Salt and Solvent Effects on the Kinetics and Thermodynamics of the Inclusion of the Ruthenium Complex $[Ru(NH_3)_5(4,4'\text{-bpy})]^{2+}$ in β-Cyclodextrin

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The influences of solvents (in water−cosolvent mixtures) and salts on the kinetics and thermodynamics of the inclusion of $[Ru(NH_3)_5(4,4'\text{-bpy})]^{2+}$ in β-cyclodextrin (β-CD) have been studied. Solvent effects on the kinetics can be described as a consequence of the competition of the cosolvent for the β-CD cavity. The salt effects on the kinetics depend on the ion pairing of the anions with the $[Ru(NH_3)_5(4,4'\text{-bpy})]^{2+}$ complex. On the other hand, the solvent effects on the equilibrium constant depend on the stabilization of the 4,4′-bipyridine ligand in the water−cosolvent mixture relative to water. Finally, salt effects on the equilibrium constant are interpreted as a consequence of ion pairing between the anion of the salt and the inclusion complex.

Introduction

In the past two decades, the study of noncovalent interactions has been a field of growing interest. These interactions are the root of phenomena of chemical and biological interest, such as the antigen−antibody union,[1] ionic transport,[2] the stabilization of membranes,[3] the binding of glycoproteins at cellular surfaces,[4] the metabolism of heavy metals,[5] the field of molecular machines,[6] molecular electronics,[7] the production of sensors,[8] and the changes in reactivity under restricted geometry conditions,[9] among others.

One of the possible consequences of noncovalent interactions is the inclusion phenomenon. For the study of these processes, cyclodextrins have been one of the favorite substrates. In this regard, there are relatively frequent studies on the thermodynamics of the inclusion of different ligands.[10] Less frequent are studies on the kinetics of inclusion and the sorting of ligands in cyclodextrins.[11] But, to the best of our knowledge, there are no systematic studies on medium (salt and solvent) effects on the kinetics and thermodynamics of the inclusion process in cyclodextrins.[12]

In this paper, we present the results of such a study concerning kinetic and thermodynamic aspects of the inclusion of the $[Ru(NH_3)_5(4,4'\text{-bpy})]^{2+}$ complex in β-CD. It is worth pointing out that there is one previous study on the thermodynamics of the inclusion of this complex in dimethyl β-CD in water.[13] However, the authors in ref 13 were not interested in the kinetics of inclusion. They were concerned with the effect of encapsulation on the kinetics of the electron transfer between this complex and $[CoEDTA]^-$; that is, their work corresponds to a study of the reactivity under restricted geometry conditions.

So, we considered it of interest to carry out a systematic study of the effects of some additives (salt and cosolvent) on the thermodynamics and kinetics of an encapsulation process, the title ruthenium complex in β-CD.

Experimental Section

Materials. The complex $[Ru(NH_3)_5(4,4'\text{-bpy})](ClO_4)_2$ was prepared and purified according to the procedure described in the literature.[14] The other reagents were all analysis R grade and used as purchased.

Equilibrium Measurements. The equilibrium constant Q for the dissociation process:

$$(Ru/\beta\text{-CD})^{2+} \overset{Q}{\rightleftharpoons} [Ru(NH_3)_5(4,4'\text{-bpy})]^{2+} + \beta\text{-CD} \quad (1)$$

where Ru/β-CD represents the inclusion complex was calculated from spectrophotometric data. These data were obtained employing a Cary 500 Scan spectrophotometer. Measurements were performed at 490 nm, corresponding to the wavelength at which the free and encapsulated ruthenium complexes show a maximum difference in their absorbances.[13] In these experiments, the concentration of the ruthenium complex was 5×10^{-5} mol dm^{-3} and the concentrations of β-CD were in the range of 8×10^{-4} to 1.5×10^{-2} mol dm^{-3}, depending on the medium, because of solubility problems.

Kinetic Measurements. The kinetics of the reactions (forward and reverse) in eq 1 were studied by the T-jump technique using a Hi-Tech model SF-61 apparatus at 490 nm. All of the experiments were conducted in an excess of the cyclodextrin ($[\beta\text{-CD}] = 8 \times 10^{-4}$ to 1.5×10^{-2} mol dm^{-3}, depending on the medium, because of solubility problems and $[Ru(NH_3)_5(4,4'\text{-bpy})^{2+}] = 5 \times 10^{-5}$ mol dm^{-3}) in such a way that both the forward and reverse processes in eq 1 follow first-order kinetics. Under these conditions, it can be shown that the relaxation time, τ, is given by

$$\frac{1}{\tau} = k_f[\beta\text{-CD}] + k_r \quad (2)$$

where k_r and k_f are the rate constants corresponding to the forward and reverse processes in eq 1 (see eq 5). For each reaction medium, we obtained τ at different β-CD concentrations. Thus, a plot of $1/\tau$ versus $[\beta\text{-CD}]$ permitted us to obtain k_f and k_r. Figure 1 gives one of these plots, corresponding to a NaCl salt solution of a concentration of 3 mol dm^{-3}.

All of the measurements were done at 298.2 ± 0.1 K.

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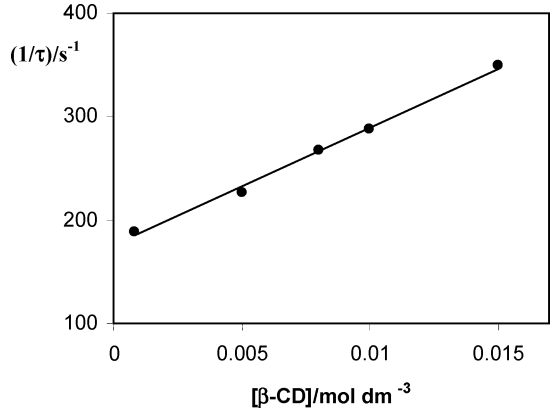

Figure 1. Plot of $1/\tau$ versus [β-CD] for a NaCl solution ([NaCl] = 3 mol dm^{-3}).

TABLE 1: Values of k_f/mol^{-1} dm^3 s^{-1} and k_r/s^{-1} for Water−Cosolvent Mixtures

cosolvent	x	$10^{-3}k_f$	$10^{-1}k_r$
ethyleneglycol	0	36.0	12.0
	0.028	26.0	13.0
	0.051	23.0	13.0
	0.105	14.0	12.0
	0.173	9.6	10.0
	0.214	7.8	8.4
	0.290	5.1	5.9
tert-butyl alcohol	0.007	24.0	12.0
	0.013	21.0	11.0
	0.025	18.0	10.0
	0.040	14.0	9.0
	0.047	11.0	7.7
	0.062	9.8	6.4
glycerol	0.020	30.0	13.0
	0.036	24.0	13.0
	0.077	19.0	12.0
	0.131	11.0	10.0
	0.164	7.7	9.3
	0.233	5.2	7.9

TABLE 2: Values of k_f/mol^{-1} dm^3 s^{-1} and k_r/s^{-1} for Salt Solutions

salt	[salt]/mol dm^{-3}	$10^{-3}k_f$	$10^{-1}k_r$
$NaNO_3$	0	36.0	12.0
	0.4	27.0	13.0
	0.6	19.0	14.0
	0.8	14.0	15.0
	1.0	8.1	15.0
	2.0	5.1	16.0
	3.0	3.8	16.0
NaCl	0.4	24.0	15.0
	0.8	15.0	16.0
	1.0	13.0	17.0
	3.0	11.0	17.0
	5.0	10.0	17.0
NaF	0.4	26.0	19.0
	0.6	18.0	20.0
	0.8	15.0	20.0
	1.0	15.0	19.0
Na_2SO_4	0.1	18.0	20.0
	0.3	12.0	18.0
	0.6	10.0	16.0
	0.8	9.8	14.0
	1.0	8.9	13.0

Results

Tables 1 and 2 contain the values of k_f and k_r corresponding to the different reaction media studied here, constituted by several salt solutions and water−cosolvent mixtures.

As matter of fact, these data can be fitted to the following equations.

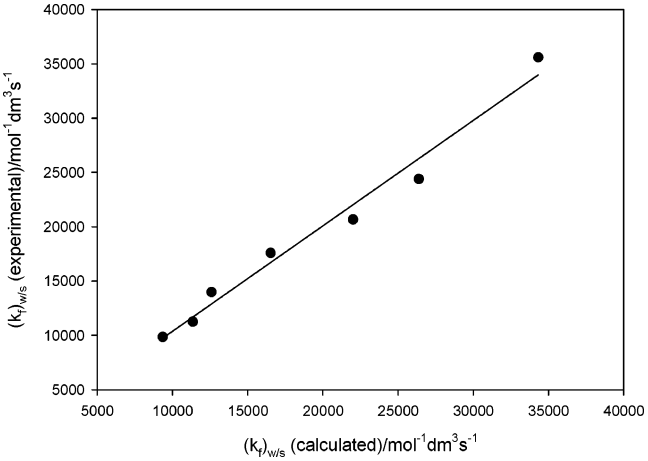

Figure 2. Best fit of eq 3a for water−*tert*-butyl alcohol mixtures.

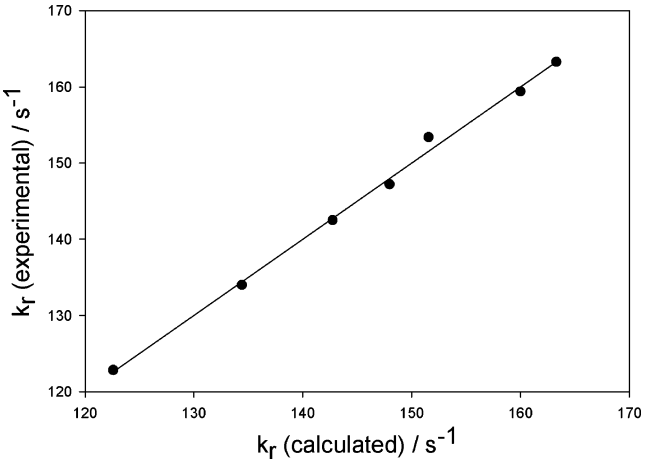

Figure 3. Best fit of eq 4b for $NaNO_3$ solutions.

(a) Water−Cosolvent Mixtures:

$$(k_f)_{w/s} = \frac{\alpha_f}{1 + \beta_f x} \tag{3a}$$

$$(k_r)_{w/s} = \frac{\alpha_r + \beta_r x}{1 + \gamma_r x + \delta_r x^2} \tag{3b}$$

x being the ratio between the mole fractions of the organic cosolvent (x_c) and water (x_w), that is, $x = x_c/x_w$.

(b) Salt Solutions:

$$k_f = \frac{\alpha_f + \beta_f[\text{salt}]}{1 + \gamma_f[\text{salt}]} \tag{4a}$$

$$k_r = \frac{\alpha_r + \beta_r[\text{salt}]}{1 + \gamma_r[\text{salt}] + \delta_r[\text{salt}]^2} \tag{4b}$$

Figures 2 and 3 are representative examples of these fits.

From the *fitted* values of k_f and k_r, the equilibrium constants, Q, for reaction 1 corresponding to the different reaction media were obtained. These data appear in Table 3. As mentioned previously, some values of Q were obtained, in some cases, directly from spectrophotometric measurements. The results are given in parentheses in Table 3. As can be seen, there is agreement between the values of the equilibrium constants obtained from spectrophotometric measurements and those calculated from kinetic data.

TABLE 3: Values of Q/mol^{-1} dm^3 for Water−Cosolvent Mixtures and Salt Solutions[a]

cosolvent	x	10^3Q	salt	[salt]/mol dm^{-3}	10^3Q
water	0	3.4 (3.3)	$NaNO_3$	0.4	6.7 (5.6)
ethyleneglycol	0.028	5.2 (5.0)		0.6	8.3
	0.051	6.1		0.8	10.0
	0.105	7.8		1.0	12.0 (15.0)
	0.173	9.5		2.0	20.0
	0.214	10.3		3.0	27.0 (32.0)
	0.290	10.0 (12.0)		6.0	44.0
tert-butyl alcohol	0.007	4.6 (4.8)	NaCl	0.4	7.1 (5.5)
	0.013	5.1 (5.3)		0.8	9.8
	0.025	5.9 (6.0)		1.0	11.0
	0.040	6.6		3.0	16.0 (18.0)
	0.047	6.8		5.0	17.0
	0.062	7.2 (6.9)	NaF	0.4	8.7 (6.3)
glycerol	0.020	4.8 (3.6)		0.6	10.0
	0.036	5.5		0.8	12.0
	0.077	7.0		1.0	13.0 (12.0)
	0.131	8.5	Na_2SO_4	0.1	11.0 (10.0)
	0.164	9.2		0.3	14.0
	0.233	10.0 (11.0)		0.6	15.0
				0.8	15.0
				1.0	15.0 (16.0)

[a] Values in parentheses correspond to Q values obtained from spectrophotometry measurements.

TABLE 4: Values of the Best Fit Parameters for Eqs 7 and 8 Corresponding to Water−Cosolvent Mixtures

cosolvent	$(k_f)_w$/ mol^{-1} dm^3 s^{-1}	K/ mol^{-1} dm^3	Q_w/ mol^{-1} dm^3	Q_c/ mol^{-1} dm^3	K'
ethyleneglycol	36.3×10^3	14.5	3.4×10^{-3}	1.5×10^{-2}	6.4
tert-butyl alcohol	34.3×10^3	43.0	3.4×10^{-3}	9.0×10^{-3}	32
glycerol	36.9×10^3	16.4	3.4×10^{-3}	1.6×10^{-2}	5.1

Discussion

In the following discussion, only the values of k_f and Q will be considered. Given that

$$Q = \frac{k_r}{k_f} \tag{5}$$

discussion of the third parameter (we eliminated k_r) would be redundant, given that its variations are a consequence of the variations of the other two parameters. However, a comment on k_r will be given at the end of the paper.

(a) Water−Cosolvent Mixtures. *Kinetic Data (k_f).* The values of k_f decrease in all of the water−cosolvent mixtures as x increases. This fact suggests a competition between the ruthenium complex and the cosolvent for the cavity in β-CD. In fact, if K represents the equilibrium constant of the inclusion of the cosolvent:

$$\text{cosolvent} + \beta\text{-CD} \overset{K}{\rightleftharpoons} \text{cosolvent}/\beta\text{-CD} \tag{6}$$

when the cosolvent is present at a proportion given by x, the *fraction* of free β-CD would be $1/(1 + Kx)$. Thus, the observed value of k_f would be

$$k_f = \frac{(k_f)_w}{1 + Kx} \tag{7}$$

Here, $(k_f)_w$ represents the value of the forward rate constant in water where, obviously, all of the β-CDs are free of the cosolvent. Notice that eq 7 is the same as eq 3a if $(k_f)_w = \alpha_f$ and $K = \beta_f$.

As can be seen, the values of K (Table 4) depend on the cosolvent, that is, on the relative affinities of the cosolvents by β-CD. The values of K increase in the order $K_{EG} \approx K_{GlyOH} < K_{tert-BuOH}$. So, the more hydrophobic cosolvent has a higher affinity for the cavity of the cyclodextrin, as expected, taking into account the hydrophobic character of the cavity.

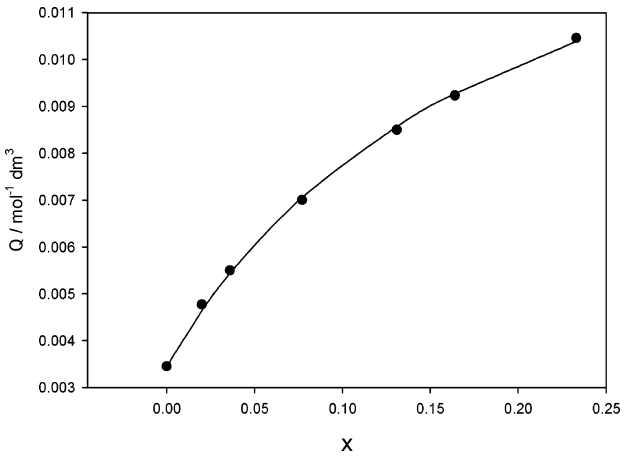

Figure 4. Plot of Q values obtained for water−glycerol mixtures versus x. Symbols represent experimental data, and the solid line represents the best fit by using eq 8.

Consequently, it can be concluded that the decrease in the rate of formation of the inclusion complex is a consequence of the competition of the cosolvent for the cyclodextrin cavity, a competition that becomes more effective when the hydrophobic character of the cosolvent increases.

It is interesting to note that not only have we obtained data concerning the kinetics and thermodynamics of the inclusion of the ruthenium complex but our results also give the thermodynamic data (K) corresponding to the inclusion of the cosolvents.

Equilibrium Data (Q). The values of Q in water−cosolvent mixtures cannot be represented by an equation similar to eq 7. However, Q is well-described by eq 8 (see also Figure 4):

$$Q = \frac{Q_w + Q_c K' x}{1 + K' x} \quad (8)$$

with the values of the parameters given in Table 4.

The interpretation of this equation is as follows:[15] *on average*, a fraction $1/(1 + K'x)$ of the solvation shell of the $(Ru/\beta\text{-CD})^{2+}$ inclusion complex is constituted by water and, thus, contributes with $Q_w/(1 + K'x)$ to the observed value of Q. Another fraction of the solvation shells of the $(Ru/\beta\text{-CD})^{2+}$ inclusion complex, given by $K'x/(1 + K'x)$, is constituted by the cosolvent and contributes with $Q_c K'x/(1 + K'x)$ to the value of Q, where Q_c would be the value of Q in the neat cosolvent. It is clear that parameter K' represents the relative affinity of the cosolvent and water for the $(Ru/\beta\text{-CD})^{2+}$ inclusion complex. It is interesting to note that Q_c is always higher than Q_w. This seems reasonable taking into account that the sorting of the complex would place the ligand 4,4′-bpy in a solvent enriched in the organic component, where this ligand would be more soluble than in water.

Of course, the values of K' are different from the K values, because K corresponds to the affinity of the cosolvent by the cavity of the cyclodextrin and K' to the affinity by the inclusion complex. However, again, $K'_{EG} \approx K'_{GlyOH} < K'_{tert-BuOH}$. This would imply that the inclusion complex behaves, as a whole, as a hydrophobic solute.

(b) Salt Effects. *Kinetic Data (k_f).* As in the case of water−cosolvent mixtures, k_f decreases when the amount of salt in the reaction medium increases. However, the variation of k_f in the presence of the salts is not the same as in the case of the cosolvents (compare eqs 3a and 4a). Equation 4a suggests that more than one form of the ruthenium complex participates in the determination of the kinetics of the inclusion process described by this equation.

We will consider that the cationic ruthenium complex can associate to the anion of the salt:

$$[Ru(NH_3)_5(4,4'\text{-bpy})]^{2+} + A^{n-} \overset{K_{ip}}{\rightleftharpoons} [Ru(NH_3)_5(4,4'\text{-bpy})/A]^{2+n-} \quad (9)$$

In agreement with eq 9, the concentrations of the free and ion-paired ruthenium complexes will be

$$[Ru(NH_3)_5(4,4\text{-bpy})]^{2+}_{free} = \frac{1}{1 + K_{ip}[salt]}[Ru(NH_3)_5(4,4\text{-bpy})]^{2+}_{total} \quad (10a)$$

$$[Ru(NH_3)_5(4,4\text{-bpy})]^{2+}_{ion-paired} = \frac{K_{ip}[salt]}{1 + K_{ip}[salt]}[Ru(NH_3)_5(4,4\text{-bpy})]^{2+}_{total} \quad (10b)$$

If, according to two state models,[16] it is assumed that free and ion-paired ruthenium complexes are included with rates given by $(k_f)_{free}$ and $(k_f)_{ion-paired}$, it is clear that

$$k_f = \frac{(k_f)_{free} + (k_f)_{ion-paired} K_{ip}[salt]}{1 + K_{ip}[salt]} \quad (11)$$

Obviously, eq 11 is the same as eq 4a, but now, the parameters have a clear meaning.

According to our results, K_{ip} values for monovalent anions are lower than K_{ip} values for SO_4^{2-}, as expected (see Table 5). In fact, K_{ip} for the sulfate salt is in good agreement with the value of this parameter for the association of $[Ru(NH_3)_5pz]^{2+}$ with $S_2O_8^{2-}$, an anion with a −2 charge like SO_4^{2-}.[17]

TABLE 5: Values of the Best Fit Parameters for Eqs 11 and 12 Corresponding to Salt Solutions

salt	$(k_f)_{free}$/ mol^{-1} dm^3 s^{-1}	$(k_f)_{ion-paired}$/ mol^{-1} dm^3 s^{-1}	K_{ip}/ mol^{-1} dm^3
$NaNO_3$	35.6×10^3	5.7×10^2	1.9
NaCl	35.6×10^3	30.0×10^2	2.6
NaF	35.6×10^3	18.0×10^2	1.7
Na_2SO_4	35.6×10^3	5.0×10^2	15

salt	Q_w/ mol^{-1} dm^3	Q_{salt}/ mol^{-1} dm^3	K'_{ip}/ mol^{-1} dm^3
$NaNO_3$	3.4×10^{-3}	1.7×10^{-1}	5.3×10^{-2}
NaCl	3.4×10^{-3}	2.1×10^{-2}	8.4×10^{-1}
NaF	3.4×10^{-3}	4.4×10^{-2}	3.5×10^{-1}
Na_2SO_4	3.4×10^{-3}	1.6×10^{-2}	15

The data in Table 5 give a clear interpretation of the cause of the diminution in k_f when the salt concentration increases. This is simply a consequence of the ion-pair formation between the ruthenium complex and the anion of the salt. This ion pair includes in the cavity slower than the free ion. So, an increase of the concentration of the salt and, thus, of the concentration of the ion-paired ruthenium complex implies a decrease in k_f.

Equilibrium Data (Q). The equilibrium data in the presence of salts are well-described by an equation similar to eq 8:

$$Q = \frac{Q_w + Q_{salt} K'_{ip}[salt]}{1 + K'_{ip}[salt]} \quad (12)$$

where the values of K'_{ip} and Q_{salt} for the different electrolytes employed in this study are given in Table 5.

The interpretation of this equation is straightforward (compare eqs 8 and 12): salts (in fact, the anions of the salts) can associate with the inclusion complex, according to

$$(Ru/\beta\text{-CD})^{2+} + A^{n-} \overset{K'_{ip}}{\rightleftharpoons} (Ru/\beta\text{-CD})^{2+}/A^{n-} \quad (13)$$

Nonassociated inclusion complexes are characterized by a value of $Q = Q_w$ and associated inclusion complexes by $Q = Q_{salt}$. Q_{salt} is greater than Q_w, in such a way that associated complexes dissociate more than free complexes, because the anion helps this dissociation by associating with the ruthenium complex.

According to our results, there are specific anion effects on k_f and Q. These effects seem to be related, mainly, to the charge of the anion. However, other contributions to these effects, such as the hydrogen-bonding ability of the anion pointed out by Johnson et al.,[18] could be possible.

Finally, we give a few words on k_r. The values of this parameter in salt solutions go through a maximum in all of the cases. As a matter of fact, the position of the maximum depends on the position of the anion of the salt in the Hofmeister series.[19] In the case of structure-maker anions (SO_4^{2-} and F^-), the maximum appears at a low concentration. For structure-breaking anions (Cl^- and NO_3^-), it appears at a much higher concentration. Consequently, some structural effects of the salt are in play, at least, in the kinetics of the dissociation process.

In conclusion, solvent effects on the kinetics of the inclusion of the ruthenium complex in cyclodextrin can be described as a consequence of the competition of the cosolvent for the β-CD cavity. The salt effects on the kinetics depend on the ion pairing of the anions with the ruthenium complex studied. The solvent effects on the equilibrium constant depend on the stabilization of the 4,4′-bipyridine ligand in a water−cosolvent mixture

relative to that in water. Salt effects on the equilibrium constant are interpreted as a consequence of the formation of ion pairing between the anion of the salt and the inclusion complex.

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