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Enthalpy and heat capacity of hydration of the cytostatic Dioxadet

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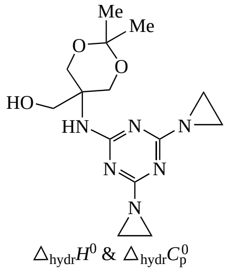
Thermochemical data on hydration of the well-established anticancer agent Dioxadet were obtained. Its enthalpies of solution and sublimation at various temperatures were determined calorimetrically, and on their basis the standard enthalpy ($\Delta_{\text{hydr}}H^0 = -154.6 \pm 3.6$ kJ mol^{-1}) and the standard heat capacity ($\Delta_{\text{hydr}}C_p^0 = 384 \pm 80$ J mol^{-1} K^{-1}) of the transfer of the solute from the state of an ideal gas to an aqueous solution at infinite dilution at 298.15 K were calculated.



Keywords: Dioxadet, solution, sublimation, hydration, enthalpy, heat capacity.

Dioxadet (DXT) is a domestic anticancer drug developed at the N. N. Petrov National Medical Research Center of Oncology.[1–3] This drug (Figure 1) was found to provide effective treatment for various malignancies and further potentiate the antitumor activity of Cisplatin, Paclitaxel, *etc*. However, experimental data on the interactions occurring in DXT solutions are still scarce, and the exact mechanisms of its antitumor activity are poorly understood.

Several years ago we studied the thermochemical behavior of another cytostatic agent, *viz*. prospidium chloride, and found a pronounced concentration dependence of the enthalpies of solution both in water and in H-bonded non-aqueous solvents.[4,5] The effect was almost linearly dependent on the reciprocal solvent dielectric permittivity,[5] indicating that ion–ion pair interactions induced a strong deviation from the limiting Debye law. In contrast, Figure 1 shows that the ‘Dioxadet’ molecule looks hydrophobic enough and does not contain any charged groups. Hence, the concentration dependence of the enthalpies of DXT solution is not expected in the limiting situation of dilute solutions.

In this work, we investigated the thermochemical behavior of DXT both in the gas phase and in dilute aqueous solutions to obtain enthalpies and heat capacities of hydration of the drug at the standard and physiological temperatures.

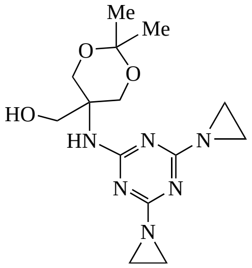


Figure 1 Molecular structure of Dioxadet or, according to IUPAC nomenclature, [5-[[4,6-bis(aziridin-1-yl)-1,3,5-triazin-2-yl]amino]-2,2-dimethyl-1,3-dioxan-5-yl]methanol.

A brief description of the chemicals and experimental methods is provided in Online Supplementary Materials, and the experimental results are summarized in Tables 1 and 2.

Experimental enthalpies of DXT solution ($\Delta_{\text{sol}}H^{\text{m}}$) obtained in highly dilute aqueous solutions were found to be independent of the molality of the solute. This indicates that the solute–solute correlations are too small to influence the experimental values at both temperatures. Thus, the standard enthalpy of DXT solution ($\Delta_{\text{sol}}H^0$) can be estimated as the mean value over the range of experimental results.

Table 1 shows that the standard enthalpies of solution are positive and exhibit a pronounced increase with temperature, as is typically observed for hydrophobic species in water[6–9] or highly associated non-aqueous solvents forming an H-bond

Table 1 Experimental and standard enthalpies of solution of DXT in water at the temperatures of 298.15 and 310.15 K.

T/K	DXT molality (m_{DXT})/mol kg^{-1}	Enthalpy of solution/kJ mol^{-1}	
		Experimental ($\Delta_{\text{sol}}H^{\text{m}}$)	Standard ($\Delta_{\text{sol}}H^0$)[a]
298.15	4.648×10^{-4}	3.76	3.93 ± 0.62
	5.059×10^{-4}	3.58	
	5.721×10^{-4}	4.23	
	6.806×10^{-4}	3.77	
	6.825×10^{-4}	4.31	
310.15	3.059×10^{-4}	7.30	7.84 ± 0.74
	4.213×10^{-4}	7.64	
	4.804×10^{-4}	7.82	
	5.977×10^{-4}	8.37	
	6.017×10^{-4}	8.08	

[a] Uncertainties in experimental quantities represent twice the standard deviation of the mean $\pm 2\sqrt{\sum(x_{\text{mean}}-x_i)^2/n(n-1)}$.

Table 2 Temperature dependence of DXT vapor pressure.

T/K	Vapor pressure (P)/Pa	$10^3(RT)^{-1}$/mol J^{-1}	ln[P (Pa)]
358.95	2.98×10^{-4}	0.33508	−8.120
369.09	9.98×10^{-4}	0.32588	−6.910
374.16	2.22×10^{-3}	0.32146	−6.111
379.23	4.65×10^{-3}	0.31717	−5.370
384.30	7.14×10^{-3}	0.31298	−4.942
393.01	2.08×10^{-2}	0.30605	−3.872
394.44	2.63×10^{-2}	0.30494	−3.638
398.13	4.13×10^{-2}	0.30211	−3.187
399.51	4.91×10^{-2}	0.30107	−3.014
403.25	8.75×10^{-2}	0.29828	−2.436
408.37	1.46×10^{-1}	0.29454	−1.926

network.[10,11] Estimating the standard heat capacity of the solution as

$$\Delta C_\mathrm{p}^0 \approx [\Delta_\mathrm{sol}H^0\ (310\ \mathrm{K}) - \Delta_\mathrm{sol}H^0\ (298\ \mathrm{K})]/\Delta T \qquad (1)$$

leads to a value of ΔC_p^0 equal to 326 ± 80 J mol^{-1} K^{-1}. This large and positive change in the heat capacity is very similar to that typically observed for hydrophobic benzene[12] or L-tryptophan[9] and indicates that the accommodation of DXT molecules into the water structure is accompanied by a relative increase in the population of water molecules with more linear and shorter H-bonds in the immediate environment of DXT molecules.[13–15]

To determine the sublimation enthalpy of DXT, we analyzed the temperature dependence of the vapor pressure (P) of solid DXT (see Table 2) using the relationship between P and the rate of sample evaporation from the surface of the USF1 chip sensor.[16,17] The ln$P$ *vs*. $10^3(RT)^{-1}$ dependence from 358 to 408 K was approximated by the following linear function (r = 0.999, s_d = 0.1):

$$\ln P = (43.26\pm0.74) - (153.6\pm2.4)(1000/RT), \qquad (2)$$

where the uncertainties represent the standard errors of fitting. The mean enthalpy of sublimation of DXT ($\Delta_\mathrm{subl}H^0$) in the studied temperature range is 153.6 ± 3.6 kJ mol^{-1}. The uncertainty given here represents the combined measurement error of vapor pressure and temperature.[18,19] The value of $\Delta_\mathrm{subl}H^0$ at 298.15 K was estimated using the known scheme[20,21] and the heat capacity of sublimation equal to −58 J mol^{-1} K^{-1}. This leads to $\Delta_\mathrm{subl}H^0 = 158.5 \pm 3.7$ kJ mol^{-1}.

The enthalpy of hydration of DXT is calculated from the standard enthalpy of solution and the enthalpy of sublimation as follows:

$$\Delta_\mathrm{hydr}H^0 = \Delta_\mathrm{sol}H^0 - \Delta_\mathrm{subl}H^0. \qquad (3)$$

This gives $\Delta_\mathrm{hydr}H^0$ values of -154.6 ± 3.7 and -150.0 ± 3.6 kJ mol^{-1} at 298.15 and 310.15 K, respectively. The heat capacity of hydration ($\Delta_\mathrm{hydr}C_\mathrm{p}^0$) of the solute in this case is calculated by the formula

$$\Delta_\mathrm{hydr}C_\mathrm{p}^0 = \Delta C_\mathrm{p}^0 - \Delta_\mathrm{subl}C_\mathrm{p}^0 \qquad (4)$$

and is 384 ± 80 J mol^{-1} K^{-1}.

In summary, our experimental investigation leads to the conclusion that hydration of DXT is accompanied by a large and positive change in heat capacity, indicating that the solute is rather hydrophobic and should exhibit a pronounced affinity for lipid membranes. The enthalpy of hydration is negative and rather large in absolute value. Both quantities appear to be important for computer modeling of DXT solvation and DXT membrane permeation to parametrize the respective potential functions to obtain reliable results on the drug accumulation in malignant cells.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.09.017.

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