



Ionic strength effects on the photodegradation reactions of riboflavin in aqueous solution



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ABSTRACT

A study of the effect of ionic strength on the photodegradation reactions (photoreduction and photoaddition) of riboflavin (RF) in phosphate buffer (pH 7.0) has been carried out using a specific multicomponent spectrometric method. It has been found that the rates of photodegradation reactions of RF are dependent upon the ionic strength of the solutions at different buffer concentrations. The apparent first-order rate constants (k_{obs}) for the photodegradation of riboflavin at ionic strengths of 0.1–0.5 (0.5 M phosphate) lie in the range of $7.35\text{--}30.32 \times 10^{-3} \text{ min}^{-1}$. Under these conditions, the rate constants for the formation of the major products, lumichrome (LC) by photoreduction pathway, and cyclodehydroriboflavin (CDRF) by photoaddition pathway, are in the range of $3.80\text{--}16.03$ and $1.70\text{--}6.07 \times 10^{-3} \text{ min}^{-1}$, respectively. A linear relationship has been observed between $\log k_{\text{obs}}$ and $\sqrt{\mu}/1 + \sqrt{\mu}$. A similar plot of $\log k/k_0$ against $\sqrt{\mu}$ yields a straight line with a value of $\sim +1$ for $Z_A Z_B$ showing the involvement of a charged species in the rate determining step. NaCl appears to promote the photodegradation reactions of RF probably by an excited state interaction. The implications of ionic strength on RF photodegradation by different pathways and flavin–protein interactions have been discussed.

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1. Introduction

The ionic strength of a solution can have a significant effect on the rate of a chemical reaction and is known as the primary kinetic salt effect. The relationship between the rate constant and the ionic strength for aqueous solution at 25 °C may be expressed by the Bronsted–Bjerrum equation [1,2]:

$$\log k = \log k_0 + 1.02Z_A Z_B \sqrt{\mu} \quad (1)$$

where Z_A and Z_B are the charges carried by the reacting species in solution, μ , the ionic strength, k , the rate constant of degradation, and k_0 , the rate constant at infinite dilution. A plot of $\log k/k_0$ against $\sqrt{\mu}$ should give a straight line of slope $1.02 Z_A Z_B$.

Eq. (1) is valid for ionic solutions up to $\mu = 0.01$. At higher concentrations ($\mu \leq 0.1$) the Bronsted–Bjerrum equation can be expressed as

$$\log k = \log k_0 + 1.02Z_A Z_B \sqrt{\mu}/(1 + \beta\sqrt{\mu}). \quad (2)$$

In Eq. (2) the value of β depends on the ionic diameter of the reacting species and is often approximated to unity.

If the rate constants of a reaction are determined in the presence of a series of different concentrations of the same electrolyte, then a plot of $\log k$ against $\sqrt{\mu}$ is linear even in the case of solutions of high ionic strength [3]. The influence of ionic strength on the kinetics of drug degradation and chemical reactions has been discussed by several workers [3–10]. Ionic strength has been found to effect the aggregation kinetics of TiO_2 [11] and the stability of Ag nanoparticles [12]. The primary salt effects on the rates and mechanism of chemical reactions have been discussed [13,14].

In drug degradation and stability studies, the reactions are normally carried out at a constant ionic strength to minimize its effect on the rate of reaction [15–20]. However, a large number of studies have been conducted to evaluate the influence of ionic strength on the kinetics of chemical [21–30] and photodegradation of drug substances [31]. The ionic strength effects have important implications in photoinduced electron transfer reactions and the binding ability of proteins to flavin species [32]. Laser flash photolysis studies of the kinetics of electron transfer between flavin semiquinone and fully reduced flavins and horse rate cytochrome *c* have shown that the presence of a charged phosphate group in the N-10 ribityl side chain leads to small ionic strength effects on the rate constant whereas a charged group attached to the dimethylbenzene ring produces a large ionic strength effect [33]. Attempts have been made to describe the dependence of bimolecular rate constants on ionic strength for small molecules and protein interactions [33–38]. A temperature dependent study of the effect of ionic strength on the photolysis of riboflavin (RF) using a low intensity

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lamp has been conducted. In higher ionic strength phosphate buffer (0.31 M) an initial faster photolysis phase is observed that is followed by a slower second phase and vice versa in lower ionic strength buffer (0.05 M) [39]. In the presence of higher concentration (>0.1 M) of divalent phosphate anions (HPO_4^{2-}) and pH values above 6.0, the normal course of RF photolysis (photoreduction) involving 10-dealkylation to form formylmethylflavin (FMF), lumiflavin (LF) and lumichrome (LC) [40] is shifted to photoaddition to yield cyclodehydroriboflavin (CDRF) [41,42]. The present study involves the evaluation of ionic strength effects on the photodegradation of RF with a change in the mode of reaction at higher buffer concentrations. These effects may significantly influence the rates and mechanism of RF degradation reactions, flavin–protein interactions and the kinetics of electron transfer reactions. The study of ionic strength effects is also necessary since the single and multivitamin parenteral and total parenteral nutrition (TPN) preparations containing RF are isotonic and the amount of NaCl present (0.9%, w/v) may influence the stability of RF on photodegradation. The effects of ionic strength on a change in the mode of photodegradation of RF need to be investigated. Some related work on the effect of factors such as pH [40] and buffer [43,44], on the photodegradation of RF has been reported.

2. Materials and Methods

Riboflavin (RF), lumiflavin (LF) and lumichrome (LC) were obtained from Sigma Chemical Co., St. Louis, MO. Formylmethylflavin (FMF) and cyclodehydroriboflavin (CDRF) were prepared by the methods of Fall and Petering [45] and Schuman Jorns et al. [41], respectively. The following buffer system was used throughout: (0.1–0.5 M) KH_2PO_4 – K_2HPO_4 , pH 7.0, the ionic strength was adjusted in the range, 0.1–0.5 M with NaCl.

2.1. Photodegradation

A 10^{-4} M aqueous solution of RF (100 ml) at pH 7.0 (0.1–0.5 M phosphate buffer) with varying ionic strength (0.1–0.5 at each buffer concentration) was prepared in a Pyrex flask and placed in a water bath maintained at 25 ± 1 °C. The solution was irradiated with a Philips HPLN 125 W high pressure mercury vapor fluorescent lamp (emission at 405 and 435 nm), fixed horizontally at a distance of 25 cm from the center of the flask. The solution was continuously stirred by bubbling a stream of air in the flask. Samples of the photolysed solution were used at various intervals for spectrometric assay.

2.2. Assay Method

The assay of RF in the photodegraded solutions was performed by a five component spectrometric method to avoid any interference of its normal photolysis (FMF, LF, LC) and photoaddition (CDRF) products. The absorption spectra of RF and photoproducts, the scheme of analysis and the details of the method have been reported [20,46]. The RSD of the method is within $\pm 5\%$.

2.3. Light Intensity Measurements

Potassium ferrioxalate actinometry [47] was used to determine the intensity of the Philips HPLN 125 W high pressure mercury vapor fluorescent lamp ($1.12 \pm 0.11 \times 10^{17}$ quanta s^{-1}). The lamp emits at 405, 436, 545 and 578 nm and only the 405 and 436 nm bands are absorbed by RF. This amount to about 54% of the photon energy available for absorption by RF on the basis of the spectral power distribution of the lamp.

2.4. Fluorescence Measurements

The fluorescence intensity of RF solutions in the presence and absence of NaCl was measured at room temperature at about (~ 25 °C) on a Spectromax 5 fluorimeter (Molecular Devices, USA) in the end point mode using $\lambda_{\text{ex}} = 374$ nm and $\lambda_{\text{em}} = 520$ nm [48]. The fluorescence intensity was recorded in relative fluorescence units using a pure 0.05 mM RF solution (pH 7.0) as a standard.

3. Results and Discussion

3.1. Preliminary Considerations

The Philips HPLN 125 W high pressure mercury fluorescent lamp emits in the visible region at 405 and 435 nm, the latter band partially overlaps the absorption maximum of RF at 445 nm [46]. Therefore, the lamp is suitable for the photolysis of RF and has been used in earlier studies [40,42–44,49,50].

An important consideration in kinetic studies is the use of a specific assay procedure to determine the desired compound in the presence of degradation products. The multicomponent spectrometric method used in this study is capable of simultaneous determination of RF and its photoreduction and photoaddition products with reasonable accuracy [20]. It has previously been applied to the assay of these compounds during the kinetic studies of photodegradation of RF [20,43,44,49,50]. Such an analysis cannot be carried out rapidly by the HPLC method. The assay of RF and photoproducts in a typical reaction carried out at pH 7.0 with an ionic strength of 0.5 is reported in Table 1. A good molar balance is obtained during the reaction indicating the accuracy of the method.

3.2. Spectral Characteristics of Photolysed Solutions

The absorption spectra of RF determined during a photolysis reaction at pH 7.0 with zero and 0.5 ionic strengths show a gradual decrease in absorbance at the maximum at 445 [20,46] indicating a greater loss of RF and an increase in absorbance around 356 nm [20] at 0.5 ionic strength (Fig. 1). There does not appear to be any drastic change in the shape of the spectra in the presence of a high ionic strength of the solution. However, at this ionic strength the magnitude of spectral changes is affected, for instance, there is a greater decrease in absorbance at 445 nm and a greater increase in absorbance at 356 nm compared to that at zero ionic strength. This supports the view that an increase in ionic strength leads to an increase in the rate of photolysis reactions.

3.3. Kinetics of RF Photolysis

A large number of studies have been conducted on the photodegradation of RF under different conditions [20,39–42,46]. It has been established that the photolysis of RF in aqueous solution follows first-order kinetics [40,42,44,51,52]. In this study the effect of ionic strength on the photodegradation of RF under different conditions has been studied. Considering the photodegradation of RF as parallel first-order reactions leading to the formation of LC (k_1) and LF (k_2) as final products by

Table 1
Concentrations of RF and photoproducts (pH 7.0) at 0.5 M ionic strength.

Time (min)	RF ($\text{M} \times 10^5$)	CDRF ($\text{M} \times 10^5$)	FMF ($\text{M} \times 10^5$)	LC ($\text{M} \times 10^5$)	LF ($\text{M} \times 10^5$)	Total ($\text{M} \times 10^5$)
0	5.00	00	00	00	00	5.00
30	2.10	0.62	0.82	1.24	0.26	5.04
60	0.78	0.88	1.10	1.79	0.43	4.98
90	0.34	0.94	1.20	1.88	0.55	4.91
120	0.13	0.99	1.22	1.98	0.74	5.06

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