

Thermodynamics and Kinetics of Indole Oligomerization: Preliminary Results in Aqueous Sulfuric Acid

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ABSTRACT: Reaction rates and equilibrium constants of indole dimerization and trimerization in aqueous sulfuric acid at 298 K are reported. The equilibrium of oligomerization is attained in about 4–5 h, and formation of oligomers with more than three monomeric unit is not observed. The equilibrium of formation of the indole dimer is influenced by the protonation equilibrium of indole, which means the pK_{IH} values of indole strongly influences equilibria and kinetics of the whole process. In the evaluation of the kinetic constants, the pK_{IH} values of indole have been taken into account; in this way, the kinetic constant of formation of the dimer (k_D) results almost four order of magnitude larger than that of the trimer (k_T), suggesting a higher electrophilicity of the 3H-indolium cations with respect to the protonated dimer (which is an aliphatic ammonium salt). Further indole addition to the trimer, which is a protonated 2-alkylaniline, does not occur, since the anilinium ion is ineffective as an electrophile. © 2008 Wiley Periodicals, Inc. *Int J Chem Kinet* 41: 107–112, 2009

INTRODUCTION

Indole derivatives play a very important role in the synthesis of several compounds with pharmacological activity such as diindolylmethane, which is synthesized from indoles [1,2]. The heterocyclic ring system of indole is present in a wide variety of natural compounds (e.g., tryptophan, serotonin, and so on), many of which have important physiological activities [1,2]. Several studies on indole and derivatives, both exper-

imental and computational, can be found in the literature [3–5]. However, no work dealing with the kinetics of dimerization and trimerization and their equilibria in aqueous media has been found. The role of these species, in processes occurring in aqueous solutions, is not investigated. For instance, indole and substituted indoles are used as a corrosion inhibitor for ferrous and nonferrous alloys, but the nature of the protective phenomenon is not completely understood and the role of the indole polymers is only faintly explored [6–9].

The reversible nature of indole oligomerization is not new, but there are no data on the equilibrium constants of these reactions [10,11]. Early studies on dimerization and trimerization of indoles pointed out

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that the oligomers formation is related to indole and acid concentration, as well as to the nature of the acid [12,13]. The synthesis of indole polymers and of their reactions in different media has been carefully studied for long time, and several strategies have been reviewed [14,15]. On the contrary, the thermodynamic and the kinetics behaviors of the process are never investigated. The early paper of Schmitz-Dumont reports some data relating to the repartition of indole, dimer, and trimer in biphasic condition starting from indole dispersed in aqueous solution of acids at different concentrations: Anyway, no thermodynamics and/or kinetics data were given [12]. Recently, the nucleophilic reactivities of indoles have been carefully investigated toward several electrophiles [16,17]. The general behavior of these reactions resembles the majority of aromatic substitutions in which the rate-determining step is the formation of a Wheland-like intermediate [16,17]. Also in this paper, however, no data on the self attack of the protonated indole are reported.

In this paper, we report some preliminary results dealing with thermodynamic and kinetics behavior of dimerization and trimerization of indole in aqueous sulfuric acid at 298 K.

EXPERIMENTAL

Material

Solvents and reagents were purchased from Aldrich (www.sigmaaldrich.com) and used after the usual purification. Aqueous sulfuric acid solutions were prepared by diluting the concentrated acid, and their composition was determined by automatic potentiometric titrations against standard solutions of NaOH. Indole dimer hydrochloride (which was used instead of indole dimer sulfate) was prepared by following the literature procedure: a chilled solution of indole in 1,2-dichloroethane was saturated with dry hydrochloric acid, a white precipitate was obtained, filtered, washed with 1,2-dichloroethane and dried under vacuum. NMR, UV-vis, and IR spectra of the precipitate coincide with the literature data [10]. Indole trimer sulfate was prepared by direct synthesis from aqueous solution of sulfuric acid following the procedure described in the literature [10]. NMR, UV-vis, and IR spectra of the compound match those already published [10,11,18].

Reaction Kinetics

The kinetic runs were performed in a well-stirred thermostated reactor at 298 K and at atmospheric pressure, containing weighed samples of sulfuric acid (volume

0.1 L) at 0.5 mol L⁻¹. The desired concentration of substrate (1–6 mmol L⁻¹) was obtained by dilution of an ethanol solution of the substrate. All the operations were carried out under nitrogen to avoid indole oxidation. Small amounts of the solution were drawn at different times, and the samples were analyzed by HPLC, using a Perkin Elmer 250 pump equipped with a Phenomenex (C-8 5 μm) column and a diode array Perkin Elmer LC 235 UV detector. From a practical point of view, the range of concentrations used for studying the reaction is compelled by the necessity of balancing the solubility of reagent and products with the equilibrium conversion. As a matter of fact, conversion of indole at concentrations lower than 1 mmol L⁻¹ is too low for kinetics purpose because of the sensibility limits of the analytical method.

Nonlinear Regression Analysis

The regression of the data was carried out on simultaneous algebraic-differential equations numerically evaluated at each experimental point (X_i, Y_i). Mass balance is the regression function (f), which accounts for the constraints of the model [19]. The minimization of the square residual sum (Eq. (1)) was achieved by a step-descent method, and the convergence was verified by reducing the step of two orders of magnitude and obtaining constant values of the square residuals sum [20]. The regression variables were the direct kinetic constants k_D and k_T , whereas equilibrium constants were independently evaluated from an average of the final values of the kinetics.

$$S = \sum_{i=0}^{i=n} [Y_i - f(X_i, k_T, k_D)]^2 \quad (1)$$

Errors and correlation matrix of the kinetic constants have been evaluated using a first-order approximation of the expectation surface at the convergence point and the variance (σ) approximated to the normalized residual mean square [$\sigma^2 \cong s^2 = S/(n - 2)$] [19].

RESULTS AND DISCUSSION

Equilibria of Indole, Dimer, and Trimer

In Fig. 1, the reactions of indole in aqueous acid solution and the respective equilibria are reported. Indole (**1**) is a weak base, which is slightly protonated at the carbon in 3-position (reaction A). The resulting carbonium ion (**2**) is an electrophile that is able to attack the unprotonated indole giving **3**: the corresponding

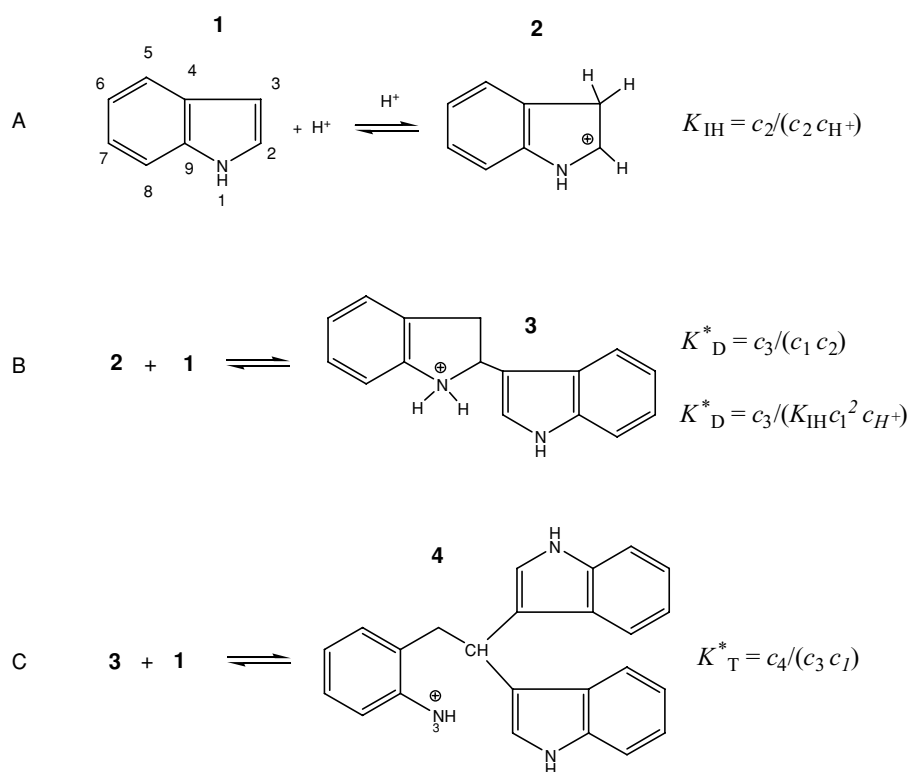


Figure 1 Reactions of indole in aqueous acid solution at 298 K.

3-substituted indole dimer ((3-(indolin 2-yl)indole), reaction B). The latter is in protonated form, and it reacts further with **1** to give **4**: the trimer ((3,3'-(2-aminophenethylidene)di-indole), reaction C). Such a compound is a fully protonated ortho-substituted alkyl-aniline, which does not react with indole under the conditions investigated.

Equilibrium B depends on the protonation of indole (equilibrium A), then the value of K_{D}^* is a function of pK_{IH} ($K_{\text{I}} = K_{\text{IH}}^{-1}$), on the H^+ concentration and on the activity coefficient of the species of the equilibrium A (see Fig. 1). In the literature, there are no univocal pK_{IH} values on the protonation equilibrium of indole, which varies from -3.5 to -2.2 (see Table I) [21–24]. Such an inconsistency is due to the different activity coefficient functions employed in the calculation, suggesting that the nature of the process is not completely explained [16,23]. In this paper, we use the more recent approach of the Mc activity coefficient function for sulfuric acid, which gives a pK_{IH} value of -2.4 [25], which is in good agreement with those reported in Andonowski and Garcia papers [23,24]. The H^+ concentration is obtained from the values of dissociation of sulfuric acid reported in the literature [26,27].

The equilibrium concentrations of **1**, **3**, and **4** together with the stoichiometric equilibrium constants

Table I Protonation Equilibrium of Indole in H_2SO_4 : K_{IH} Calculated by Using Different Activity Coefficient Functions

| Activity Coefficient Function | pK_{IH} | K_{I} | Reference |
|-------------------------------|------------------|----------------|-----------|
| H_0 | -2.8 | 0.00159 | [24] |
| H_1 | -3.5 | 0.000316 | [21] |
| X | -2.2 | 0.00631 | [24] |
| X | -2.43 | 0.00398 | [23] |
| Mc^a | -2.7 | 0.0020 | [22] |
| Mc^b | -2.4 | 0.00398 | This work |

^aBased on Mc 1971 [22].

^bBased on Mc 1998 [25].

are listed in Table II. The evaluation of thermodynamic equilibrium constants is not practicable, since the activity coefficients of the species are not available and their estimate on theoretical basis is an objective of further studies.

Unexpected features of these reactions are their reversibility in aqueous acid at 298 K, since the starting indole is a weak base (see Table I), whereas the oligomers **3** and **4** are fairly strong bases ($pK_{\text{A}} \cong 11$ and $pK_{\text{A}} \cong 5$, respectively [28]), which are completely protonated in the presence of H_2SO_4 0.5 mol L^{-1} and

Table II Equilibria of Indole Dimer and Trimer in H_2SO_4 0.5 mol L^{-1}

| Time of Reaction (s) | 1 ($\times 10^3 \text{ mol L}^{-1}$) | | 3 ($\times 10^3 \text{ mol L}^{-1}$) | | 4 ($\times 10^3 \text{ mol L}^{-1}$) | | $10^5 K_D^*$ (L mol^{-1}) | $10^2 K_T^*$ (L mol^{-1}) |
|----------------------|--|------------------|--|------------------|--|------------------|---|---|
| | t_0 | t_{end} | t_0 | t_{end} | t_0 | t_{end} | | |
| 18,000 | 3.0 | 1.18 | 0 | 0.39 | 0 | 0.32 | 1.52 | 7.01 |
| 19,800 | 3.0 | 1.17 | 0 | 0.38 | 0 | 0.33 | 1.50 | 7.52 |
| 23,400 | 3.0 | 1.13 | 0 | 0.37 | 0 | 0.32 | 1.59 | 7.76 |
| 14,400 | 5.0 | 1.54 | 0 | 0.53 | 0 | 0.73 | 1.23 | 8.93 |
| 18,600 | 5.0 | 1.53 | 0 | 0.50 | 0 | 0.75 | 1.18 | 9.79 |
| 16,800 | 6.3 | 1.62 | 0 | 0.77 | 0 | 1.03 | 1.61 | 8.32 |
| 21,600 | 6.3 | 1.60 | 0 | 0.76 | 0 | 1.04 | 1.62 | 8.59 |
| 20,100 | 0 | 0.98 | 1.01 | 0.26 | 0 | 0.17 | 1.51 | 6.60 |
| 17,400 | 0 | 1.12 | 0 | 0.32 | 0.94 | 0.33 | 1.55 | 7.93 |
| | | | | | | | Average 1.48 ± 0.16 | Average 8.05 ± 0.98 |

t_0 = Initial time; t_{end} = final time.

consequently stabilized by solvation in aqueous solutions. An explanation to the phenomenon can be given by considering in the depolymerization reactions a positive entropic term that balances the enthalpy of solvation of the ions; this is, however, a conjecture that needs further research.

Kinetics of Oligomerization

Figure 2 reports a reaction profile of indole oligomerization. The reactions reach practically the equilibrium

after 3–4 h depending on the starting conditions. From a qualitative analysis of the rate profile (see Figs. 2–4), formation of **3** is faster than **4**, but the application of the stationary state approximation to the former reaction gave unreliable results. For this reason in the kinetic model, only the protonation process can be considered in the stationary state and the complete set of equations relating the formation of dimer and trimer must be used (Eqs. (2)–(4)). From a mathematical point of view, the model is based on the kinetic laws in differential form and the material balance of **1–4**, where the analytical

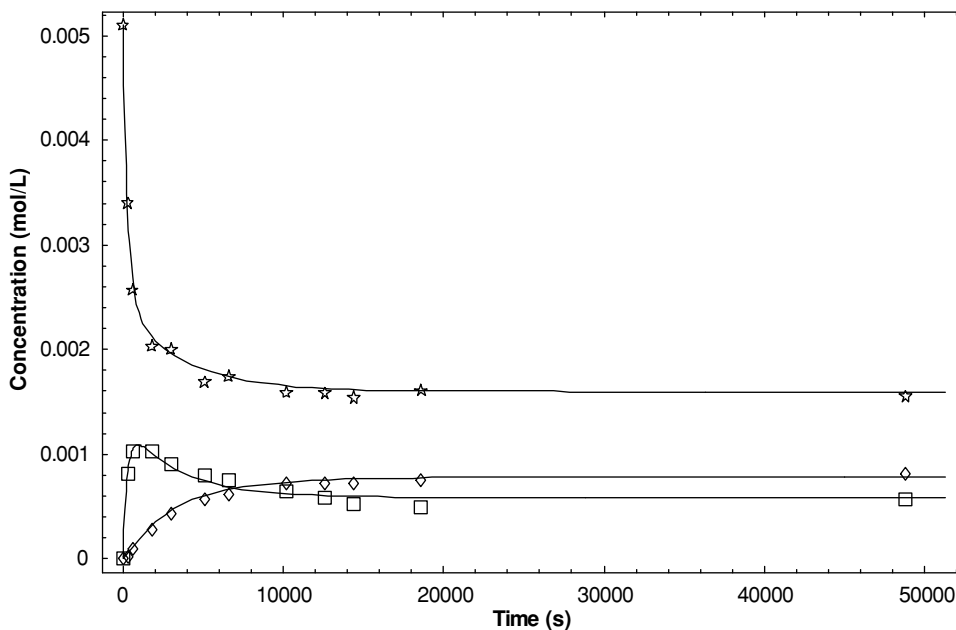


Figure 2 Concentration profiles of indole, dimer, and trimer in H_2SO_4 0.5 mol L^{-1} at 298 K initial concentration of indole $0.0051 \text{ mol L}^{-1}$: indole (\star), indole dimer (\square), and indole trimer (\diamond).

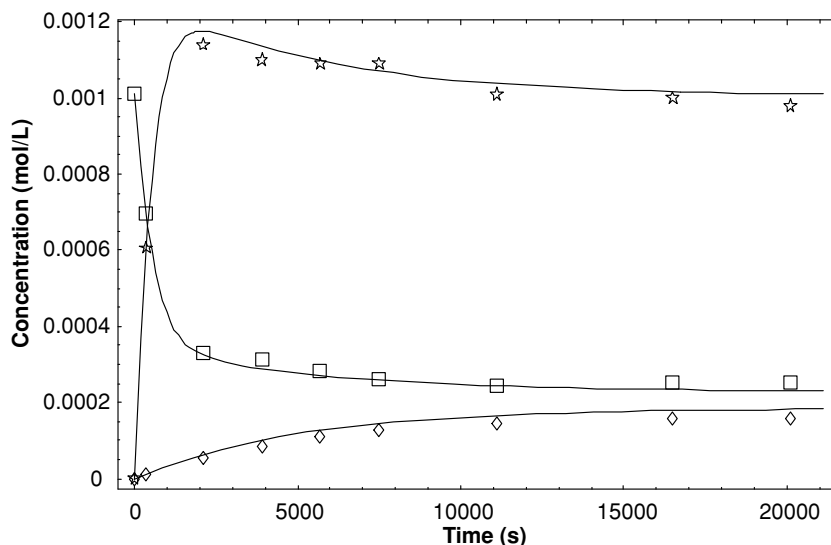


Figure 3 Concentration profiles of indole, dimer, and trimer in H_2SO_4 0.5 mol L^{-1} at 298 K initial concentration of indole dimer 0.001 mol L^{-1} : indole (\star), indole dimer (\square), and indole trimer (\diamond).

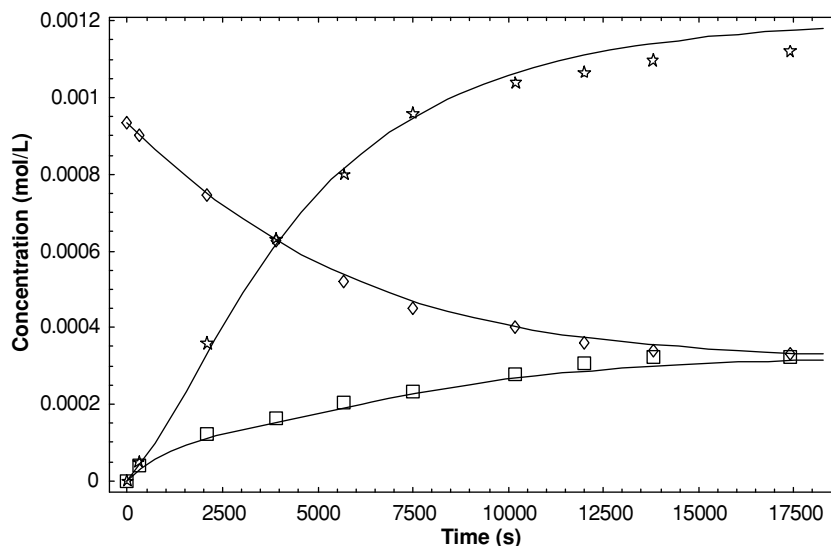


Figure 4 Concentration profiles of indole, dimer, and trimer in H_2SO_4 0.5 mol L^{-1} at 298 K initial concentration of indole trimer 0.001 mol L^{-1} : indole (\star), indole dimer (\square), and indole trimer (\diamond).

concentrations of the species at the initial conditions are expressed with the 0 suffix.

$$-\frac{dc_1}{dt} = k_D c_1 c_2 - k_{DR} c_3 + k_T c_1 c_3 - k_{TR} c_4 \quad (2)$$

$$\frac{dc_4}{dt} = k_T c_3 c_1 - k_{TR} c_4 \quad (3)$$

$$c_1^0 + 2c_3^0 + 3c_4^0 = c_1 + c_2 + 2c_3 + 3c_4 \quad (4)$$

The concentration of **1** (c_1) and **2** (c_2) is calculated by taking into account the thermodynamic proto-

nation equilibrium (see Fig. 1). In Table III, the results of the regression analysis are reported. The direct kinetic constants (k_D and k_T) are obtained by fitting the data, whereas the kinetic constants of the reverse reactions (k_{DR} and k_{TR}) are obtained from the stoichiometric equilibrium constants by the relationship: $K_D^* = k_D/k_{DR}$ and $K_T^* = k_T/k_{TR}$. In this way, the reverse kinetic constants are a function of an activity coefficient term since thermodynamic equilibrium constants are not available. The small variation of the reverse kinetic constant, however, suggests that the

Table III Kinetic Constants Calculated by Nonlinear Fitting of the Experimental Data

| 10 ³ Initial Concentration (mol L ⁻¹) | 10 ² k_D (L mol ⁻¹ s ⁻¹) | 10 ⁻³ k_{DR} (s ⁻¹) | 10 ⁻² k_T (L mol ⁻¹ s ⁻¹) | 10 ⁻³ k_{TR} (s ⁻¹) | εk_D^a | 10 ⁴ εk_T^a | 10 ⁸ σ^2 |
|--|--|--|---|--|---------------------|-------------------------------------|----------------------------|
| 1 | 3.0 | 2.65 | 1.79 | 9.11 | 9.26 | 1.1 | 2.8 |
| 1 | 5.0 | 2.59 | 1.75 | 9.72 | 9.87 | 1.6 | 3.2 |
| 1 | 6.3 | 2.26 | 1.53 | 8.63 | 8.75 | 1.5 | 8.5 |
| 3 | 1.01 | 3.09 | 2.08 | 8.41 | 8.55 | 1.0 | 0.36 |
| 4 | 0.94 | 1.71 | 1.15 | 8.63 | 8.75 | 4.3 | 0.6 |

^aThe correlation matrix values of the regression variables (k_D and k_T) are comprised between 0.1 and 0.4.

activity coefficient factor is practically constant in the range investigated.

Except indole protonation, which is in stationary state, the faster step is the formation of **3** that is the direct consequence of the high reactivity of the carbocation (**2**). The values of the kinetic constant (k_D) are comparable with those measured by other authors for the additions of benzhydrylium ions to indoles [17]. As expected, the nucleophilic attack of indole to the protonated indole dimer (**3**) is much slower because the positive charge is mainly localized on the nitrogen atom, which is, in this case, a secondary ammonium ion. Furthermore, the protonated 2-alkyl-aniline (**4**) does not react with (**1**), since the positive charge is on the nitrogen atom and the anilinium ion is ineffective as electrophile. Nevertheless, under different experimental conditions, Plancher rearrangement, additions and aromatization reactions occur [3,4,10,18].

The complete thermodynamic and kinetics analysis of the reactions are in course of study.

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