

Enthalpic interactions of anti-tumor drug matrine in aqueous sodium chloride solutions

Xiang Jun Sun · Xiang Yu Xu · Min Liu ·
Lin Wei Li · De Zhi Sun

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Abstract The enthalpies of dilution of matrine (MAT) in pure water and aqueous sodium chloride solutions were determined by isothermal titration microcalorimetry at 298.15 K, and the corresponding homogeneous enthalpic interaction coefficients were calculated according to the modified McMillan–Mayer model. The values of enthalpic pair-wise interaction coefficients, h_2 , are all positive and become more positive with increasing concentration of sodium chloride.

Keywords Aqueous sodium chloride solution · Enthalpic pair-wise interaction coefficients · Enthalpy of dilution · Matrine

Introduction

Investigation of the interaction between anti-tumor drug and the chemical composition of cell is a basic path to approach mechanism of tumor-cell apoptosis induced by the drug [1–3], and it is also an important content of study on cell apoptosis intervention, which is a developing therapeutical method of the fatal disease [4]. The apoptosis of cell should happen in medium which consisted of biochemical substances, and the chemical component of cell inside body is a very complex system. Therefore, the asymptotic simulation of the medium of cell outside body and the approaching of changes of thermodynamic property of anti-tumor drug in the simulated medium are significant for study on the medium effect to the drug.

A lot of studies on anti-tumor function of matrine (MAT) show that the drug can restrain the multiplication of tumor cells via restraining the synthesis of DNA and the enzyme activity and effecting the normal cycle, and also can restrain the transfer of the tumor through controlling the expression of the genes, and result in the death of the tumor cell and induce the tumor cell to differentiate into common cell through controlling the expression of the genes and affecting the telomerase activity [5–7]. Water (H_2O), Na^+ , and Cl^- are important substances in cell, and play vital roles to dissolving and metabolism of other substances, temperature conditioning, structure stability of protein and other biomacromolecules, enzyme reaction, and acid–base equilibrium, etc. [8, 9].

In this article, the enthalpies of dilution of MAT in pure water and aqueous solutions of sodium chloride were determined by nano-watt-scale isothermal titration microcalorimetry, and the enthalpic interaction coefficients were calculated from the modified McMillan–Mayer theory. The results are discussed in terms of the solute–solute and solute–solvent interactions.

Experimental

Instrument and materials

Isothermal titration microcalorimeter, TAM 2277 (Thermometric, Sweden) is controlled by Digitam 4.1 software. This instrument has an electrical calibration with a precision better than $\pm 1\%$ that was verified by measuring the dilution enthalpy of a concentrated sucrose solution and the fluctuation of baseline is $\pm 0.02 \mu\text{W}$.

Matrine (MAT) (98%, in purity) is a product of Huacui biological technology Limited Co. (China). Sodium

X. J. Sun · X. Y. Xu · M. Liu · L. W. Li (✉) · D. Z. Sun
College of Chemistry and Chemical Engineering,
Liaocheng University, Liaocheng 252059, China
e-mail: liliwei666977@163.com

Table 1 Enthalpies of dilution of MAT in aqueous NaCl solutions of different concentrations at 298.15 K

$m_i/$ mol kg ⁻¹	$\Delta_{dil}H_m/$ J mol ⁻¹	$m_f/$ mol kg ⁻¹	$\Delta_{dil}H_m/$ J mol ⁻¹	$m_f/$ mol kg ⁻¹
Pure water $m_{NaCl} = 0$				
0.1015	-355.37	0.00288	-249.80	0.03233
	-348.97	0.00560	-244.74	0.03368
	-341.05	0.00818	-237.48	0.03498
	-332.84	0.01062	-231.57	0.03623
	-325.68	0.01293	-226.89	0.03743
	-317.57	0.01514	-221.07	0.03859
	-310.41	0.01723	-215.34	0.03971
	-302.30	0.01923	-209.80	0.04079
	-294.47	0.02113	-204.17	0.04183
	-286.83	0.02294	-198.73	0.04284
	-281.49	0.02468	-193.29	0.04381
	-275.95	0.02634	-189.19	0.04475
	-268.03	0.02793	-183.84	0.04567
	-261.44	0.02946	-178.59	0.04655
	-256.29	0.03092	-172.10	0.04741
$m_{NaCl} = 0.09989/\text{mol kg}^{-1}$				
0.1020	-369.91	0.00289	-264.46	0.03247
	-364.71	0.00563	-258.78	0.03383
	-355.99	0.00821	-253.24	0.03513
	-348.32	0.01067	-247.73	0.03639
	-339.80	0.01299	-242.30	0.03760
	-330.96	0.01520	-236.79	0.03876
	-322.57	0.01731	-231.29	0.03989
	-314.82	0.01931	-225.88	0.04097
	-307.70	0.02122	-220.43	0.04202
	-300.93	0.02305	-214.95	0.04303
	-294.49	0.02479	-209.56	0.04401
	-288.32	0.02646	-204.11	0.04496
	-282.02	0.02806	-198.47	0.04587
	-276.04	0.02959	-192.80	0.04676
	-270.19	0.03106	-187.23	0.04762
$m_{NaCl} = 0.3014/\text{mol kg}^{-1}$				
0.1017	-393.65	0.00291	-283.21	0.03265
	-386.33	0.00566	-277.52	0.03402
	-377.15	0.00826	-271.87	0.03533
	-367.14	0.01072	-266.24	0.03659
	-358.40	0.01306	-260.64	0.03781
	-349.58	0.01529	-254.96	0.03898
	-341.91	0.01740	-249.35	0.04011
	-334.20	0.01942	-243.57	0.04120
	-327.17	0.02134	-238.08	0.04225
	-320.52	0.02318	-232.53	0.04327
	-313.96	0.02493	-227.19	0.04425
	-307.44	0.02661	-221.96	0.04520

Table 1 continued

$m_i/$ mol kg ⁻¹	$\Delta_{dil}H_m/$ J mol ⁻¹	$m_f/$ mol kg ⁻¹	$\Delta_{dil}H_m/$ J mol ⁻¹	$m_f/$ mol kg ⁻¹
	-301.12	0.02821	-216.39	0.04613
	-294.93	0.02976	-210.78	0.04702
	-288.98	0.03123	-205.21	0.04788
$m_{NaCl} = 0.5002/\text{mol kg}^{-1}$				
0.1018	-412.73	0.00289	-299.64	0.03242
	-401.91	0.00562	-294.04	0.03377
	-390.67	0.00820	-288.34	0.03507
	-381.34	0.01065	-282.90	0.03633
	-372.33	0.01297	-277.41	0.03753
	-364.74	0.01518	-271.93	0.03870
	-357.39	0.01728	-266.16	0.03982
	-349.77	0.01928	-260.50	0.04090
	-342.99	0.02119	-254.98	0.04195
	-336.20	0.02301	-249.48	0.04296
	-329.14	0.02475	-244.00	0.04394
	-322.83	0.02642	-238.61	0.04488
	-316.73	0.02801	-233.22	0.04579
	-310.96	0.02954	-227.71	0.04668
	-305.35	0.03101	-222.31	0.04754
$m_{NaCl} = 0.7102/\text{mol kg}^{-1}$				
0.1021	-460.81	0.00290	-340.92	0.03250
	-447.75	0.00563	-334.81	0.03386
	-436.29	0.00822	-328.71	0.03517
	-425.82	0.01068	-322.68	0.03642
	-415.97	0.01300	-316.76	0.03763
	-407.67	0.01522	-310.89	0.03880
	-399.70	0.01732	-305.19	0.03992
	-392.52	0.01933	-299.53	0.04101
	-385.82	0.02124	-293.86	0.04206
	-379.04	0.02307	-288.28	0.04307
	-372.25	0.02482	-282.77	0.04405
	-365.61	0.02649	-277.33	0.04500
	-359.26	0.02809	-271.84	0.04592
	-353.10	0.02962	-266.40	0.04680
	-347.02	0.03109	-260.95	0.04766
$m_{NaCl} = 0.8912/\text{mol kg}^{-1}$				
0.1019	-478.52	0.00289	-356.71	0.03244
	-466.92	0.00562	-350.38	0.03380
	-455.52	0.00821	-344.24	0.03510
	-445.10	0.01066	-338.23	0.03635
	-435.54	0.01298	-332.28	0.03756
	-427.29	0.01519	-326.41	0.03873
	-419.22	0.01729	-320.60	0.03985
	-411.84	0.01929	-314.88	0.04093
	-404.65	0.02120	-309.33	0.04198
	-397.63	0.02303	-303.89	0.04299

Table 1 continued

$m_i/$ mol kg ⁻¹	$\Delta_{dil}H_m/$ J mol ⁻¹	$m_f/$ mol kg ⁻¹	$\Delta_{dil}H_m/$ J mol ⁻¹	$m_f/$ mol kg ⁻¹
	-390.42	0.02477	-298.50	0.04397
	-383.38	0.02644	-293.23	0.04491
	-376.50	0.02803	-287.93	0.04583
	-369.83	0.02956	-282.78	0.04671
	-363.20	0.03103	-277.61	0.04757

chloride (GR grade) was purchased from Tianjin Guangfu Fine Chemical Research Institute (China). All the solid reagents were stored over P₂O₅ in a vacuum desiccator for 72 h at 393 K. Twice distilled water prepared with a quartz sub-boiling purifier was used in the preparation of solutions. Aqueous NaCl solutions and MAT solutions were prepared by mass using a Mettler AE 200 balance with a precision of ±0.01 mg, and were used within 12 h to prevent from contaminated by germs.

Microcalorimetric measurements

Matrine was dissolved in aqueous NaCl solution at different concentrations. The sample vessel was initially loaded with 0.5 ml aqueous NaCl solution, and MAT solution at the molality, m_i , was injected into the stirred sample within the vessel in 30 portions of 15 μL using a Hamilton syringe controlled by a 612 Lund Pump. The time interval between two injections was 35 min, which was sufficiently long for the signal to return to the baseline. The stirrer was a gold propeller at 30 rpm. All the experiments were performed at a fixed temperature of (298.15 ± 0.01) K and repeated three times. The reproducibility was within 4%. The output signal was collected as power versus time and was integrated and quantified against the amount of MAT injected. The experimental molar dilution enthalpy of MAT, $\Delta_{dil}H_m$, was calculated by the following equation:

$$\Delta_{dil}H_m = [(1 + m_iM)/nW_t m_i] Q_{dil} \tag{1}$$

where Q_{dil} (J) is the heat attributed to the dilution of MAT; M is the molar mass of MAT (kg mol⁻¹); m_i is the initial molality (mol kg⁻¹) of the MAT solution; W_t is the mass of each titration (kg); and n is the number of the titration, $n = 1, 2, 3, \dots, 30$.

The final molality of MAT, m_f , was calculated from the equation:

$$m_f = nW_t m_i / [W_0(1 + m_iM) + nW_t] \tag{2}$$

where W_0 is the mass of the aqueous NaCl solution before titration (kg).

Results and discussion

According to the modified McMillan–Mayer model [10–12], the thermodynamic properties of multicomponent solutions can be expressed through a virial expansion in molality (m), which relates the non-ideal contributions of any total thermodynamic function to a series of interactions parameters. If the aqueous solutions of NaCl used in this study are regarded as “solvent,” then the excess enthalpy per kg of solvent, H^E , of a solution containing a single molecular solute at molality m can be given by [11]:

$$H^E = h_2m^2 + h_3m^3 + h_4m^4 + \dots \tag{3}$$

where, h_2, h_3, h_4 , etc. are the enthalpic coefficients representing pair-wise and, at least notionally, triplet, quarter, and higher-order interactions between the diluted solute species. The molar enthalpy change, $\Delta_{dil}H_m$, on diluting a solution of non-electrolytic solute from an initial molality, m_i , to a final molality, m_f , can be written as:

$$\begin{aligned} \Delta_{dil}H_m = H_m^E(m_f) - H_m^E(m_i) = & h_2(m_f - m_i) \\ & + h_3(m_f^2 - m_i^2) + h_4(m_f^3 - m_i^3) \\ & + \dots \end{aligned} \tag{4}$$

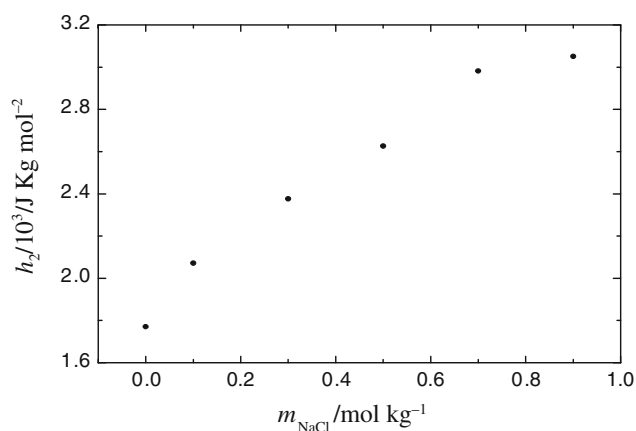
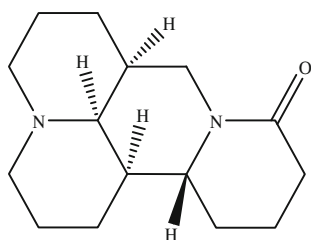
in which $H_m^E(m_i)$ and $H_m^E(m_f)$ are the molar excess enthalpies of the diluted component in the solvent (pure water and different concentrations of the salt solutions) before and after dilution.

The $\Delta_{dil}H_m$ values of MAT in NaCl solutions at different molalities were obtained from the titration experiment, and the coefficients of Eq. 4 were obtained from least-squares analyses of the calorimetric data (Table 1).

The enthalpic interaction coefficient is a measure of thermodynamic effect caused by interactions of solute molecules approaching each other in solution. In the mutually approaching process, there is overlapping of the solvation cospheres of solute molecules, partial reorganization of solvent structure, and solute–solvent and solute–solute interactions. Since trimolecular interacting system is very complex and much less probable than biomolecular system, we discuss the latter interaction only. It is generally thought that the enthalpic pair-wise interaction coefficients mainly result from electrostatic and structural interactions [13]. Electrostatic interaction is exothermic and makes the enthalpic interaction coefficients more negative, while structural interaction includes two sections, i.e., partial desolvation of the solute molecules and structural reorganization of solvent molecules around solutes [14]. Desnoyer et al. [15] have pointed out that the structural interaction is endothermic at most cases and makes the enthalpic interaction coefficients more positive, thus its influence is quite large, and, sometimes, becomes the dominant factor of the enthalpic interaction coefficients [16, 17].

Table 2 Enthalpic interaction coefficients of MAT in aqueous NaCl solutions of different concentrations at 298.15 K

NaCl/kg mol ⁻¹	$h_2 \times 10^{-3}/\text{J kg mol}^{-2}$	$h_3 \times 10^{-4}/\text{J kg mol}^{-3}$	$h_4 \times 10^{-5}/\text{J kg mol}^{-4}$	R^a	Range of $m_f/\text{mol kg}^{-1}$
0	1.77 ± 0.15	6.73 ± 0.40	-4.91 ± 0.26	0.99956	0.00288–0.04741
0.1	2.07 ± 0.20	5.60 ± 0.52	-3.95 ± 0.34	0.99922	0.00289–0.04762
0.3	2.38 ± 0.20	4.80 ± 0.54	-3.22 ± 0.36	0.99919	0.00289–0.04751
0.5	2.63 ± 0.23	3.99 ± 0.63	-2.51 ± 0.41	0.99892	0.00289–0.04754
0.7	2.98 ± 0.24	3.28 ± 0.64	-1.71 ± 0.42	0.99895	0.00290–0.04766
0.9	3.05 ± 0.16	3.33 ± 0.44	-1.62 ± 0.29	0.99953	0.00289–0.04757

**Fig. 1** Enthalpic pair-wise interaction coefficients (h_2) of MAT versus the concentrations of aqueous NaCl solutions at 298.15 K**Fig. 2** Molecular structure of matrine

From the data in Table 2 and the points in Fig. 1, it can be seen that the enthalpic pair-wise interaction coefficients of MAT, h_2 , are all positive and become more positive with increase of the NaCl molality, which indicates that if each in a pair of MAT molecules approaches one another, then an endothermic process will occur. In order to explain the thermodynamic phenomenon, we should consider several interactions in this research system as follows: (a) The molecular structure of solute MAT (Fig. 2) is quinoilizidine with four-loop of six-membered rings including polar and non-polar groups. When two MAT molecules approach each other in the solution, there are probably hydrophilic–hydrophobic and hydrophobic–hydrophobic interactions, and the overlapping of the solvation cospheres around the

solute molecules can weaken the two types of interactions in competitive balance. In general, the weakening effect of hydrophobic hydration of non-polar groups is prominent and manifested as endothermic process which can lead to positive contribution to h_2 [15]. Simultaneously, MAT molecule is in a relatively rigid structure [18], the steric effect of ring structure can also weaken the above mentioned interactions. (b) Nature of hydrogen bond is essentially electrostatic interaction [19], an MAT molecule carries the fragment of $\text{O}=\text{C}-\text{N}-\text{C}-\text{C}-\text{N}$ as shown in Fig. 2, and both oxygen and nitrogen atoms facilitate the formation of hydrogen bond. Besides, the hydrogen bond between solute molecules, the whole solution system electrostatic interactions also include ion–dipole interaction of the salt ions with the solute molecules and water molecules, and dipole–dipole interaction of solute–solute and solute–solvate molecules. All the above mentioned interactions can lead to negative contribution to h_2 . (c) The interaction between solute molecules and the salt ions can also produce respective disturbance of the solvation cospheres, and result in the release of some water molecules from the hydration shells of the solute molecules into the solution bulk medium. This is an endothermic process, and leads to positive contribution to h_2 [20]. (d) The relatively strong hydrogen bond between water molecules lead to a highly ordered structure, but as a water structure breaker [21, 22], NaCl destroys the iceberg structure in hydration shells of the solute molecules [23] and the water structure in bulk medium, which is an endothermic process, and eventually makes positive contribution to h_2 [24]. On the whole, the sign and value of h_2 of MAT depend on comprehensive balancing of the above mentioned interactions in the solution system, while the changing tendency of h_2 with increase in concentration of NaCl is mainly decided by destructive effect of the salt.

Conclusions

The enthalpies of dilution of MAT in different concentrations of aqueous NaCl solutions have been determined with isothermal titration microcalorimetry at 298.15 K. The

homogeneous enthalpic interaction coefficients are obtained by the modified McMillan–Mayer theory. The values of the enthalpic pair-wise interaction coefficient of MAT, h_2 , are all positive and become more positive with increase of the NaCl molalities. The value of h_2 depends on comprehensive balancing of several types of interactions, while its change trend is mainly decided by destructive effect of the salt.

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