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Solvation and ion–ion interactions in aqueous and non-aqueous solutions of cationic cytostatic agent prospidium chloride

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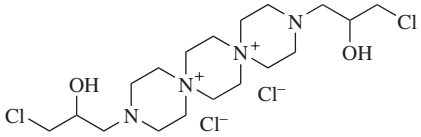
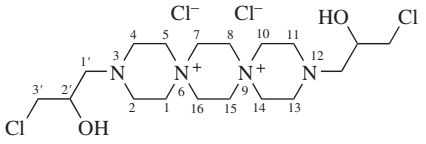
The thermochemical behavior of well-established heterocyclic anticancer drug, prospidium chloride, was comparatively evaluated in water and two other non-aqueous solvents, formamide and ethylene glycol, forming the three dimensional H-bond network. Standard enthalpies and heat capacities of solution, as well as, enthalpic parameters of solute–solute pair interactions were estimated at 298 and 318 K and compared with the available values for some ionic species. A linear correlation between the energetics of ion–ion interactions and the reciprocal dielectric constant of the medium for tetraethylammonium bromide and prospidium chloride was revealed.



Prospidium chloride

Interactions of biological species with surrounding water molecules are known as affecting their activity in many processes including the transport of small molecules and ions through cellular membranes, structure and catalytic ability of many important enzymes, distribution of drug molecules between water- and lipid-like compartments, *etc.*[1,2] Despite of intense structural and thermodynamic studies of these phenomena, the behavior of these solutes in water-like media still remains incompletely understood. Water possesses a unique ability to hydrate different groups of biological species being a driving force for them to adopt special structures, where hydrophilic units are mainly exposed to water and the hydrophobic ones are sequestered from solvent molecules.[1,2] These so-called hydrophobic effects are usually associated with the existence of the three-dimensional H-bond network.[1,3–5] Several important works were performed to highlight the existence of similar phenomena in non-aqueous media.[5–10] However, solvophobic effects seem to be much weaker than hydrophobic ones occurring in water.[5,7–9] Our previous report on the solvation thermochemistry of tetraalkylammomiun ions in water, formamide, and ethylene glycol has confirmed much weaker pronounced solvophobic solvation in non-aqueous media,[10] *i.e.*, the amide was found to be a more water-like solvent than the glycol.

Prospidium chloride, *viz.* 3,12-bis(3-chloro-2-hydroxypropyl)-3,12-diaza-6,9-diazoniadispyro[5,2,5,2]hexadecane dichloride, is a low toxic cytostatic agent highly soluble in polar media. Its structure is similar to that of spiro tetraalkylammonium halides.



Prospidium chloride

It is widely administered for treating many malignancies and precancerous conditions.[11–13] This solute is believed to be dissociated as 1 : 2 electrolyte, the organic cation revealing a tendency to be localized in polar regions of human cells, in particular, in guanidine-rich regions of DNA molecules (G-quadruplexes). The latter aspect implies that the direct binding of solute with nucleus targets may occur. The strength of such binding is strongly dependent on the drug local environment suggesting that ion solvation and ion–ion interactions may play an important role in the successful cancer treatment.

We are currently involved in a fairly extensive and continuing series of investigations on solvation of biologically active species, such as antitumor drugs and potential sensitizers for antitumor and antimicrobial photodynamic therapy in aqueous and non-aqueous media.[14,15] Here, we performed a comparative analysis of the behavior of prospidium chloride in water, ethylene glycol and formamide forming the three dimensional H-bond network at the supramolecular level. It was aimed at highlighting common features and differences in the energetics of prospidium chloride solvation and ion–ion interactions in aqueous and highly associated non-aqueous media that reveal some importance for biological chemistry.

Experimental and standard enthalpies of solution of prospidium chloride are given in Table S1 (see Online Supplementary Materials). Figure 1 shows $\Delta_{sol}H^m$ *vs.* $m^{1/2}$ curves compared with those in water.[14] One can see a strong concentration dependence of the values $\Delta_{sol}H^m$ for ethylene glycol as a solvent, while enthalpies of solution in formamide are almost independent of the drug concentration. In both cases, the experimental curves deviate from the limiting Debye's slope a_H, and the deviation is stronger for glycol solutions. Such solute behavior can be easily explained by stronger ion–ion interactions in ethylene glycol since its dielectric constant is three times smaller.[16]

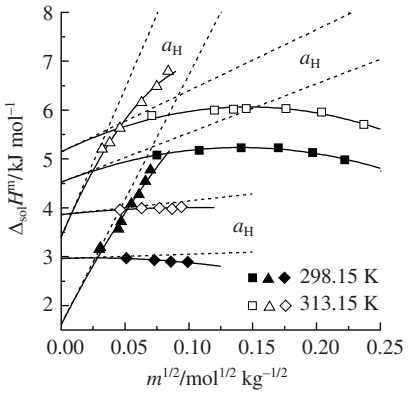


Figure 1 Experimental enthalpies of solution for prospidium chloride in water (□, ■), ethylene glycol (△, ▲), and formamide (◇, ◆). Solid lines denote the description according to equation (1), and dashed lines give the appropriate Debye's limiting slopes a_H.

The experimental curves (Figure 1) are often approximated with the Redlich–Rosenfeld–Meyer-type equation:[16,17]

$$\Delta_{sol}H^m = \Delta_{sol}H^0 + a_H m^{1/2} + bm, \quad (1)$$

where $\Delta_{sol}H^0$ is the enthalpy of solution at an infinite dilution and a_H is the limiting Debye slope.

The latter can be represented as follows:[16,17]

$$a_H = -\sqrt{v/2}\,|z_+z_-|^{3/2} vRT^2 A\left(\frac{1}{T} + \frac{1}{\varepsilon}\frac{\partial\varepsilon}{\partial T} - \frac{1}{3\rho}\frac{\partial\rho}{\partial T}\right), \quad (2)$$

where z and v are the charge and number of corresponding ions after dissociation of prospidium chloride as a 1 : 2 electrolyte; ρ and ε are density and dielectric permittivity of an appropriate solvent (all the necessary values were known[16]), respectively, and the coefficient A is obtained from the following relationship:[16,17]

$$A = \sqrt{\frac{2\pi N_A e^6 \rho}{1000(\varepsilon\kappa T)^3}}. \quad (3)$$

The $b = h_{22}$ coefficient in equation (1) represents the sum of the cation–cation, cation–anion and anion–anion pair interactions in a liquid phase, which contribute to the deviation of $\Delta_{sol}H^m$ values from the limiting Debye's slope.[14]

The $\Delta_{sol}H^m$ values have been fitted into equation (1) to estimate the $\Delta_{sol}H^0$ and h_{22} quantities using the least squares technique. The h_{22} parameters and the heat capacities of solution are given in Table 1, where they are compared with similar values for well-known hydrophobic or hydrophilic species.

The standard enthalpies (see Table S1 and Figure 1) are small, positive, and increase with the temperature for both non-aqueous solvents. The similar trend was observed in water, but the heat capacity change was smaller. One can see from Table 1 that the heat capacity of solution for hydrophilic species is negative, while it is positive for hydrophobic tetraalkylammonium bromides and increases with the size of tetralkylammonium ion. The latter tendency is much stronger pronounced in water as compared to that in formamide and, especially, ethylene glycol. This heat capacity change for nonpolar species is often associated with the angular ordering of neighboring water molecules.[1,19] The larger the hydrophobic solute size, the more significant population of linear and shorter water–water H-bonds around the solute appears.[19] Although the data in Table 1 shows that heat capacity values for prospidium chloride and tetraalkylammonium bromides are positive for both non-aqueous solvents, the difference between values for small and large tetraalkylammonium ions is insignificant. Furthermore, the heat capacities of solutions of Bu_4NBr and prospidium chloride in ethylene glycol are found to be almost identical, while they differ by a factor of sixteen in an aqueous solution. These facts signify that for formamide and, especially, ethylene glycol, the angular solvent ordering around apolar solutes mentioned above, if any, is small.

Table 1 Standard heat capacities of solution (ΔC_p^0) and enthalpic pair interaction parameters (h_{22}) for some electrolytes in water, formamide, and ethylene glycol.

Solute	ΔC_p^0/J mol^{-1} K^{-1}	h_{22}/kJ kg mol^{-2}	
	T = 298.15 K	T = 298.15 K	T = 313.15 K
	Water		
NH_4Br[a]	–149(3)[c]	–2.00(0.1)	–1.8(0.1)
Et_4NBr[a]	131(3)	–5.2(0.2)	–5.5(0.2)
Bu_4NBr[a]	751(5)	12.6(0.5)	8.8(0.3)
$CaCl_2$[a]	–321(10)	–6.1(2.0)	–12.2 (1)
Prospidium chloride[a]	45(2)	–35.7(0.5)	–42.7(1.1)
	Formamide		
Et_4NBr[b]	35(1)	0.33(0.8)	–0.05(0.1)
Bu_4NBr[b]	168(2)	–11.4(1.3)	–4.5(0.5)
Prospidium chloride	60(2)	–17.3(2)	–13.6(3)
	Ethylene glycol		
Et_4NBr[b]	46(7)	–29.9(5)	–37.1(3)
Bu_4NBr[b]	103(3)	–28.5(2)	–49.5(2)
Prospidium chloride	121(6)	–108(22)	–258(14)

[a] Values from ref. 14. [b] Calculated from known enthalpies of solution.[18] [c] Error bars represent a standard deviation.

Since the heat capacity is positive and increases in the homological series of tetraalkylammonium bromides, it leads to a conclusion that large organic cations make a positive contribution to the total heat capacity change, while bromide and chloride ions contribute in the opposite manner. The final heat capacity value depends mainly on the cation size. For prospidium chloride, however, there are additional effects resulting from two hydrophilic hydroxyl groups in the cation structure and an additional chloride ion. Both of them should weaken the angular ordering of neighboring water molecules and decrease the solvent contribution to the total heat capacity change. This seems to be the major reason for the relatively small heat capacity change observed. Similar phenomena occur in highly associated formamide and ethylene glycol, however they are pronounced much weaker than those in water. Meantime, in terms of thermochemistry, the amide seems to be more water-like than the glycol. The similar findings have been previously drawn from the behavior of small and large tetraalkylammonium ions, urea and tetramethylurea.[9,20]

Table 1 also provides a comparison of the enthalpic pair interaction parameters for solvated ions in three highly associated media. These quantities are negative for all the cases except for the aqueous solution of Bu_4NBr, where hydrophobic forces induce strong cation–cation correlations[21] leading to the large and positive enthalpy change.[14] Along with increasing tetraalkylammonium ion size from Me_4N^+ to Bu_4N^+, the electrostatic cation–anion interaction is weakened in water. Simultaneously, the hydrophobic interaction induces the dramatically increased cation–cation correlations. Thus, at concentrations of 1 mol kg^{-1}, which are appropriate for extended X-ray absorption investigations,[21] the Bu_4N^+–Bu_4N^+ contact pairs were detected. This strong cation–cation attraction is accompanied by a large dehydration effect leading to the positive h_{22} value. Hence, for organic electrolytes containing large hydrophobic units, the cation–cation interaction makes a positive contribution to the enthalpy of pair interaction. In contrast, the cation–anion and anion–anion interactions seem as contributing in the opposite manner. For slightly amphiphilic Et_4NBr and prospidium chloride, this effect in water was much smaller and totally masked by strong electrostatic interactions.

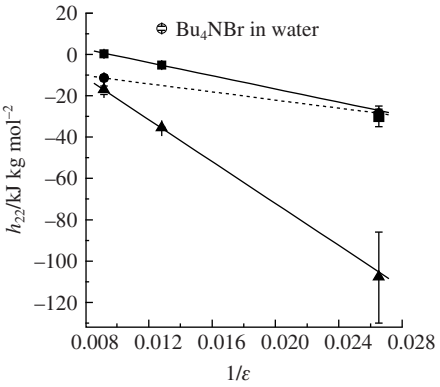


Figure 2 Enthalpic parameters of ion–ion pair interactions for Et_4NBr (■), Bu_4NBr (●), and prospidium chloride (▲) *vs.* the reciprocal dielectric constant of formamide, water and ethylene glycol at 298.15 K, respectively. Solid lines represent linear functions: h_{22}(prospidium chloride) = 31.1(7) – 5241(40)/ε, R = 0.999 and s_f = 0.51 kJ kg mol^{-2}; h_{22}(Et_4NBr) = 16.9(12) – 1764(51)/ε, R = 0.999 and s_f = 0.65 kJ kg mol^{-2}. Error bars represent the standard deviation.

The behavior of Bu_4NBr is similar to that for other electrolytes (see Table 1) in both non-aqueous solvents indicating that a tendency to solvophobic association in non-aqueous media seems to be totally masked by electrostatic interactions. For prospidium chloride, the h_{22} values are significantly lower than those for other solutes due to cation–anion interactions. These interactions are strongly thermochemically attractive and reveal a tendency to be enhanced in ethylene glycol at elevated temperatures. In contrast, the h_{22} values in formamide are almost identical at both temperatures. The most important feature is that the energetics of interactions between solvated ions reveals a linear correlation with the reciprocal dielectric constant of the solvent. Figure 2 shows the existence of such correlations for prospidium chloride and Et_4NBr but not for Bu_4NBr. The reason of such behavior is the hydrophobic interaction between Bu_4N^+ ions in water. This interaction is accompanied by a large and positive enthalpy change leading to significantly more positive values h_{22} than it would be expected from the linear relationship. In the case of two other solutes, this empirical correlation implies that the energetics of ion–ion pair interactions is mainly defined by electrostatic forces, *i.e.*, the stronger the ion–solvent interaction, the more positive h_{22} value. This result is in a clear accordance with a general chemical intuition and many similar effects observed in ionic media.

In conclusion, our results do indicate that solvophobicity of prospidium chloride is quite small, and its solvation behavior is very similar to that of Et_4NBr. The behavior of prospidium chloride in highly associated non-aqueous media does not reveal any principal differences as compared to water. The existence of the linear correlation between enthalpic parameters of pair interactions between solvated ions and the reciprocal dielectric constant of the solvent for prospidium chloride and Et_4NBr suggests that the energetics of ion–ion interactions for these slightly hydrophobic species is mainly defined by electrostatic forces both in water and non-aqueous solvents. The cation–anion pair interaction is strongly enthalpically attractive for solvents with the middle value of dielectric constant (such as ethylene glycol). In constrast, for water and, especially formamide, these attractive forces are significantly weakened.

Another important result is that the linear relationship mentioned above should have a predictive value, *i.e.*, it can provide at least the semi-quantitative description of the deviation of $\Delta_{sol}H^m$ *vs.* $m^{1/2}$ curve from the limiting Debye's slope for prospidium chloride in any highly associated solvent, such as heavy water, monoethanolamine, glycerol, *etc*.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.07.029.

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