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Study Self-Association of Norfloxacin and Ciprofloxacin, and their Thermodynamic Properties

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ABSTRACT:

UV/Vis spectroscopy has been used to investigate the self-association of the Quinolone drugs (Norfloxacin and Ciprofloxacin) in aqueous solution at room temperature (295) K. The calculated value for the dimerization constant of these drugs self-association analyzed using dimer model equation by fitting to the experimental value are $5.424\times10^{3}M^{-1}$ and $4.377\times10^{3}M^{-1}$ respectively. The thermodynamic parameters (Gibbs free energy, enthalpy and entropy) of dimerization reactions for the self-association of the drugs were also investigated using Vant's Hoff equation at the temperature ranges (295-304 K). The change of enthalpy calculated for Norfloxacin and Ciprofloxacin are $-(5.35\pm0.459)$ and $-(1.98\pm0.25)$ $kJ.mol^{-1}$ respectively. The values of change in enthalpy and entropy indicate that the electrostatic forces play the major role in the interaction between the molecules of the drugs. Finally the results of the study are useful in order to design the advanced and controllable carriers of drug components and for controlling the effect of physicochemical properties (such as the degree of ionization, reaction rates and reaction mechanisms) of the drugs.

Key words: Norfloxacin, Ciprofloxacin, UV-Vis Spectroscopy, Self-association, Thermodynamic property.

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1. INTRODUCTION

Quinolone drugs are namely as quinolone carboxylic acids, which are class of antibiotics or a group of synthetic antibacterial agents containing a 4-oxo-1,4-dihydroquinoline skeleton that have found wide use in therapy [1,2]. The Quinolone drugs (such as Norfloxacin and Ciprofloxacin) are a group of fluoroquinolones that have a series of synthetic antimicrobials and active against both Gram-negative and Gram-positive microorganisms [2,3,4]. These are the important bacterial enzymes DNA gyrase [1,3,4,5] and extremely useful for the treatment of a variety of infections including urinary tract infections, soft tissue infections, respiratory infections, bone-joint infections, typhoid fever, sexually transmitted diseases, prostatitis, community acquired pneumonia, acute bronchitis and sinusitis [2,6].

The interest arises to study the self-association of the quinolone (Norfloxacin and Ciprofloxacin) drugs are because most probably these compounds could be used in many patients for the purpose of treating different variety of infections. Since the analysis of the effects of drugs upon membranes requires the knowledge of the actual amount of bound drug, the major purpose of this study was to investigate the self-association and thermodynamic properties of these quinolone drugs. And this study helps for

understanding their binding in biological system and controlling the effect of physicochemical properties (such as the degree of ionization, reaction rates and reaction mechanisms) of the drugs. On the other hand, as far as our knowledge concerns the self-association of quinolone drugs (Norfloxacin and Ciprofloxacin) to elucidate structures and the thermodynamic properties of the molecules are not yet investigated. The simplest, highly sensitive, rapid easily implemented technique to study such kind of interactions is UV-Vis spectroscopy [7,8,9].

2. MATERIALS AND METHODS

The electronic absorption spectra were recorded on a Perkin-Elmer Lambda 19 UV-Vis spectrophotometer (Maryland, United State) using 1cm fused quartz cuvette in a spectrum region 200-500 nm at room temperature (295). The analyzed spectra were obtained by subtracting the spectrum of the pure solvent (water) from that of the solution containing compounds.

Norfloxacin (NOR, Figure 1(a)) and Ciprofloxacin (CIP, Figure 1(b)) from Sigma-Aldrich were used with no additional purification. In order to avoid photo degradation of the compounds the solutions were prepared in a darkened room and all the studied solutions were prepared using Bi-distilled water immediately before the measurements. All glassware was thoroughly cleaned, rinsed with distilled water and dried before use.

In the self-association studies, aqueous solutions of NOR and CIP in the concentration range $(3.806-9.807)\times10^{-5}M$ and $(3.122-7.148)\times10^{-5}M$ respectively were obtained by the method of successive dilution. The absorbance as a function of concentration has been measured at absorption maximum 272.8 nm for both of the drugs in order to obtain the greatest accuracy of detection. For numerical analysis of the parameters of the self-association, the dimer model equation were fitting to the experimental data using a nonlinear curve fitting based on Levenberg-Marquardt algorithm by origin 8 software. The self-association parameters were used as searching parameters in order to achieve minimum discrepancy between the experimental data and theoretical values.

The thermodynamic parameters of the self-association NOR and CIP were studied in the temperature range of (295 – 304) K. These thermodynamic parameters (enthalpy, Gibbs free energy and entropy) have been determined using the model of Vant's Hoff's equation by linear curve fitting for the experimental data with that of the experimental values.

3. RESULTS AND DISCUSSION

3.1. Self-association of Norfloxacin and Ciprofloxacin

Figure 2(a) and 2(b) shows the experimental spectra of aqueous solutions of Norfloxacin measured at concentrations in the range A to D $(9.807-7.33)\times10^{-5}M$ and Ciprofloxacin measured at concentrations in the range A to H $(7.148-3.122)\times10^{-5}M$. As we see, when the NOR and/or CIP concentration is increased in aqueous solution, the absorbance increases at the wavelength of the monomer absorption maximum (λ_{max} = 272.8 nm) for both of the drugs and an isosbestic points were also appears on the spectra which observed in overlaid spectra when a chromophoric precursor is converted to product with different spectrum. The spectral changes and the presence of an isosbestic point suggest the existence in solution of an equilibrium state between the monomer and dimer forms of the drug molecules.

The dynamic equilibrium in the solution was modeled by the reaction formula:

$$D_1 + D_1 \xleftrightarrow{K_d} D_2, \qquad (1)$$

where, D_1 and D_2 are monomers and dimers of the drug molecules respectively and K_d is the equilibrium dimerization constant. The total concentration of the dissolved molecules in solution is,

$$[D_0] = [D_1] + 2[D_2], \qquad (2)$$

where $[D_1]$ is the monomer concentration; $[D_2] = K_d[D_1]^2$ is the dimer concentration and $[D_0]$ is the initial concentration of the drugs. The contribution of the monomer and dimer components to the overall molar absorption coefficient ε of the drug molecules can be represented in the form;

$$\varepsilon = \varepsilon_m f_m + \varepsilon_d f_d, \quad (3)$$

where $f_m = \frac{[D_1]}{[D_0]}$ is equilibrium mole fraction of the molecules in the monomer concentration; $f_d = 2K_d \frac{[D_1]^2}{[D_0]}$ is equilibrium mole fraction of the molecules in the dimer concentration, ε_m is molar monomer extinction coefficients, ε_d is molar dimer extinction coefficients. The concentration can be derived from the solution of the mass conservation law of equation (2) by substituting on the account of equation (3).

The extinction coefficients of the monomer (ε_m) and dimer (ε_d) forms of the drug molecules and the equilibrium dimerization constant (K_d) of the molecules are determined from the model known as dimer model;

$$\varepsilon = \varepsilon_d + (\varepsilon_d - \varepsilon_m)\frac{1-\sqrt{8[D_0]K_d + 1}}{4[D_0]K_d} \quad (4)$$

by fitting to the experimental data at the wavelength 272.8 nm Figure 3 (a) and 3(b). Nonlinear curve fitting based on the Levenberg-Marquardt algorithm was used for computing the values of the above three quantities using origin 8 software. They are serving as search parameters being adjusted in order to achieve the minimum discrepancy between the experimental data and the theoretical value of Equation (4) and these values were obtained as table 1. The result of the dimerization constant for NOR is comparable with the previously calculated result given by $1.3\times10^2 M^{-1}$ at a temperature of 298K using ^{1}H NMR Spectroscopy [10].

Figure 4(a) and 4(b) shows the mole fraction of monomer and dimer versus concentration of the drug molecules under the peak of 272.8 nm of Norfloxacin and Ciprofloxacin respectively. The graphs show increase and decrease in the mole fraction of dimer and monomer as the concentrations of the drugs are increasing. The results indicated dimerization is favored at high concentration of the drugs.

On the other, the extinction coefficient of the drugs was found from calibration graph as in table 1 from Figure 5(a) and 5(b) over the above concentration range described on the method of the self-association. Thus, the values of the extinction coefficients for NOR and CIP are in a good agreement with the results obtained previously $1.253\times10^4 L.mol^{-1}cm^{-1}$ [11] and $3.0614\times10^4 L.mol^{-1}cm^{-1}$ [12] calculated using UV-Vis spectroscopy.

3.2. Thermodynamic Properties of the Self-Association of Norfloxacin and Ciprofloxacin

Study the thermodynamics of the aqueous solubility of NOR and CIP may be necessary to understanding transport of the drugs across biologic membranes, whether bacterial or gastrointestinal membranes. This is because the bioavailability of a drug, minimum inhibitory concentration and hence its antimicrobial activity are dependent on the entry of the drug molecule into the bacterial cell and its interaction with its target within the cell [10]. The spontaneity of solubility of a drug and its transport across the bacterial cell wall depends on the relative size of the changes in the thermodynamic parameters such as enthalpy and entropy values. Thus, heating the aqueous solution of Norfloxacin and Ciprofloxacin shows that the absorption spectra of the molecules are strongly dependent on the temperature in the range of (295 –304) K. The equilibrium constants of the drug molecules at the above mentioned temperature were calculated at peak of wavelengths of the using Equation (3). Figure 6 (a) and 6(b), shows the graph of $\ln K$ versus $f(\frac{1}{T})$.

The magnitude of the enthalpy was estimated from the slope of the approximating line according to Vant's Hoff's equation:

$$\frac{d\ln(K_{dc})}{f(\frac{1}{T})} = -\frac{\Delta H}{R}, \quad (5)$$

where ΔH is the molar enthalpy change, $R = 8.31 J.mol^{-1}K^{-1}$ is the universal gas constant and T the temperature in Kelvin. The entropy was derived from Gibbs free energy and enthalpy. The Gibbs free energy and entropy can be expressed as;

$$\Delta G = -RT\ln(K_{dc}), \quad (6)$$

$$\Delta S = -\frac{\Delta G - \Delta H}{T}. \qquad (7)$$

Finally, the Vant's Hoff's equation can be given by

$$\ln K = \frac{\Delta S}{R} - \frac{\Delta H}{R}\frac{1}{T}. \qquad (8)$$

Plots of $\ln K$ versus T^{-1} gives a straight line, whose slope and intercept can be used to determine ΔS and ΔH from Figure 7 (a) and 7(b), and Gibb's free energy can be determined at a specific temperature using equation (7). The calculated value for the Gibbs free energy, enthalpy, and entropy of the drug molecules at a temperature 299 for the self-association is obtained as table (1). The values of the thermodynamics parameters enthalpy and Gibb's free energy of the self-association is similar with the previously reported thermodynamic results given by $\Delta H = -(18 \pm 3.6) kJ.mol^{-1}$ and $\Delta G = -(12 \pm 1.6) kJ.mol^{-1}$ [10]. The negative value for the Gibb's free energy indicates that the absorption process of the drug is continuous. In addition, the negative value of enthalpy shows that the process is exothermic reaction; this indicates as the temperature increases the equilibrium constant decreases. Also, the positive value of entropy confirms the increasing randomness of the solution interface during the absorption process of the drug molecules [13].

4. CONCLUSIONS

This research indicates that the molecules of NOR and CIP effectively aggregates in a solution. The values for the self-association and thermodynamic properties of the compounds are interpreting the study of kinetic chemical reaction system of the compounds. Thus, sympathetic the mechanism of self-association of NOR and CIP are useful in order to design the advanced and controllable carriers of drug components and for controlling the effects of physiochemical properties. In addition, the thermodynamic parameters, such as enthalpy, entropy and Gibbs free energy change on dimerization, which are derived from the temperature dependency of the dimerization constant, have given insight in to the forces that maintain the dimer association structures in the solutions. The values of change in enthalpy and entropy indicated that the electrostatic force play the major role in the interaction between the molecules NOR and CIP. Therefore, the investigated results have wider applications in pharmaceutical companies in terms of economic and scientific utility.

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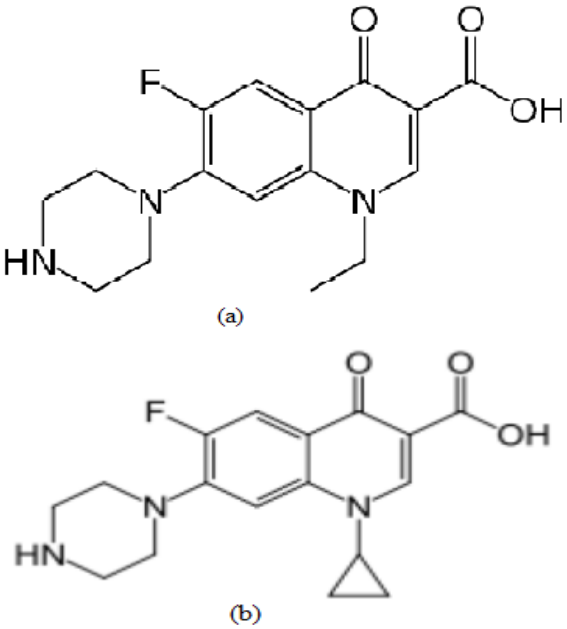
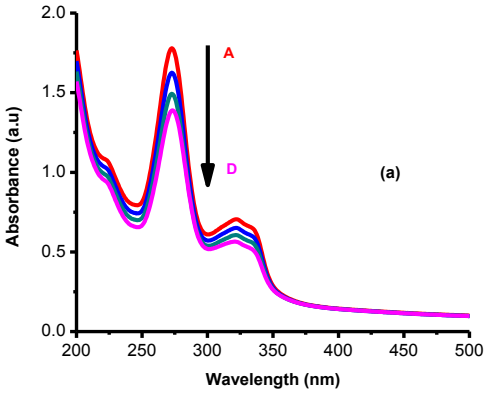


Figure 1: Chemical Structure of (a) Norfloxacin (NOR) and (b) Ciprofloxacin (CIP)



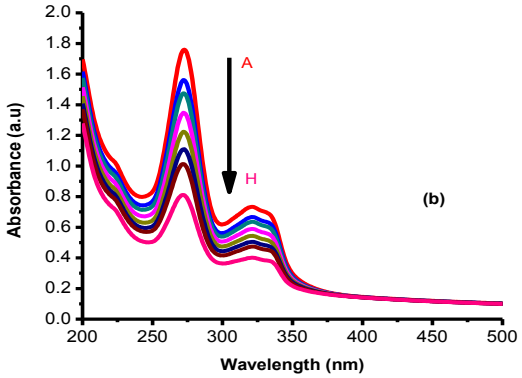
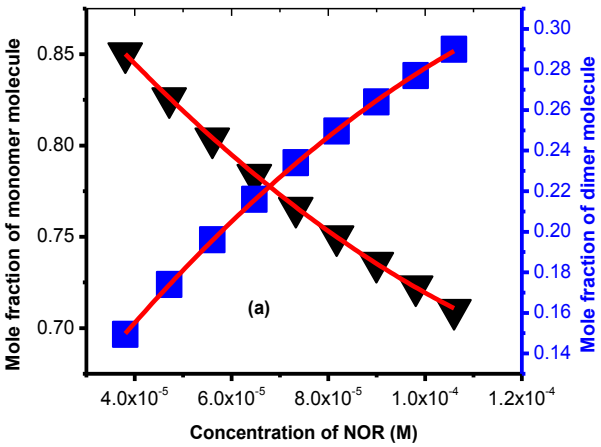


Figure 2: UV-Vis Absorption Spectrum of (a) Norfloxacin for concentrations A to D $(9.807-7.33)\times10^{-5}M$, (b) Ciprofloxacin for concentrations A to H $(7.148-3.122)\times10^{-5}M$ in Distilled Water.



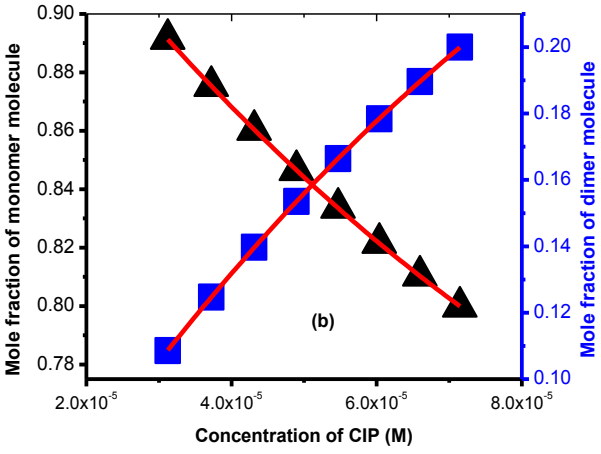
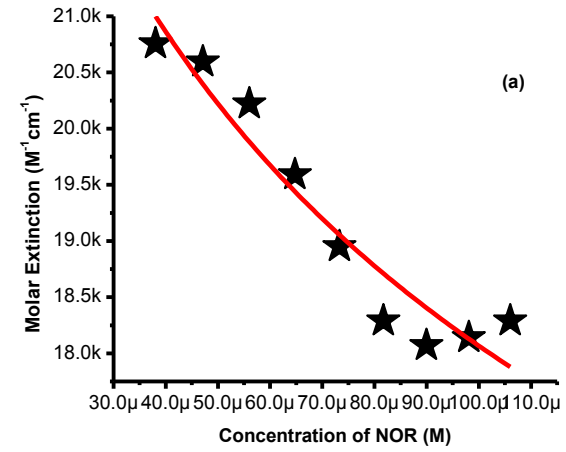


Figure 4: The Mole Fraction of Monomer and Dimer versus Total Concentration of (a) Norfloxacin (b) Ciprofloxacin under the Peak of 272.8 nm



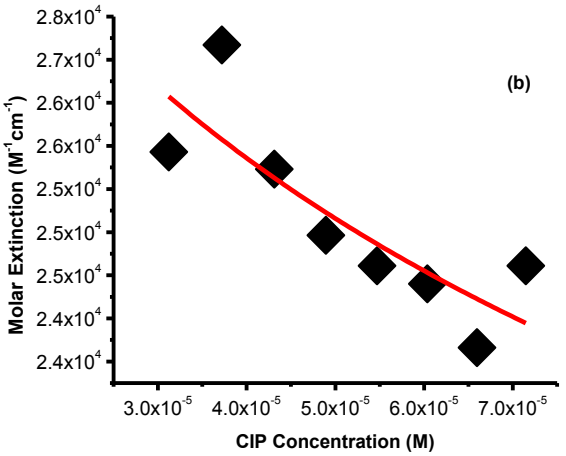
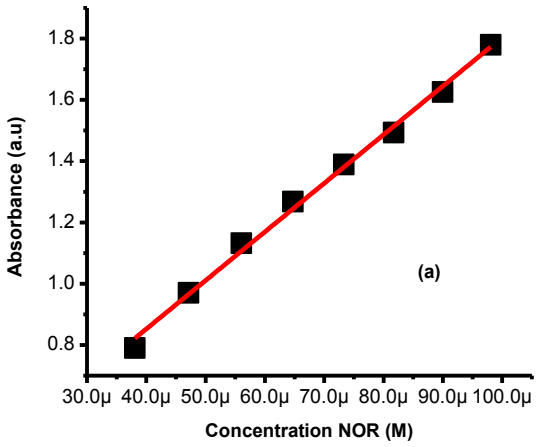


Figure 3: Molar extinction Coefficient Versus Concentration at λ_{max} = 272.8 nm of (a) Norfloxacin (b) Ciprofloxacin



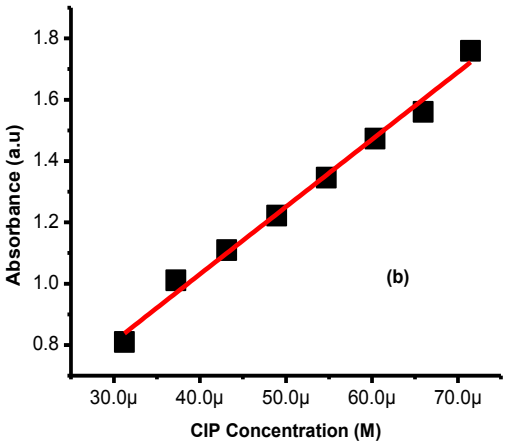
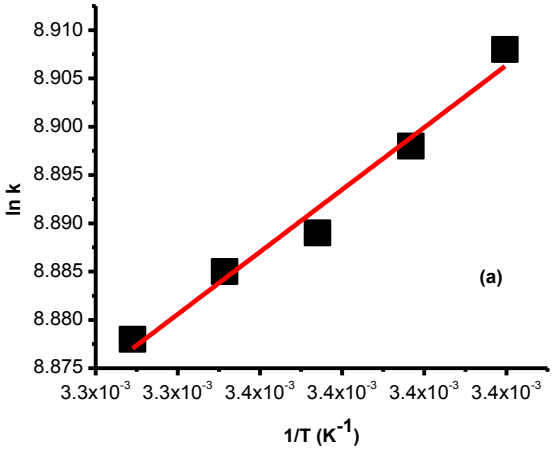


Figure 5: Absorbance Vs Concentration linearity of (a) NOR (b) CIP at 272.8 nm



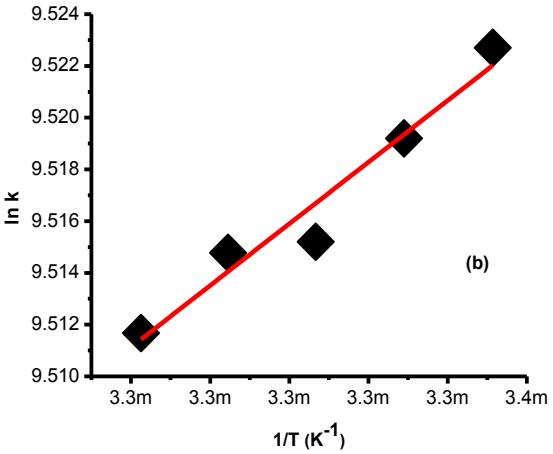


Figure 6 : $\ln K$ Vs $\frac{1}{T}$ of (a) NOR at $(8.312\times10^{-5})M$ (b) CIP at $(7.148\times10^{-5})M$

Table 1: Calculated values of self-association parameters and thermodynamic Parmeteries

Parameter	*NOR*	*CIP*
$\varepsilon_m\ (M^{-1}.cm^{-1})$	2.547×10^4	3.054×10^4
$\varepsilon_d\ (M^{-1}.cm^{-1})$	6.77×10^3	8.805×10^3
$\varepsilon\ (M^{-1}.cm^{-1})$	1.585×10^4	2.196×10^4
$K_d\ (M^{-1})$	5.424×10^3	4.377×10^3
$\Delta G\ (kJ.mole^{-1})$	$-(21.994\pm0.92)$	$-(23.725\pm4.96)$
$\Delta H(kJ.mole^{-1})$	$-(5.35\pm0.459)$	$-(1.98\pm0.25)$
$\Delta S\ (kJ.mole^{-1}.K^{-1})$	(0.056 ± 0.0015)	(0.0725 ± 0.001)

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