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Thermodynamics of pyrimethamine and sulfadiazine binding to a chitosan derivative

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Abstract

A thermodynamic investigation of the interaction of pyrimethamine (PYR) and sulfadiazine (SDZ) with immobilized copper on chitosan (chit-Cu) was done by heat-conduction calorimetry at 298.15 K. Langmuir isotherm describes the adsorption equilibrium behaviour in the entire concentration range studied. The molar enthalpies for formation of a monolayer of drug, $\Delta_{mon}H_m$, from linear and (non-linear) data analysis methods were found to be -40.2 ± 1.2 (-42.1 ± 1.5) and -69.0 ± 2.2 (-68.5 ± 1.9) kJ mol^{-1} for PYR and SDZ, respectively.

Keywords: Heat-conduction calorimetry; Chitosan; Sulfadiazine; Pyrimethamine

1. Introduction

Chitin, one of the most abundant natural polymers extracted from crustaceous shells or from some fungi [1], presents a large unexplored commercial potential. Chitosan is partially or completely *N*-deacetylated chitin, and mainly consists of β-(1-4)-linked 2 amino-2-deoxy-β-D-glucopyranose. Since chitosan is readily available, and has unique physiological and biological properties, it is regarded as a versatile starting material for the preparation of various biomedical products [2,3].

This study assesses the thermodynamics of the interaction of chitosan containing complexed copper (chit-Cu) with pyrimethamine (PYR) and sulfadiazine (SDZ), Fig. 1, which are antifolate drugs in infectious toxoplasmosis microorganisms [4]. Drug–polymer interactions can have considerable importance in optimizing drug delivery [5]. The drug/chit-Cu is expected to yield higher interaction energies than drug/chitosan interaction [6].

2. Experimental

2.1. Chemicals

Chitosan was from Primex Ingredients A.S. (Norway). Twenty-five percent glutaraldehyde aqueous solution (Sigma Chemicals), $CuCl_2$ of analytical grade (Merck) and dimethyl sulfoxide (DMSO) from Merck were used as received. Pyrimethamine (PYR) and sulfadiazine (SDZ) greater than 99% purity were purchased from Sigma.

2.2. Determination of the deacetylation degree of the chitosan

Acid–base titration was used to determine the degree of deacetylation of the chitosans [7]. Two samples of dried chitosan of 0.2 g were accurately weighted and dissolved in 0.05 mol dm^{-3} HCl. The solutions were titrated with 0.17 mol dm^{-3} NaOH. The degree of deacetylation was calculated as follows:

$$\text{degree of deacetylation (\%)} = \frac{161[\text{base}](V_2 - V_1)}{m} \times 100 \quad (1)$$

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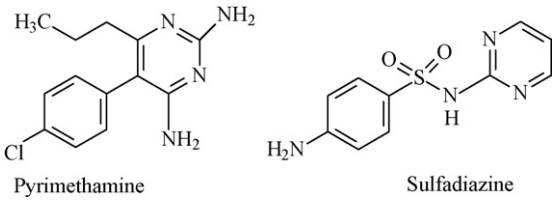

Fig. 1. Structures of pyrimethamine and sulfadiazine.

where [base] is the concentration of NaOH (mol dm^{-3}); V_1 and V_2 are, respectively, the volume (L) of NaOH used to neutralize the excess of HCl and the volume (L) of the protonated chitosan sample, 161 the molecular weight of the monomeric unit of chitosan and m is the sample weight (g) of the sample in the dry state before titration. The deacetylation degree of the chitosan was found to be 71.16%.

2.3. Preparation of chitosan beads

Chitosan beads with 0.70–0.80 mm diameter were prepared as previously described [6]. Briefly, chitosan (3.0 g) was dissolved in 3% acetic acid (100 cm^3). The solution was dropped through a syringe needle into 2.5 mol dm^{-3} sodium hydroxide, and the beads were formed instantaneously. The raw chitosan beads were washed with double-distilled water and dried at room temperature for 24 h. The resultant chitosan beads (7 g) were cross-linked with 2.5 mol dm^{-3} glutaraldehyde aqueous solution (100 cm^3) for 24 h. These beads (chit-GLT) were allowed to stand for 8 h in the 2×10^{-2} mol dm^{-3} $CuCl_2$ solution at pH 6 (phosphate buffer was employed) with stirring at room temperature. Thereafter, the chit-Cu beads were thoroughly washed with double-distilled water and dried at 333 K. The amount of immobilized copper was determined by recording the absorbance value of the equilibrium concentration and, due to the fact that Cu(II) is removed during washing steps, by subtracting the Cu(II) content in the water used during the chit-Cu washing. A FEMTO UV–vis spectrophotometer 800 XI (wavelength of maximum absorbance 796 nm) was employed. The Cu(II) content was 0.51×10^{-4} mol g^{-1}. Characterization of the material has been described in a recent study [6].

2.4. Calorimetric determinations

Calorimetric measurements of the interaction processes of the drugs with chit-Cu beads were performed at 298.15 K in a SETARAM C80 mixing calorimeter. The calorimeter performance and details of operation have been previously described [8]. Samples of approximately 100 mg of the chit-Cu beads were put into the lower part of the mixing cell closed by a circular membrane of Teflon. Because the drugs are not soluble in water, the upper part of mixing cell contained 3.0 cm^3 of drug solution in the concentration range of 2.5×10^{-3}–1.5×10^{-2} mol dm^{-3} in DMSO. After complete stabilization of the base line, a movable rod enables the drug solution to be pushed into the container with the chit-Cu beads through the membrane of Teflon. Each individual experiment yields a thermal effect, Q_r, which was corrected by subtracting the corresponding wetting effect, Q_w, obtained by adding pure DMSO to the chit-Cu beads. The thermal effects of membrane breaking for the empty cell and addition of DMSO in the cell without the chit-Cu beads were found to be negligible compared to Q_r and Q_w values. After each Q_r recording, the drug equilibrium concentration, C_{eq}, was determined in the supernatant (at the wavelength of maximum absorbance 280 nm (PYR) and 274 nm (SDZ), on a FEMTO UV–vis spectrophotometer, 800 XI), and thus the drug amount that interacts, n_{int}, was calculated. Each experiment was repeated in duplicate.

3. Results and discussion

Adsorption isotherms were obtained from simultaneous determination of thermal effects and the corresponding quantities of drug that interact, as described in Section 2.4. Heat effects from the interaction of the drugs with chit-Cu, $Q_{int} = Q_r - Q_w$, were calculated with both Q_r and Q_w normalized for 1 g of chit-Cu.

The Langmuir adsorption isotherms used in this work are shown in the following equations [9]:

$$n_{int} = \frac{N_{mon} b C_{eq}}{1 + b C_{eq}} \quad (2)$$

$$Q_{int} = \frac{Q_{mon} K C_{eq}}{1 + K C_{eq}} \quad (3)$$

The respective linearized forms of these equations are:

$$\left(\frac{C_{eq}}{n_{int}}\right) = \left(\frac{C_{eq}}{N_{mon}}\right) + \left(\frac{1}{b N_{mon}}\right) \quad (4)$$

$$\left(\frac{C_{eq}}{Q_{int}}\right) = \left(\frac{C_{eq}}{Q_{mon}}\right) + \left(\frac{1}{K Q_{mon}}\right) \quad (5)$$

where N_{mon} is the maximum adsorption capacity to form a monolayer, Q_{mon} the heat of interaction for a saturated monolayer per gram of chit-Cu, and b and K are parameters of affinity that include the equilibrium constant. Plots of C_{eq}/n_{int} against C_{eq} and C_{eq}/Q_{int} against C_{eq} (whose mean values are shown in Table 1) give straight lines, the slopes and intercepts of which correspond to N_{mon} or Q_{mon} and b or K, respectively.

The Langmuir model was found to fit the experimental data with mean relative deviations varying from 1.7 to 2.2%. Addi-

Table 1
Drug equilibrium concentration, C_{eq}, drug amount that interacts, n_{int}, and heat effects, Q_{int}, originating from the interaction of the drugs with chit-Cu, at 298.15 K

C_{eq} (mmol dm^{-3})		n_{int} (μmol g^{-1})		Q_{int} (J g^{-1})	
PYR	SDZ	PYR	SDZ	PYR	SDZ
1.19	1.15	39.3	40.5	−1.851	−3.123
3.21	3.05	53.7	58.5	−2.625	−4.321
5.37	5.25	63.9	67.5	−2.984	−4.917
7.58	7.33	72.6	80.1	−3.259	−5.658
9.85	9.62	79.5	86.4	−3.432	−6.121
12.34	12.11	79.8	86.4	−3.432	−6.113

Table 2
Maximum adsorption capacity to form a monolayer, N_{mon}, and heat of interaction for a saturated monolayer per gram of chit-Cu, Q_{mon}

Interactions	Linear regression method				Non-linear regression method			
	N_{mon} ($\times 10^{-4}$ mol g^{-1})	r^2	Q_{mon} (J mol^{-1})	r^2	N_{mon} ($\times 10^{-4}$ mol g^{-1})	r^2	Q_{mon} (J mol^{-1})	r^2
chit-Cu/SDZ	1.022 ± 0.019	0.9962	−7.05 ± 0.16	0.9971	1.003 ± 0.016	0.9971	−6.87 ± 0.15	0.9969
chit-Cu/PYR	0.934 ± 0.013	0.9969	−3.75 ± 0.07	0.9987	0.907 ± 0.017	0.9973	−3.82 ± 0.05	0.9977

Table 3
Thermodynamic data for the interaction of pyrimethamine and sulfadiazine with chit-Cu

Interactions	Linear regression method				Non-linear regression method			
	ln K	$\Delta_{mon}H_m$ (kJ mol^{-1})	ΔG (kJ mol^{-1})	ΔS (J K^{-1} mol^{-1})	ln K	$\Delta_{mon}H_m$ (kJ mol^{-1})	ΔG (kJ mol^{-1})	ΔS (J K^{-1} mol^{-1})
chit-Cu/SDZ	6.323	−69.0 ± 2.2	−15.7 ± 0.6	−178.7 ± 4.3	6.424	−68.5 ± 1.9	−15.9 ± 0.6	−177.1 ± 3.8
chit-Cu/PYR	6.758	−40.2 ± 1.2	−16.7 ± 0.4	−78.6 ± 3.8	6.607	−42.1 ± 1.4	−16.4 ± 0.4	−86.2 ± 4.2

tionally, we employed the non-linear regression analysis in the Origin® computer package version 6.0. From Table 2, the linear method produced N_{mon} and Q_{mon} values similar to that of non-linear method.

The molar enthalpy of interaction for formation of a monolayer of anchored drugs per gram of chit-Cu, $\Delta_{mon}H_m$, was directly obtained from the ratio Q_{mon}/N_{mon}.

Table 3 shows the thermodynamic parameters obtained. $\Delta_{mon}H_m$ is exothermic. The Gibbs free energy change is negative. The values of ΔS for the interactions chit-Cu/PYR and chit-Cu/SDZ are both negative. The least entropically favourable process for SDZ seems to be compensated by the more favourable enthalpic parameter.

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