Enthalpy - Entropy Compensation in the Hydrolysis of Four Tetracycline Antibiotics

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An article recently published analyzed the hydrolytic transformation of four tetracycline antibiotics - tetracycline, chlortetracycline, oxytetracycline, and doxycycline - under various environmental settings and determined their parents and transformation products in the wastewater treatment plants [1]. In the article, the authors found that the hydrolytic behavior of the four tetracycline antibiotics followed first-order reaction kinetics and that the rates of the acid-catalyzed hydrolysis were significantly lower than the rates of the base-catalyzed and neutral pH hydrolysis. By applying the Arrhenius approach, the authors identified activation energy, which measures the effect of temperature on tetracycline hydrolysis, to range from 42 kJ/mol to 77 kJ/mol at pH 7. Hydrolytic degradation rates for all four tetracycline antibiotics increased with elevating temperatures, providing a clear indication of temperature-dependent kinetics.

While the authors displayed the hydrolytic stability of the four tetracycline antibiotics under different environmental conditions based on their measurements of activation energy, we found the kinetic results could be further analyzed in terms of thermodynamics using the transition-state theory [2]. We also included an enthalpy-entropy compensation [3] to facilitate a deeper understanding to the phenomenon of tetracycline hydrolysis.

We first obtained the Gibbs free energy of activation ($\Delta G^{\circ\ddagger}$) at absolute temperature T (in Kelvin) using the rearranged version of the Eyring equation (Eq. 1):

$$\Delta G^{\circ\ddagger} = -RT \, In \frac{kh}{k_B T} \qquad (1)$$

Where R is the ideal gas constant, k is the rate constant, h is Planck's constant, and k_B is the Boltzmann constant. Prior to the calculations, a conversion of the units of rate constant from per hour as in the paper [1] to the standard units of per second was made to properly utilize the Eyring equation (Eq. 1). The derived values of $\Delta G^{\circ\ddagger}$ for the hydrolytic degradation of tetracycline are shown as a function of temperature in Figure 1a. A direct correlation is exhibited between $\Delta G^{\circ\ddagger}$ and temperature through all four tetracycline antibiotics. As seen in Figure 1a, the differences of $\Delta G^{\circ\ddagger}$ in the hydrolysis converge together at low temperatures and diverge at high temperatures. The hydrolysis rate of chlortetracycline was the fastest amongst the four, followed by oxytetracycline,

tetracycline, and lastly doxycycline at 323.15 K (50 °C). This was also stated in the original paper [1]; however, it lacked the thermodynamics basis of the phenomenon.

To elucidate this phenomenon using thermodynamics, a linear regression of $\Delta G^{\circ\ddagger}$ with the function of temperature was generated to obtain the molar entropy $\Delta S^{\circ\ddagger}$ and enthalpy $\Delta H^{\circ\ddagger}$ of activation in tetracycline hydrolysis using Eq. 2 [2]:

$$\Delta G^{\circ\ddagger} = \Delta H^{\circ\ddagger} - T \Delta S^{\circ\ddagger} \qquad (2)$$

In the regression, the slope and *y*-intercept correspond to $-\Delta S^{\circ\ddagger}$ and $\Delta H^{\circ\ddagger}$, respectively. The resulting values of $\Delta H^{\circ\ddagger}$ and $\Delta S^{\circ\ddagger}$ are displayed in Figure 1b. For all four tetracycline antibiotics, $\Delta S^{\circ\ddagger}$ are negative values, whereas the $\Delta H^{\circ\ddagger}$ values are all positive. A linear regression line in Figure 1b demonstrates a clear correlation between the two thermodynamics parameters and advocates that the stability of these antibiotics is not directed solely upon the molar enthalpy or entropy magnitudes, but by a combination of both that varies significantly in proportion yet remains near constant in total value represented by $\Delta G^{\circ\ddagger}$ (Eq. 2).

The thermodynamic features can be concluded from the acquired results. First, the hydrolytic degradation is kinetically unfavorable with regards to both enthalpy and entropy throughout all tetracycline compounds. Second, each compound exhibited a different thermodynamic basis despite having high hydrolytic stability. For instance, the stability of chlortetracycline is credited to its high value of $\Delta H^{\circ\ddagger}$, whereas the stability for doxycycline is attributed to its low value of $\Delta S^{\circ\ddagger}$. Through the visual representation, we observed a relatively strong correlation of 0.9982 between $\Delta H^{\circ\ddagger}$ and $\Delta S^{\circ\ddagger}$. This phenomenon is known as the enthalpy-entropy

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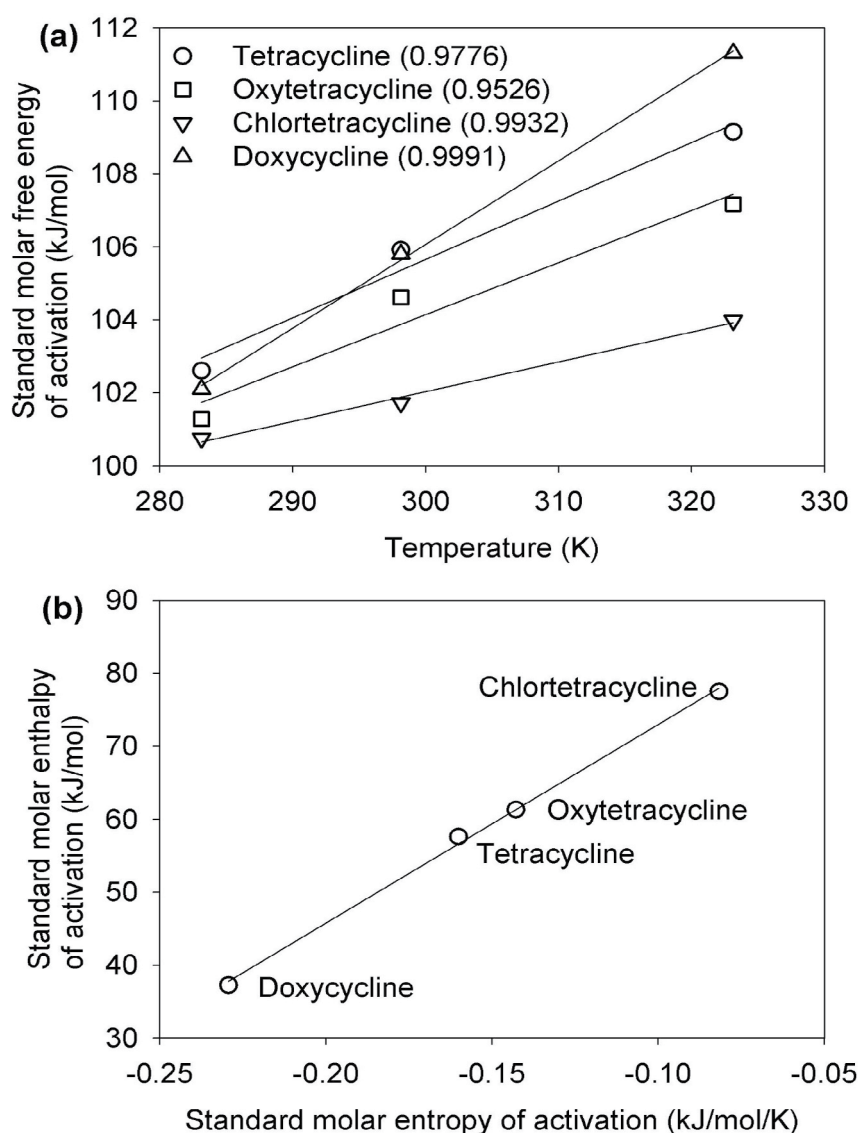
Figure 1: a) Temperature-dependent standard molar free energy of activation ($\Delta G^{\circ\ddagger}$) for the hydrolytic degradation of tetracycline. Standard molar enthalpy ($\Delta H^{\circ\ddagger}$) and entropy ($\Delta S^{\circ\ddagger}$) of activation were obtained by linear fitting. R^2 of the fitting is shown in the legend; b) Relationship between enthalpy and entropy of activation. R^2 value of the fitting is 0.9982. Sigma Plot (version 11, Systat Software Inc., San Jose, CA) was used for graph preparation and fitting.

compensation, which is widely invoked as an illustrative principle for the limited variation of Gibbs free energy change despite significant variations in the enthalpy and entropy values. From the data, the $\Delta H^{\circ\ddagger}$ values for the tetracycline ranged from 37.27 to 77.51 kJ/mol and the $\Delta S^{\circ\ddagger}$ values ranged from -0.082 to -0.229 kJ/mol/K. Contrastingly, the $\Delta G^{\circ\ddagger}$ values displayed slight variations at all temperatures. It is evident that enthalpy-entropy compensation is accountable for the relatively small variation in $\Delta G^{\circ\ddagger}$ of the hydrolytic degradation of tetracyclines (Figure 1a).

In conclusion, our thermodynamic analysis specifies that the combination of $\Delta H^{\circ\ddagger}$ and $\Delta S^{\circ\ddagger}$ indicates the hydrolytic degradation of tetracycline. The compensation between $\Delta H^{\circ\ddagger}$ and $\Delta S^{\circ\ddagger}$ limits the variation of $\Delta G^{\circ\ddagger}$. Further investigation can be conducted to observe the behavior other tetracyclines and see if they follow a similar trend.

References

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