATE CONSTANTS OF N-HYDROXYMETHYL ETHIONAMIDE AT 37 ± 0.1°C (μ = 0.4)

Buffer	pH	K_{obs} (Min^{-1})	K_1 ($M^{-1}min^{-1}$)
Acetate	5.0	-	-
Phosphate	7.4	0.009	0.00149
Borate	8.0	0.023	0.00962
	8.4	0.041	0.00683
	8.8	0.079	0.00523

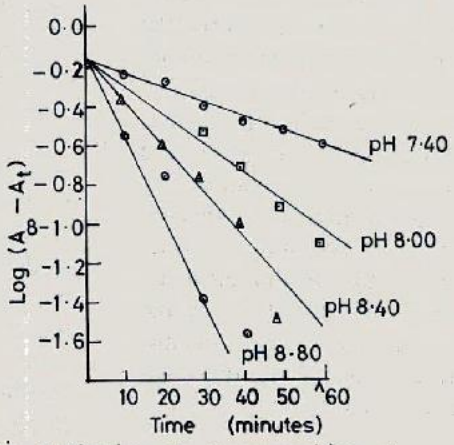

Fig. 3: Kinetics of decomposition of N-hydroxymethyl ethionamide in agueous solution at 37 ± 0.1°C

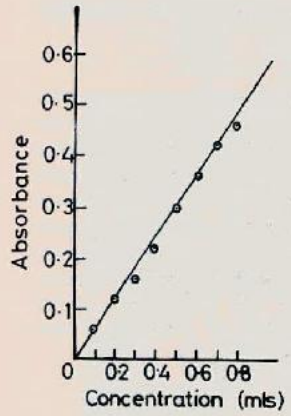

Fig. 1: Calibration graph of ethionamide, stock solution = 3.008×10^{-4} M