**Cyclodextrin Phenothiazine-based Drugs Binding**

The Gilson group is contributing binding data for two hosts (β-CD and Hexakis-2,6-dimethyl- β-CD) binding to five phenothiazine-based drugs.

**Structures of Guest Molecules**

Five guest molecules were used: a) Thioridazine hydrochloride; b) Trifluoperazine dihydrochloride; c) Promazine hydrochloride d) Promethazine hydrochloride; e) Chlorpromazine hydrochloride



**(TDZ) (TFP) (PMZ). (PMT) (CPZ)**

**Figure 1** - Structures of five guest molecules used with expected protonation state.

### **Host Molecules**

The two host molecules used were: 1) β-cyclodextrin (**β-CD**) and 2) Hexakis-2,6-dimethyl- β-cyclodextrin (**H26DM-β-CD**).

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### **Standard Experimental Conditions**

All ITC results have been collected in triplicate on an ITC200 in phosphate buffer (sodium counterion, no potassium), pH 7.4, 25mM at 25 °C with a 20-point binding isotherm (1-1.5µL injections). Enthalpograms will be provided for each complex. In each case the guest was in the cell and the host in the syringe. Concentrations of solutions varied for each complex depending on binding affinity.

Table 1. Binding measurements for β-Cyclodextrin to Phenothiazine Drug Titrations.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Guest** | **N** | **Ka**  **(M-1)** | **Kd**  **x10-3(M)** | **ΔH**  **( kJ/mol)** | **ΔS**  **(J/K/mol)** | **ΔG**  **(kJ/mol)** |
| PMZ | 1.09 | 4440 | 0.225 | -24.76 | -3.94 | -20.81 |
| PMT | 0.94 | 1903 | 0.525 | -16.45 | 2.28 | -18.73 |
| CPZ | 0.77 | 9387 | 0.107 | -26.62 | -3.96 | -22.66 |
| TDZ | 1.14 | 15066 | 0.066 | -20.62 | 3.24 | -23.86 |
| TFP | 1.18 | 5103 | 0.196 | -16.31 | 4.87 | -21.18 |

Table 2. Binding measurements for Hexakis-2,6-dimethyl-β-Cyclodextrin to Phenothiazine Drug Titrations.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Guest** | **N** | **Ka**  **(M-1)** | **Kd**  **x10-3(M)** | **ΔH**  **( kJ/mol)** | **ΔS**  **(J/K/mol)** | **ΔG**  **(kJ/mol)** |
| PMZ | 0.99 | 5083 | 0.197 | -21.41 | -0.26 | -21.15 |
| PMT | 1.06 | 8416 | 0.119 | -16.96 | 5.46 | -22.42 |
| CPZ | 0.77 | 9113 | 0.110 | -24.95 | -2.36 | -22.60 |
| TDZ | 0.87 | 54866 | 0.018 | -38.34 | -11.31 | -27.03 |
| TFP | 0.56 | 11500 | 0.087 | -31.05 | -7.89 | -23.17 |

Chart, histogram

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**PMZ/ β-CD PMT/ β-CD**

Chart, histogram

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**CPZ/ β-CD TFP / β-CD**

**Figure 1.** Enthalpograms of Phenothiazine drugs and **β-CD**, each performed in triplicate with freshly made solutions.

**Chart, scatter chart

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**TDZ/ β-CD**

**Figure 1 .** Enthalpograms of Phenothiazine drugs and **β-CD**.

Chart, histogram

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**PMZ/ H26DM-β-CD PMT/ H26DM-β-CD**

**Chart, histogram

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Description automatically generated**

**CPZ/ H26DM-β-CD TDZ/ H26DM-β-CD**

**Chart, scatter chart

Description automatically generated**

**TFP/ H26DM-β-CD**

**Figure 2.** Enthalpograms of Phenothiazine drugs and **H26DM-β-CD,** each performed in triplicate with freshly made solutions.

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