Calorimetric study of the molecular recognition of nucleic acid bases by β-cyclodextrin in aqueous solution

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10.1070/MC2002v012n06ABEH001648

As found by calorimetry, β-cyclodextrin can recognise nucleic acid bases and their derivatives in aqueous solutions by forming inclusion complexes with only purine bases (adenine and caffeine).

Purine and pyrimidine bases and their derivatives are of great biochemical and pharmacological interest. They are DNA and RNA components and fragments of vitamins and co-enzymes. It is known that pyrimidine bases are applied as anticarcinogenic drugs, the analogues of purine bases are immunodepressants, and caffeine is a stimulant of the central nervous system.[1] These compounds are slightly soluble in aqueous solutions (for example, at 298.15 K, $S_{adenine} = 8.7\times10^{-3}$ mol kg^{-1} and $S_{uracil} = 2.7\times10^{-2}$ mol kg^{-1}).[2,3] The host–guest complexes of natural cyclic oligosaccharides (cyclodextrins) can be used for increasing the solubility of purine and pyrimidine bases.[4] The capillary-electrophoretic separation of adenosine nucleotides using β-cyclodextrin is based on the formation of inclusion complexes.[5]

The complex formation of cyclodextrins with different guest molecules was described.[6–9] However, the interactions of cyclodextrins with nucleic acid bases were not investigated. The aim of this work was to study the ability of β-cyclodextrin (β-CD) to complexation with adenine (Ade), thymine (Thy), uracil (Ura), 6-aza-uracil (6-azaUra), cytosine (Cyt) and caffeine (Caf) in aqueous solutions using calorimetry.

The enthalpies of dissolution of β-CD in twice-distilled water and aqueous solutions of nucleic acid bases and their derivatives† were measured using an isothermal calorimeter[10] at 298.15 K. The concentration of β-CD was $(7.0\pm0.2)\times10^{-4}$ mol kg^{-1}. The concentration of the aqueous solutions of nucleic acid bases was varied within the ranges: $m_{Ade} = 0.001$–0.008, $m_{Caf} = 0.01$–0.08, $m_{Cyt} = 0.01$–0.06, $m_{Thy} = 0.004$–0.020, $m_{Ura} = 0.006$–0.020 and $m_{6\text{-azaUra}} = 0.006$–$0.020$ mol kg^{-1}. The heats of dissolution were measured to within 0.03 J.

We found that the thermal effects of β-CD dissolution in aqueous Ade and Caf solutions after a significant decrease became practically constant with increasing concentrations of Ade and Caf. This suggests complex formation in the test systems. The thermodynamic functions of complex formation (Table 1) were calculated using the HEAT computer program, in which a search of unknown parameters (lg K and $\Delta_c H$) is reduced to the numerical minimization of a function of experimental data.[11]

The thermodynamic functions presented in Table 1 referred to a 1:1 complexation model. Published data on the complexation of β-CD with aromatic guest molecules such as benzoic acid, phenols and their derivatives indicate the formation of 1:1 inclusion complexes.[7–9]

Table 1 indicates that the complexes of β-CD with Ade and Caf are characterised by negative enthalpies and positive entropies. Thus, they are enthalpically–entropically stabilised, the entropic contribution being prevailing. Positive $\Delta_c S^0$ values may be explained by dehydration occurring at the penetration of guest molecules in a cavity of β-CD.

Table 1 The equilibrium constants, free energies, enthalpies and entropies of complex formation of β-cyclodextrin with adenine and caffeine in water at 298.15 K.

Complex	K/kg mol^{-1}	$\Delta_c G^0$/kJ mol^{-1}	$\Delta_c H^0$/kJ mol^{-1}	$T\Delta_c S^0$/kJ mol^{-1}
β-CD/Ade	2291(±68)	–19.2(±0.6)	–3.4(±0.1)	15.8(±0.9)
β-CD/Caf	30(±2)	–8.4(±0.5)	–2.2(±0.3)	6.2(±1.2)

† Commercial nucleic acid bases, caffeine (monohydrate) and β-CD (ICN Pharmaceuticals) were used.

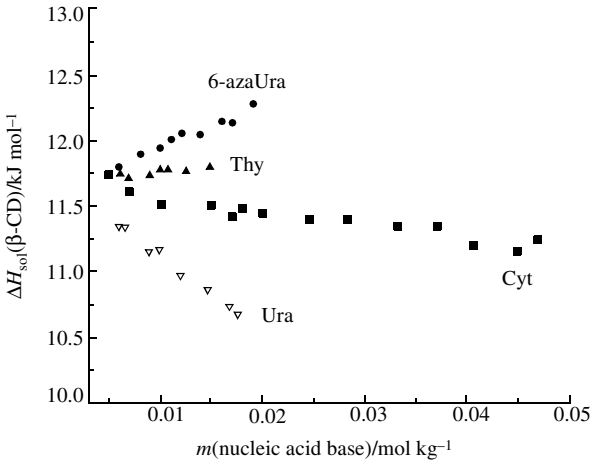

Figure 1 Enthalpy of β-CD solution in the aqueous solutions of nucleic acid bases *vs.* nucleic acid base molality (T = 298.15 K).

The stability constant of the β-CD/Ade complex is many times greater than the stability constant of the β-CD/Caf complex. The thermodynamic characteristics suggest that the Ade molecule penetrates into a macrocyclic cavity more deeply.

Figure 1 shows the thermal effects of β-CD dissolution in the solutions of Cyt, Thy, Ura and 6-azaUra.

In this case, complex formation did not occur, and weak interactions between β-CD and specified nucleic acid bases were described based on virial enthalpic coefficients obtained according to the McMillan–Mayer theory:[12,13]

$$\Delta_{tr}H(\text{w} \rightarrow \text{w} + \text{y})/m_y = 2h_{xy} + 3h_{xyy}m_y + 3h_{xxy}m_x + \ldots \quad (1)$$

In equation (1) $\Delta_{tr}H$ (w → w + y) is the enthalpy of transfer of β-CD (x) from water (w) to aqueous solutions of nucleic acid bases (y); m_x and m_y are the molalities of x and y in ternary solution, respectively; h_{xy}, h_{xxy}, h_{xyy} are the enthalpic coefficients of pair and triplet interactions. Since the concentration of β-CD was constant and very low ($m_x \rightarrow 0$), the last term in equation (1) can be neglected. The values of h_{xy} were calculated by a least-squares method to be h_{xy}(β-CD + Cyt) = –1055(±634), h_{xy}(β-CD + Thy) = 750(±334), h_{xy}(β-CD + Ura) = –44800(±12345) and h_{xy}(β-CD + 6-azaUra) = 10700(±4900) J kg mol^{-2}.

Enthalpic coefficients h_{xy} provide information on the energetic relationship between solute–solute and solute–solvent interactions.[14] Enthalpic coefficients are positive for β-CD + Thy and β-CD + 6-azaUra systems. In this case, the process of dehydration (endo-effect) is dominant. The interactions of β-CD with Ura and Cyt are characterised by negative h_{xy} values, which indicate the prevalence of exothermic effects in these systems.

Thus, β-CD forms complexes only with Ade and Caf (purine bases) with strongly different stability constants. The interactions of β-CD with Cyt, Thy, Ura and 6-azaUra (pyrimidine bases) are weak. This is indicative of the ability of β-CD to the molecular recognition of nucleic acid bases and their derivatives in aqueous solution.

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Received: 25th July 2002; Com. 02/1975