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*NOTE*

# Thermodynamic Properties of Cyclophosphamide in Citric Acid Solution

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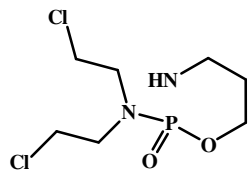
The dissolution behaviors of cyclophosphamide in citric acid solution were studied by a microcalorimetric method, The measured integral and differential heat of solution was used to build equations of the solute and the heat, so that dissolution thermodynamic equations, $\Delta_{sol}H_m$ were achieved, The results show that, using the thermodynamic parameters of microcalorimetric method cyclophosphamide is simple and feasible. The method provides strong data support for the clinical application of cyclophosphamide.

**Keywords: Cyclophosphamide, Thermodynamics, Microcalorimetric, Citric acid, Method.**

Cyclophosphamide is broad-spectrum antitumor drugs were stabled at room temperature. It is colorless and odorless or white needly crystal or crystalline powder. The molecular formula: $C_7H_{17}N_2O_3Cl_2P$. molecular weight: 279.1012. It is slightly soluble in water. But the solution is not stable. The structures of cyclophosphamide is as follows[1-3]:




Structure of cyclophosphamide

This product has significant immune inhibition, is the most commonly used alkylating antineoplastic agents. It is used for clinical treatment of malignant lymphoma, multiple myeloma, leukemia, breast cancer, ovarian cancer, cervical cancer, prostate cancer, colon cancer, carcinoma of the bronchus, lung cancer, has certain curative effect[4].

However, there are fewer literatures studied the half-life and the stability of the injection. making the preparation and the use of the drug remains at relatively low experience and semi-theoretical level. Although scientists have calculated the half-life by using high performance liquid chromatography to detect its concentration change in human bloods based on pharmacokinetic principles, such a method has complicated procedures and leads to errors in results because of individual difference in living bodies. To address this problem, the calorimetric method was applied to mimic body temperature, and the heat of solution of medicine were investigated in different solvents and their half-time was further calculated based on thermodynamic treatment. The results are consistent to the ones from pharmaco-kinetics, but the method is simple[5]. Moreover, the distribution of different systems and thermal stabilities of solutions can be generated from the Δsol Hm during the dissolution process. So the studies of its thermodynamic functions and determination of its kinetic parameters have significant meanings on improving medicines quality and clinic applications[6].

Cyclophosphamide (97 %). Citric acid solution (> 99 %). Electronic scale (Mianyang CAEP Thermal Analysis Instrument Company, China). The microcalorimeter was calibrated by Joule effect and its sensitivity was 64.22 ± 0.04 $\mu VmW^{-1}$ at 309.65 K. The enthalpy of dissolution of KCl (spectrum purity) in distilled water (about 20 mg/2 g) measured at 298.15 K was 17.535 kJ $mol^{-1}$, which was consistent with the value 17.536 kJ $mol^{-1}$ reported in literature[7], and this can demonstrate that the measurement of enthalpy in this work was reliable.

Accurate weighing a certain amount of cyclophosphamide and dissolved in 1.5 mL citric acid solution solution under the atmospheric pressure and certain temperatures. The RD 496-2000 microcalorimeter was used to monitor thermodynamic enthalpy changes.

For the discussion convenience, the released heats during these dissolution processes were listed in Table-1. Table shows that the increasing mass of cyclophosphamide led to increasing released heats, but kept the molar enthalpy constant. So the

average of molar enthalpies from different masses can be considered as the molar enthalpy in the infinitely diluted citric acid solution. As shown, the dissolution process of cyclophosphamide in citric acid solution was endothermic. linear curves (Fig. 1) were generated from the released heats (Q) and sample masses.

Dissolution enthalpy of cyclophosphamide in 1.50 mL citric acid solution is given in Table-1.

TABLE-1

| Sample mass/mg | n/(× $10^{-3}$ mol) | Q/J | $\Delta_{sol}H_m$/(kJ $mol^{-1}$) |
|---|---|---|---|
| Citric acid solution | | | |
| 14.83 | 5.31 | -1.23 | -23.21 |
| 19.82 | 7.10 | -1.65 | -23.28 |
| 24.82 | 8.89 | -2.09 | -23.54 |
| 29.69 | 10.64 | -2.48 | -23.34 |
| 34.93 | 12.52 | -2.96 | -23.62 |
| Average | | | -23.40 ± 0.22 |
| DMSO | | | |
| 19.96 | 7.15 | -1.58 | -22.15 |
| 40.07 | 14.36 | -3.41 | -23.78 |
| 50.27 | 18.01 | -3.91 | -21.69 |
| 70.02 | 25.09 | -5.81 | -23.14 |
| 79.78 | 28.58 | -6.10 | -21.34 |
| Average | | | -22.42 ± 1.36 |

Their corresponding linear equations of these two parameters are shown as equations:

$$Q = -23832n + 35.479, r = 0.9998 \quad (1)$$

$$Q = -21585n + 38.72, r = 0.9882 \quad (2)$$

Linear relationship between the heat effect (Q) and the amount of (a) the cyclophosphamide in 1.50 mL citric acid solution and (b) the cyclophosphamide in 1.50 mL DMSO.

These equations show that the mass of substances and heat Q has well linear relationships, so the calculated molar enthalpy change from eqn. (1) and (2) are -23.39 and -22.42 kJ $mol^{-1}$, respectively.

## Conclusion

• Melting heat of cyclophosphamide in citric acid and DMSO were -23.39 and -22.42 kJ $mol^{-1}$ that are consistent with the literature.

• Citric acid solution the solvent is the value of R is 0.9998; DMSO the solvent is the value of R is 0.9882; Chemical reactions may occur in the solution of DMSO.

• Obviously, cyclophosphamide in citric acid is more stable than cyclophosphamide in DMSO.

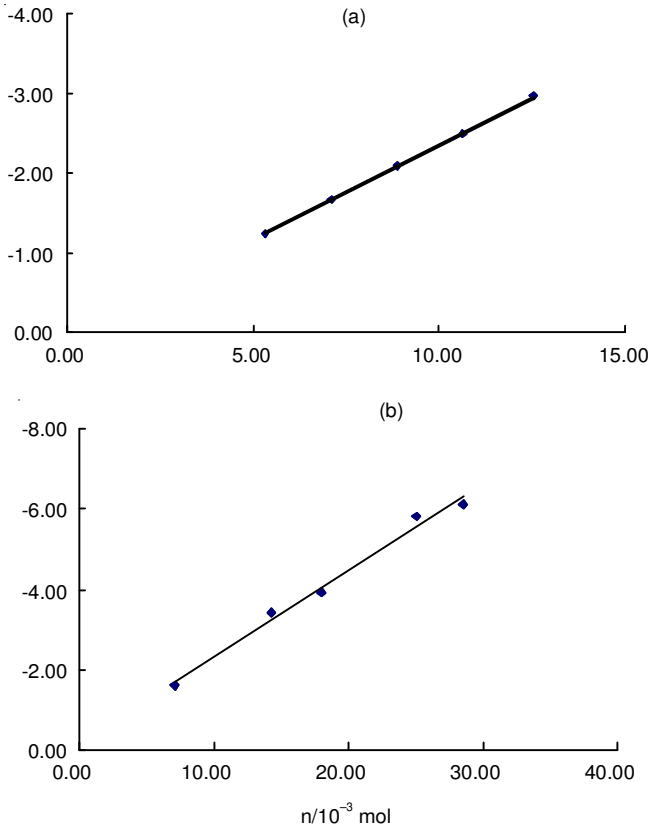



Fig. 1. Linear curve

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