

Kinetic Study on the Anelation of Heterocycles. 1. Quinoxalinone Derivatives Synthesized by Hinsberg Reaction

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Kinetic studies on the Hinsberg condensation were performed trying to improve yields and achieve regioselectivity in the attainment of benzene-substituted 3-methylquinoxalin-2(1*H*)-ones. The course of the reactions between *o*-phenylenediamine (*o*-PDA) and substituted *o*-PDA with pyruvic acid (**2a**) or ethyl pyruvate (**2b**) were followed by uv spectrophotometry at different pH values. The formation of 3-methylquinoxalin-2(1*H*)-one (**6a**) was improved using sulphuric acid-water mixtures, in which the reaction proceeded by a different mechanism. 3-Methyl-7-methoxyquinoxalin-2(1*H*)-one (**7b**) was regioselectively synthesized independently of the pH of the reaction media. Reaction of 2-amino-4-methylamine (**1c**) with **2a** or **2b** led to a mixture of 6 and 7-quinoxalinone isomers, **6c** and **7c**, while 2-amino-4-nitroaniline (**1d**) and 2,4-diaminoaniline (**1e**) with **2a** or **2b** did not afford the heterocycle. In every case reactions with **2a** were 100-1000 times faster than those with **2b**. Mechanisms are proposed trying to account for the experimental results.

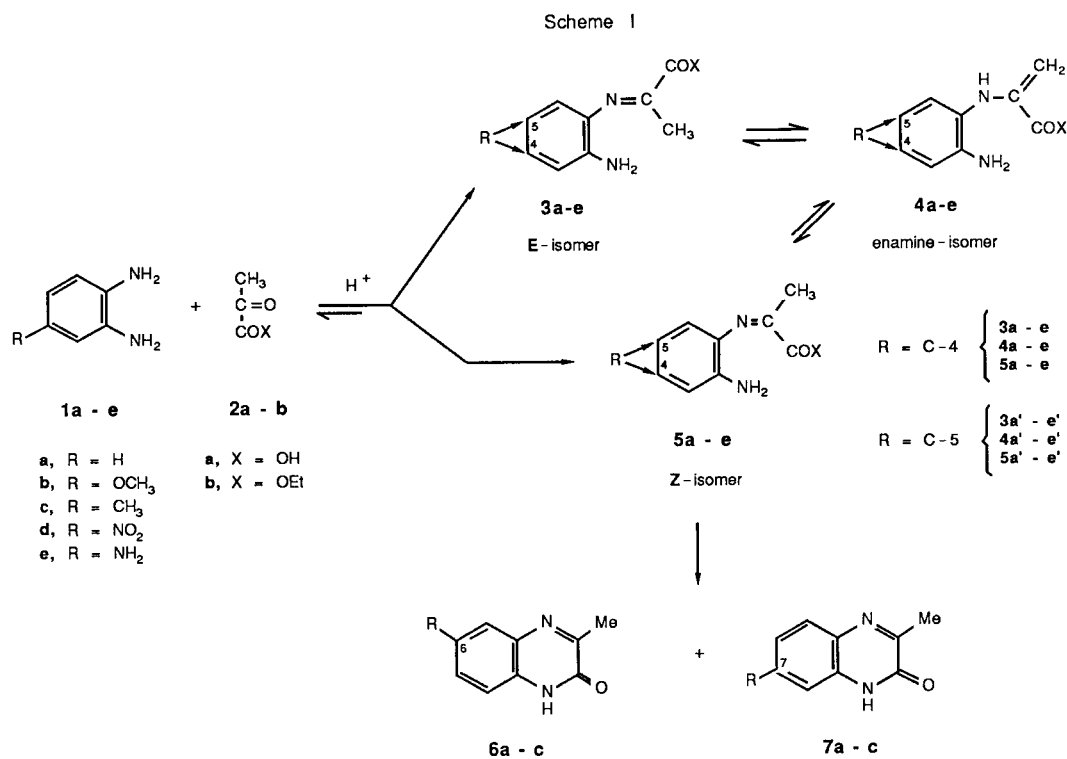
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The antineoplastic agent echinomycin is a bis-quinoxalincarboxamide that acts by a DNA bisintercalative process. The synthesis of siamese molecules based on simplified models of echinomycin stated the problem of the attainment of substituted quinoxalinones [1].

The Hinsberg reaction [2] is a practical method to obtain 3-methylquinoxalin-2(1*H*)-ones employed in the synthesis of these compounds. However, this reaction applied to substituted *o*-phenylenediamines leads to position

isomers and low yields. On this matter Lumma *et al.* [3] tried to attain regioselectivity performing the synthesis of some related compounds in acid media. Consequently, looking for better yields and unambiguous conditions for regioselective reactions we developed this investigation on the kinetics and mechanism of the Hinsberg reaction.

From the kinetic point of view, the synthesis of each 3-methylquinoxalin-2(1*H*)-one derivative presents its own characteristics so each reaction will be treated in par-



ticular.

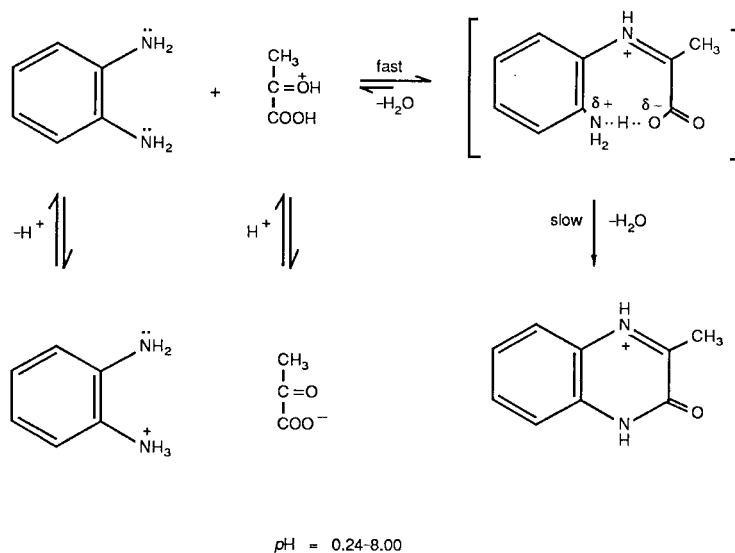
a) Reaction of *o*-Phenylenediamine (**1a**) with Pyruvic Acid (**2a**).

The reaction was performed in water at 25° at different *pH* values and in several organic solvents (Scheme I). When **6a** precipitated it was separated and the solution components, analysed by tlc. Yields of **6a** in water varied from 70 to 80% at *pH* values 0.24-8.00 but the best yield was obtained in 10% sulphuric acid ($H_o = -0.16$, 95%) where competitive reaction to the *E* \rightleftharpoons enamine isomers does not take place. Below $H_o = -0.16$ **6a** did not precipitate and above *pH* = 8.5 the reaction did not occur because the Schiff base was not formed. Reaction in 0.1 *M* hydrochloric acid rendered the higher yield of the isomeric mixture **3a** \rightleftharpoons **4a** which could be separated by tlc

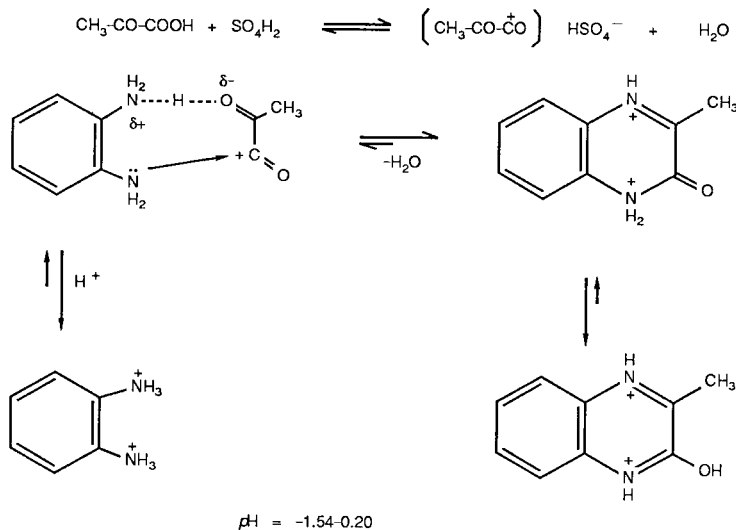
using benzene-methanol (9:1) as the eluent. When other eluents were used it was observed that the composition of this mixture at the equilibrium varied according to the polarity of the solvent. The same results were observed when this reaction was performed in organic solvents but yields in **6a** were always lower than in water.

The kinetic study on this reaction (Scheme I) was followed in buffers of *pH* values from -1.54 to 8.00 at 25°. The appearance of **6a** [4] was followed by uv spectrophotometry at 335 nm being the anelation of the *Z*-isomer the rate determining step of the reaction. Pseudo-first order reactions were observed at every *pH* range with a kinetic constant $k_{obs} = 1.003 \pm 0.002 \text{ min}^{-1}$. Experimental results and tlc observations allow us to propose the following mechanisms for this reaction (Schemes II and III).

Scheme II



Scheme III



At pH values above 0.24 (Scheme II) where competitive reactions to **3a** \rightleftharpoons **4a** and **6a** take place, a fast acid catalysed first step is considered to give almost complete transformation of **1a** into the Schiff bases isomers. The Z-isomer is then rapidly transformed into **6a** in the subsequent slower step of dehydration.

The fact that **3a** and **4a** are not formed at pH values below -0.16 (concentrated sulphuric acid solution) enables us to propose another mechanism for the reaction in these conditions, based on the basic character of pyruvic acid under acidic conditions (Scheme III).

A rapid nucleophilic attack by the amino group of **1a** upon the C=O group of **2a** and a concerted dehydration would avoid the formation of the Schiff bases and, consequently, give heterocycle as the only product of reaction.

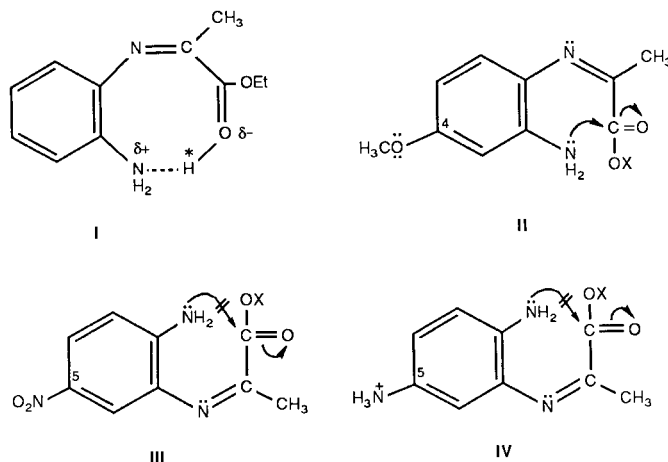
b) Reaction of *o*-Phenylenediamine (**1a**) with Ethylpyruvate (**2b**).

The change of pyruvic acid by the ethyl ester caused a decrease in reaction rate of three logarithmic units but observed yields were rather better.

Reactions were performed in a large range of H_0 -pH (-4.32-8.00) following the appearance of **6a** spectrophotometrically.

The acid catalysed formation of the Z-isomer was rate determining and pseudo-first order rate constants at pH values where they are maxima are given in Table 1.

The plot of $\log k_{obs}$ vs. pH/H_0 (Figure 1) shows the increase of rate constants with acid catalysis on going to the pH of maximum stability for the imines (~ 4) [5] and between pH 0.5-2.5 reaction becomes pH independent. The isotope effect was determined for this pH-independent section of the curve (Figure 1). The existence of a substantial primary isotope effect $K_H/k_D = 5.0$ in the pH range close to the pK_a value of the 2-NH₂ group ($pK_a \sim 1.0$) [6] is a strong evidence that the bond to the substituted hydrogen atom is being broken in the transition state, and the value



of 5.0, near the theoretical maximum (about 7.0) is good evidence that the transition state involves strong bonding of the hydrogen to both, its old and its new bonding partner. This fact enables us to propose an intramolecular acid catalysis for the reaction in the pH range 0-3 with formation of a benzoxadiazocine ring by intramolecular hydrogen bond (I). The structure of rings of this type and their stability was confirmed in related compounds by Chiale *et al.* [7] by means of uv and ¹H nmr studies.

At H_0 values below -0.5 the kinetic constant for the hydrolysis **2b** \rightarrow **2a** is two logarithmic units higher than that of anelation. This enables us to conceive for the H_0 range -4.32 to -0.5 the same concerted mechanism of dehydration as that proposed in Scheme III. Rate constants below $H_0 = -0.5$ increase towards the left hand side on increasing the amount of pyruvic acid coming from the hydrolysis of its ester and decrease with major protonation of the starting material (Figure 1).

Table 1

Observed Rate Constants at 25° for the Formation of 3-Methylquinoxalin-2(1H)-one Derivatives from *o*-Phenylenediamine (**1a**) and Substituted **1a** with Pyruvic Acid (**2a**) or Ethyl Pyruvate (**2b**) at Different pH Values

Compound No.	UV spectrum λ max (nm)	Reactants	Selected λ (nm)	pH/H_0	Max. k_{obs} (min ⁻¹)	$\log k_{obs}$
6a	227, 277, 335	1a + 2a 1a + 2b	335	-2.54-8.0	1.003	0.001
				-2.28	6.13×10^{-3}	-2.21
				0.5-2.5	3.15×10^{-2}	-1.50
				4.00	1.94×10^{-1}	-0.71
				1.50	8.51×10^{-3}	-2.07
7b	216, 234, 270, 345	1b + 2a 1b + 2b	345	6.99	1.76×10^{-2}	-1.76
				-2.28	8.50×10^{-4}	-3.07
				0.5-2.2	1.10×10^{-3}	-2.96
				6.99	3.95×10^{-2}	-1.40
				1.50	2.50×10^{-4}	-3.60
6c	228, 284, 340	1c + 2a	340	1.50	2.50×10^{-4}	-3.60
7c	228, 284, 340	1c + 2a	340	1.13	2.14×10^{-2}	-1.67

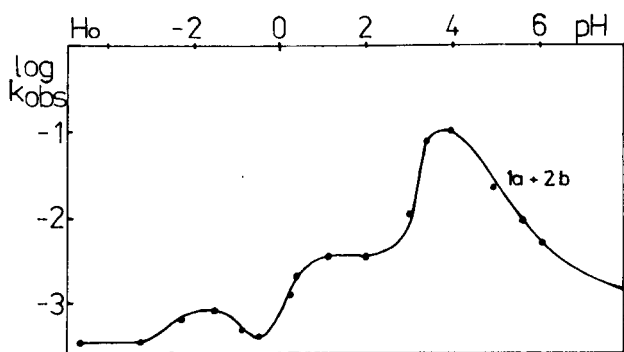


Figure 1

Influence of Ring Substitution upon the Reaction Rates.

c) Reaction of 2-Amino-4-methoxyaniline (**1b**) with Pyruvic Acid (**2a**) and Ethyl Pyruvate (**2b**).

As a result of the introduction of an electron donor group (such as -OMe) on the benzene ring we might expect an increase in reaction rates caused by the enhanced basicity of one of the amino groups of **1b**. However, differing from the reaction of **1a** + **2a**, kinetic rate constants depended on proton concentration and were somewhat lower than those observed for reaction **1a** + **2b** (Table 1). The Schiff base is formed with the more basic 1-NH₂ group of **1b** as it was observed by ¹H nmr analysis of the product **3b**. Subsequent anelation is then not favoured by the -I effect of the methoxy group in the *meta* position for the ring closure. As a result, lower rate constants were observed (Table 1).

Over all of the pH ranges studied the synthesis of 3-methyl-7-methoxyquinoxalin-2(1*H*)-one (**7b**) was regioselective (Scheme I), the yield of the 6-methoxy derivative **6b** [1] being lower than 1%. Yields of **7b** varied from 50 to 60% using **2a** as the reactant in water and were always lower when **2b** was the reactant.

Plots of k_{obs} for reactions **1b** + **2a** and **1b** + **2b** vs. pH are shown in Figure 2. The top of the curves corresponding to pH values of maximum stability for the Schiff bases is displaced to the right hand side as it was expected due

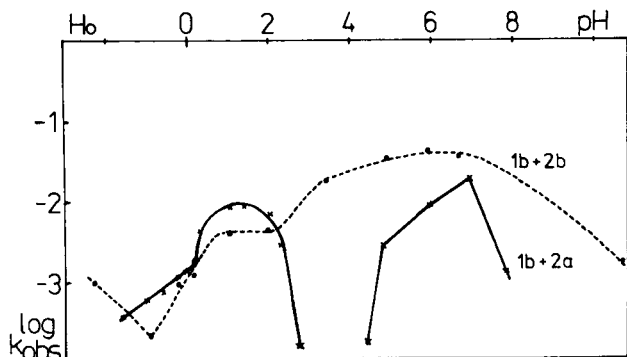


Figure 2

to the higher basicity of the 1-NH₂ group of **1b**. The curve of the reaction for **1b** + **2b** resembles that of the reaction of **1a** + **2b** and the same mechanisms apply to them (Schemes II and III).

On the other hand, the curve corresponding to the reaction of **1b** + **2a** presents atypical results below pH 4 having a range between pH 3-4 where reaction practically does not occur.

d) Reaction of 2-Amino-4-methylaniline (**1c**) with Pyruvic Acid (**2a**) and Ethyl Pyruvate (**2b**).

Reaction of **1c** with **2a**, and more slowly with **2b**, leads to a mixture of 6 and 7-methylquinoxalinones, **6c** and **7c**, (Scheme I).

Due to the similar basicity of both amino groups of **1c**, regioselectivity is not achieved on varying the pH. Reactions were followed at 340 nm and a plot of the logarithm of A_t/A_0 versus time gave a biexponential curve according to $A_t/A_0 = M \exp(b_1t) + N \exp(b_2t)$.

Feathering was employed to obtain the larger rate constants for the appearance of **7c** (Table 1). Quinoxalinones **6c** and **7c** were not separated on a preparative scale but they were isolated in solution by tlc using ethyl acetate as the eluent and their λ_{max} absorptions were determined in methanol showing identical uv spectra.

e) Reaction of 4-Nitro-2-aminoaniline (**1d**) with Pyruvic Acid (**2a**) and Ethyl Pyruvate (**2b**).

Considering the rate of formation of **6a** as a reference and taking into account that the -I effect of the methoxy group in **4** (II), quantitatively represented by a Hammett sigma value (σ_m) of 0.115 [8], causes a decrease in the rates of anelation of about one thousand times, a simple look at the sigma value for the *p*-NO₂ group in III ($\sigma = +0.778$) indicates "a priori" that reaction of the anelation **1d** + **2a** or **1d** + **2b** cannot occur; (theoretical $k' \sim 10^{-11} \text{min}^{-1}$). In fact, the mixture of the Schiff bases **3d'** \approx **4d'** \approx **5d'** in equilibrium could be isolated at pH > 1 and it was corroborated by ¹H nmr [9] that they were formed with the more basic 2-NH₂ group of **1d** but, as could be predicted applying the Hammett relationship [10], the 6-nitroquinoxalinone is not achievable.

f) Reaction of 2,4-Diaminoaniline (**1e**) with Pyruvic Acid (**2a**) and Ethyl Pyruvate (**2b**).

Compound **1e** reacted with **2a** and **2b** at pH values above 4.5 to give a mixture of Schiff bases with the 2 and 4-NH₂ groups of **1e**. At pH values below 4 at which the 4-NH₂ of **1e** is almost completely protonated, the imine formation involved the 2-NH₂ group of **1e** but the deactivating -I effect of the 4-NH₃ group ($\sigma_{p-\text{NH}_3} = 0.86$) [8] in the *para* position for the anelation (IV) also frustrated the attainment of **6e**, similarly as it had been observed with the 4-NO₂ derivative (III).

Thus we can conclude that in the preparation of benzene-substituted 3-methylquinoxalin-2(1*H*)-ones from substituted *o*-phenylenediamines, whichever the electronic effect being exerted by the substituents, condensation will not be favoured. On varying the *pH* of the reaction media changes in the mechanisms of reactions are observed and sometimes better yields are achieved, but they are always lower than those obtained with unsubstituted *o*-phenylenediamine (**1a**) under the same experimental conditions.

EXPERIMENTAL

The ultraviolet absorption spectra were measured on a Shimadzu 210A spectrophotometer. The nmr spectra were obtained on a Varian FT 80A spectrometer with tetramethylsilane as internal reference. The ir spectra were recorded on a Beckman IR-20A spectrophotometer using potassium bromide pellets. Tlc were carried out on 10 x 20 cm silicagel F₂₅₄ chromatoplates and were not activated. Analytical samples of the starting materials were used to perform the kinetic studies.

3-Methyl-7-methoxyquinoxalin-2(1*H*)-one (**7b**).

Compound **7b** used as reference was prepared by the same procedure as **6b** [1] from *N*-(2-nitro-5-methoxyphenyl)-2-oxopropanamide, mp 217-218° (from ethanol); ir: (cm⁻¹) 2850 (m) (NH=OH), 1675 (s) (C=O), 1250 (s) (Ar-O-C); ¹H nmr (DMSO-d₆): 7.9 (m, 2H, aromatics and NH), 7.0 (m, 2H, aromatics), 3.98 (s, 3H, OCH₃) and 2.52 (s, 3H, CH₃); uv (methanol): λ max nm 216, 234, 270, 345.

Anal. Calcd. for C₁₆H₁₀N₂O₂: C, 63.16; H, 5.26; N, 14.73. Found: C, 63.26; H, 5.30; N, 14.65.

Reactions of Substituted *o*-Phenylenediamines with Pyruvic Acid (**2a**) and Ethyl Pyruvate (**2b**).

4-Substituted 1,2-phenylenediamines reacted in some cases with **2a** or **2b** (sometimes with acid catalysis) to give phenyl-substituted 3-methylquinoxalin-2(1*H*)-ones (Scheme I).

4-Substituted 1,2-phenylenediamines [substituent in C-4 = OCH₃ (**1b**), CH₃ (**1c**) and NH₂ (**1e**)] were obtained by catalytic reduction of the corresponding 2-nitro derivatives, and in the case of compound **1e** from 2,4-dinitroaniline.

General Procedure.

A solution of the 4-substituted 2-nitroaniline (0.006 mole) in 50 ml of ethanol with 5% Pd-charcoal (0.1 g) was put under 30 psi of hydrogen at room temperature for two hours. The catalyst was removed by filtration under nitrogen atmosphere and **2a** or **2b** (0.1 mole) was added and allowed to react at room temperature for 24 hours. The resulting precipitate was filtered, washed with ethanol and recrystallised from the appropriate solvent.

Kinetic Measurements.

Reactions were performed at 25° using buffers over the *pH* range 1-8.50 and sulphuric acid-water mixtures for reactions below *pH* 1.0. The *pH* of each solution above 0.40 was measured at 25° in a Metrohm E632 *pH* meter using a standardized glass electrode. Values of *H*₀ were taken from Hine [11]. Reactions performed with initial concentrations 2 x 10⁻³ to 2 x 10⁻⁵*M* of **1a-e** showed a first-order dependence on the substrate at every hydrogen ion concentration at which anelation occurred. All rate constants were obtained from 1.85 x 10⁻⁵*M* initial concentrations of **1a-e**

and 9.60 x 10⁻⁴*M* of **2a-b**.

The appearance of **6a-c** and **7a-c** was followed spectrophotometrically at the characteristic quinoxalinone absorption around 325-345 nm.

Rate constants were obtained from plots of **6a-c** and **7a-c** absorbance (A_∞) against time on semilogarithmic graph paper.

Linear profiles accounted for pseudo-first order kinetics which followed the equation $v = k_{obs}[\text{amine}]$ and hyperbolic profiles accounted for kinetics which consisted of two linear segments according to the biexponential equation (A_∞) = M exp(b₁t) + N exp(b₂t) where M and N are preexponential constants and b₁ and b₂ are exponential factors related to the observed rate constants for the attainment of 7- and 6-substituted quinoxalinone derivatives respectively when competitive reactions take place.

General Kinetic Procedure.

Solutions (1.85 x 10⁻⁵*M*) of **1a-e** and (9.60 x 10⁻⁴*M*) **2a-b** in the buffers were prepared and thermostated at 25° ± 0.1. Both solutions were mixed and appearance of the reaction product was followed by uv spectrophotometry until 70-80% of its final concentration was achieved. The absorbance at time zero was estimated by extrapolation.

Kinetic Isotope Effect.

Deuterium oxide solutions were prepared by dissolving dried, crystalline **1a** in solutions of 98% deuteriosulphuric acid/deuterium oxide in 99.7% deuterium oxide. Measurements of *pD* were obtained from the relation *pD* = *pH* + 0.40 where *pH* refers to the reading of the *pH* meter in deuterium oxide solutions [12].

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REFERENCES AND NOTES

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