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Effect of Temperature on the Encapsulation of the Drug Tetracaine Hydrochloride by β-Cyclodextrin and Hydoxypropyl-β-Cyclodextrin in Aqueous Medium

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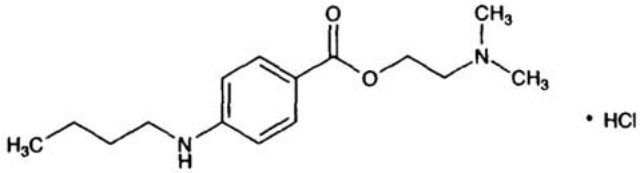
Abstract

The encapsulation of tetracaine hydrochloride (TTAC·HCl) by β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HPBCD) has been analyzed from a thermodynamic point of view, by means of conductometric studies at different temperatures. Conductivity measurements of aqueous solutions of the drug were performed: (i) in the absence of CD, as a function of drug concentration; and (ii) in the presence of CD, as a function of CD concentration, both studies at different temperatures ranging from 15 to 40 °C. The stoichiometry of the complexes, the association constants, and the ionic molar conductivities at infinite dilution of the free ($\lambda^0_{\mathrm{DRUG}}$) and complexed ($\lambda^0_{\mathrm{CD:DRUG}}$) drug were obtained from these conductivity data. From the dependency of the association constants with temperature (van't Hoff analysis), the inclusion complexes formed by β-CD and/or HPBCD and the drug were found to be enthalpy driven, with a favorable enthalpic term dominant over an unfavorable entropic term. This pattern could be revealing the contribution of van der Waals interactions, hydrophobic effect and solvent reorganization as the main driven forces promoting the interaction.

Introduction

The use of cyclodextrins as a new family of pharmaceutical excipients and drug carriers has become an increasingly successful method to improve the general performance of many therapeutic molecules, whose bioavailability is often threatened by problems such as limited solubility or stability, and a series of undesirable adverse effects [1–10]. The parent cyclodextrins (CD's) are well-known nontoxic macrocyclic sugars of natural origin, with doughnut-shaped structure, consisting of 6 (α-CD), 7 (β-CD) or 8 (γ-CD) $\alpha(1 \rightarrow 4)$ joined glucopyranose units. Their hydrophilic external faces and hydrophobic inner surface, make them one of the most important simple organic compounds, capable of forming noncovalently bonded inclusion complexes with a variety of drug molecules in aqueous solution. The physical, chemical and biological properties of these complexes may be totally different from those of either the parent drug or the cyclodextrin [1, 6, 8, 11]. The rational design of pharmaceutical CD formulations requires a good knowledge of the encapsulation process. Structural information such as the stoichiometry and the geometry of the complex, and thermodynamic information such as the association constant ($K_{\mathrm{CD:DRUG}}$) and the change on the enthalpy (ΔH^0) and entropy (ΔS^0) of binding, are necessary to draw a complete picture of the driven forces governing the CD:Drug interaction [12].



Scheme 1.

Tetracaine hydrochloride (Scheme 1) belongs to an important class of synthetic drugs of the therapeutic family of local anesthetics, whose structures resemble natural compounds actively participating in nerve impulse transmission. It is believed that the cationic form of the drug, which seems to be the active principle, joins the Na^+ channels on the nerve membrane, thus blocking the initiation and transmission of nervous impulses [13, 14]. However, local anesthetics often show a short duration of action, and adverse side effects, such as cardiac and neurological toxicity, accompanied sometimes by allergic reactions. It is then expected that the formulation of tetracaine hydrochloride as a microencapsulate with a cyclodextrin may show a better bioavailability [6], with all or some of these undesirable effects masked or abolished.

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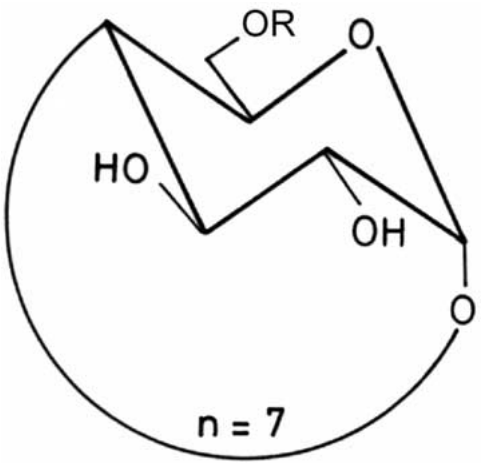

Scheme 2. β-CD: R = H; HPBCD: R = $CH_2CH(OH)CH_3$.

The complete conductometric study reported herein, consisting on the measurement of the specific conductivity of aqueous solutions of tetracaine hydrochloride, at constant concentration, as a function of CD concentration at several temperatures, allowed us to carry on a thermodynamic analysis of the effect of the presence of the parent β-cyclodextrin and its hydroxypropylated derivative, HP-BCD, (see Scheme 2) on the properties of aqueous solutions of the anesthetic drug. We believe that the results of these studies will show the convenience of characterizing the CD:Drug complexes, not only from a pharmacological (pharmacokinetic and *in vivo* experiments), but also from a physicochemical point of view, in order to improve the understanding of the CD:Drug interactions.

Materials and methods

Materials

4-(Butylamino)benzoic acid 2-(dimethylamino)ethyl ester monohydrochloride, usually named tetracaine hydrochloride (TTAC·HCl) and β-cyclodextrin (β-CD) were purchased from Sigma. 6-Hydroxypropyl-β-cyclodextrin (HPBCD), containing an average of 0.64 hydroxypropyl groups per glucopyranose unit was from Janssen Biotech (Belgium). All of them, with 99% purity or greater, were used without further purification. Thermogravimetric analysis (TG) revealed that β-CD and HPBCD consist of 11% and 2.8% of water mass content, respectively, which were considered in the calculations of solute concentrations. All the solutions were freshly prepared with distilled, and deionized water (taken from a Millipore Super-Q System, with a conductivity lower than 18 μS cm^{-1}). The homogeneity of the initial solutions was assured by sonicating them for three hours in an ultrasonic bath.

Conductivity measurements

Conductivity data were collected with a Hewlett-Packard 4263A LCR Meter, using a Metrohm electrode, whose calibration with a KCl standard solution yields a cell constant of 0.8129 cm^{-1}. Mixtures were prepared from a digital burette, whose cylinder was kept at the same constant temperature as the measuring cell. Details of the apparatuses and the experimental procedure of the fully computerized technique, were described earlier [15]. The reproducibility on the specific conductivity, κ, obtained as an average of 2400 measurements for each concentration, is believed to be better than 0.03%. The accuracy on the molarity of the solutions is better than 1×10^{-5} M, and the temperature is held constant within ± 0.001 °C. The conductivity of the aqueous solutions was measured as a function of the drug concentration for the binary drug/water system, and as a function cyclodextrin concentration, keeping constant the concentration of the drug, for the ternary cyclodextrin/drug/water system. In the latter case, the cyclodextrin concentration ranges were chosen to guarantee a proper binding constant determination [16].

Results and discussion

Tetracaine hydrochloride, an ester of the p-aminobenzoic acid, may suffer hydrolysis in aqueous media. Furthermore, its cationic form ($TTACH^+$) is in equilibrium with its non-ionized form (TTAC), as follows:

$$\underset{\text{TTAC·HCl}}{CH_3\text{-}(CH_2)\text{-NH-Ph-COO-}(CH_2)_2\text{-NH}(C_2H_5)_2^+Cl^-}$$

$$\overset{K_a}{\leftrightarrows} \underset{TTACH^+}{H_2N\text{-Ph-COO-}(CH_2)_2\text{-NH}(C_2H_5)_2H^+} + Cl^-$$

where K_a is the equilibrium constant. The pH of the aqueous solutions of TTAC·HCl, measured as a function of drug concentration at 25 °C with a computerized procedure described previously [17], revealed ($pK_a = 8.4$) that the ester is not hydrolyzed in aqueous solution with the concentration ranges used herein and that the above mentioned equilibrium is almost totally shifted towards the ionized form of the drug ($TTACH^+$), with a negligible contribution of the non-ionized form (TTAC).

Figure 1 reports the values of the specific conductivity, κ, for the binary drug/water solutions as a function of drug concentration at various temperatures ranging from 15 to 40 °C. The conductivity of the solution can be expressed as a function of the ionic molar conductivities λ_i, and the concentration of the charged species, as follows,

$$\kappa = \lambda_{TTACH^+}[TTACH^+] + \lambda_{Cl^-}[Cl^-], \qquad (1)$$

where the species OH^- and H^+ have been excluded, since their contribution to the conductivity is negligible at the neutral pH of the aqueous drug solution, compared with that of $TTACH^+$ and Cl^-.

The λ_i values at low concentrations can be estimated by the Onsager relation:

$$\lambda_i = \lambda_i^0 - \frac{(\alpha + \beta\lambda_i^0)I^{1/2}}{1 + Ba_nI^{1/2}}, \qquad (2)$$

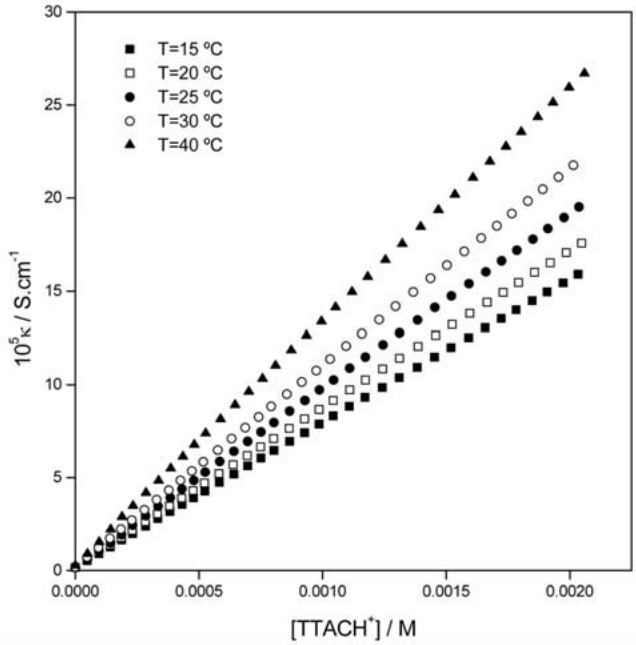

Figure 1. Plot of the specific conductivity, κ, of the aqueous solutions of tetracaine hydrochloride as a function of concentration, at different temperatures.

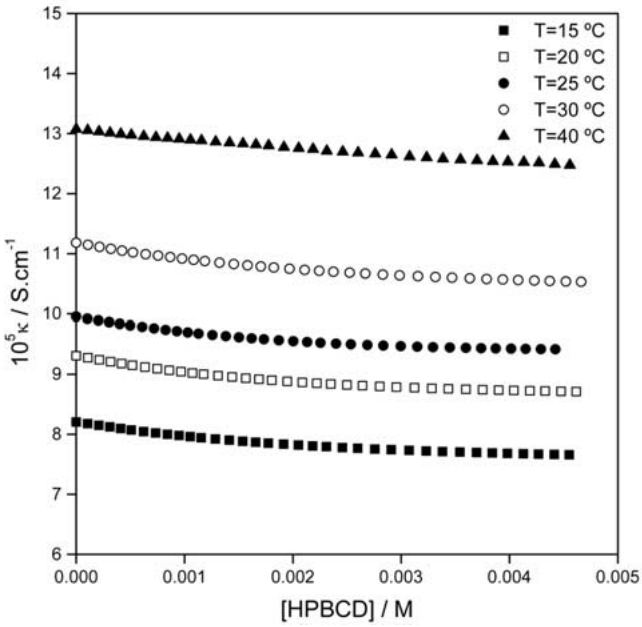

Figure 2. Plot of the specific conductivity, κ, of drug aqueous solutions as a function of [HPBCD], at different temperatures. The drug concentration is kept constant at ∼1.0 mM.

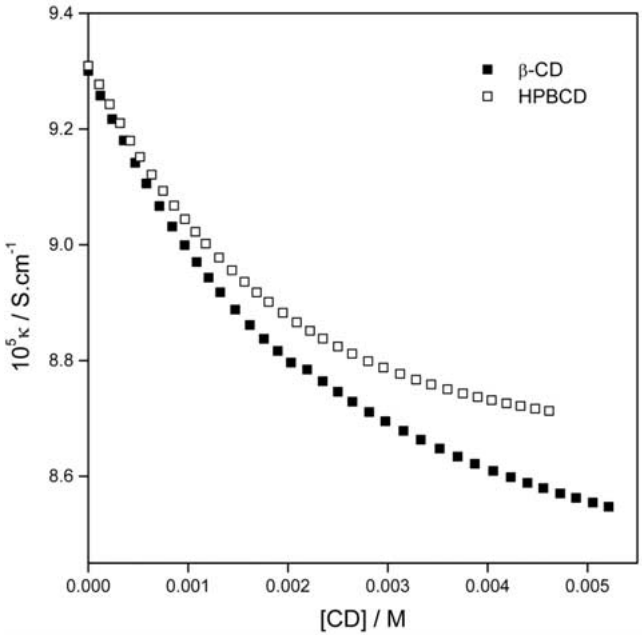

Figure 3. Plot of the specific conductivity, κ, of drug aqueous solutions as a function of [CD], at 20 °C. The drug concentration is kept constant at ∼1.0 mM.

where λ_i^0 represents the ionic molar conductivity at infinite dilution, a_n is the effective size of the hydrated ion, I is the ionic strength, and α, β and B are constants whose values are taken from the literature [18]. The values of $\lambda^0_{Cl^-}$ at different temperatures, shown in Table 1, were taken from the literature as well [18, 19]. The parameter a_n of $TTACH^+$ (8.4 Å) has been estimated from $\lambda^0_{TTACH^+}$, at 25 °C, with an empirical relation [20]. The values of $\lambda^0_{TTACH^+}$ have been calculated by fitting the experimental κ data of Figure 1 to Equations (1) and (2) with a NLR method, and are reported in Table 1 as well.

Figure 2 shows the plot of specific conductivity, κ, for aqueous solutions of tetracaine hydrochloride at a constant concentration of about 1 mM, as a function of [HPBCD], at the different temperatures studied herein. A similar plot has been obtained for the ternary system β-CD + $TTACH^+$ + H_2O. The formation of the inclusion complexes β-CD:$TTACH^+$ and HPBCD:$TTACH^+$ can be clearer observed in Figure 3, where the conductivity curves for both systems at 2 °C, as an example, have been plotted. The decrease in κ when CD is added points to the inclusion of the $TTACH^+$ moiety into the β-CD cavity, since the mobility of the associated cation is expected to be less than that of the free cation. The stoichiometry of this inclusion complex has been determined as the ratio between [CD] and [$TTACH^+$], [CD] being the concentration at which two straight lines intercept at each temperature, and [$TTACH^+$] the initial drug concentration, kept constant in the experiment (∼1 mM). A value of 1.1 ± 0.1, averaged over the results obtained at all the temperatures for each inclusion complex, indicates that the complexes β-CD:$TTACH^+$ and HPBCD:$TTACH^+$ are formed by the association of a molecule of CD per each molecule of drug, as usually found for most cyclodextrin/drug complexes [1, 3, 8, 17, 21]. Thus, the encapsulation process can be represented by the following equilibrium:

$$TTACH^+ + CD \leftrightarrows CD{:}TTACH^+ \tag{3}$$

governed by the binding constant expressed in activity terms (a_i) as:

$$K_{CD:TTACH} = \frac{a_{CD:TTACH^+}}{a_{CD}a_{TTACH^+}}. \tag{4}$$

The binding constants $K_{\beta-CD:TTACH^+}$ and $K_{HPBCD:TTACH^+}$ can be calculated from the conductivity

Table 1. Values of ionic molar conductivities at infinite dilution of $TTCAH^+$ drug cation, both in the free ($\lambda^0_{TTCAH^+}$) and complexed ($\lambda^0_{CD:TTCAH^+}$) forms, of Cl^- ($\lambda^0_{Cl^-}$) taken from literature, and values of the association constants ($K_{CD:TTCAH^+}$), at different temperatures, for the ternary systems β-CD + TTCA·HCl + H_2O and HPBCD + TTCA·HCl + H_2O[a]

T (°C)	$\lambda^0_{TTCAH^+}$ (S cm^2 mol^{-1})	$\lambda^0_{Cl^-}$ (S cm^2 mol^{-1})	[$TTCAH^+$] (mM)		$K_{CD:TTCAH^+}$ (M^{-1})		$\lambda^0_{CD:TTCAH^+}$ (S cm^2 mol^{-1})	
			β-CD	HPBCD	β-CD	HPBCD	β-CD	HPBCD
15	20.5	61.4	1.037	1.026	293	205	11.7	11.1
20	23.0	68.9	1.042	1.030	260	177	11.4	12.7
25	24.6	76.4	0.955	1.001	225	138	11.3	14.0
30	29.0	84.2	1.015	1.016	180	108	13.8	13.3
40	36.7	100.4	0.978	1.023	111	73	17.9	18.5

[a]Uncertainties on $\lambda^0_{TTCAH^+}$, $\lambda^0_{Cl^-}$, $\lambda^0_{CD:TTCAH^+}$, $K_{CD:TTCAH^+}$ are estimated to be less than ±0.4, ±0.2, ±0.9, and ±8%, respectively.

data on Figure 2, and that for the β-CD + $TTACH^+$ + H_2O ternary system, by using a model proposed by us [22], which is mainly based on: (i) the relation of conductivity data in terms of the complex concentration,

$$\kappa = \lambda_{Cl^-}[Cl^-] + \lambda_{TTACH^+}[TTACH^+] + \lambda_{CD:TTACH^+}[CD:TTACH^+], \quad (5)$$

(ii) the activity coefficients of the charged species, obtained through the extended Debye–Hückel theory; (iii) the ionic molar conductivities of the charged species, λ_i related with the corresponding values at infinite dilution, λ^0_i, through the Debye–Hückel–Onsager theory; (iv) the ionic molar conductivity at infinite dilution of $TTACH^+$, $\lambda^0_{TTACH^+}$, determined from the conductivity data of the binary system, as commented before. Thus, as widely explained elsewhere [22], Equations (2), (4) and (5), and the mass and charge balances have been used to fit the experimental κ data as a function of β-CD and/or HPBCD concentrations with a nonlinear regression method, based on a nonlinear Newton–Raphson and a Marquardt algorithm. The fit coefficients, i.e., the binding constant, $K_{CD:TTACH^+}$, and the ionic molar conductivity at infinite dilution of the complex, $\lambda_{CD:TTACH^+}$, are reported in Table 1 at the five temperatures, for the systems studied in this work. Figure 4 shows the plot of $\lambda^0_{TTACH^+}$, $\lambda^0_{Cl^-}$, $\lambda^0_{\beta-CD:TTACH^+}$ and $\lambda^0_{HPBCD:TTACH^+}$ as a function of temperature. As can be seen, the ionic molar conductivities at infinite dilution of the drug cation, free ($\lambda^0_{TTACH^+}$) or associated with β-CD ($\lambda^0_{\beta-CD:TTACH^+}$) and/or HPBCD ($\lambda^0_{HPBCD:TTACH^+}$), and of Cl^- ($\lambda^0_{Cl^-}$) increase roughly linearly with the temperature, revealing an expected increase of the ionic mobilities with the temperature. Furthermore, the ionic molar conductivity of the associated drug, $\lambda^0_{\beta-CD:TTACH^+}$ and $\lambda^0_{HPBCD:TTACH^+}$, decreases, at all temperatures, around 40–50% with respect to the value for the free drug, $\lambda^0_{TTACH^+}$. This fact is indicative of the clear decrease in the mobility of the cation as well as of the conductivity of the solution upon binding the CD, as initially observed in Figure 2 and/or 3. In addition, the differences between ionic molar conductivities at infinite dilution of both complexes, $\lambda^0_{\beta-CD:TTACH^+}$ and $\lambda^0_{HPBCD:TTACH^+}$, are minima (Figure 3 and Table 1) for a given temperature,

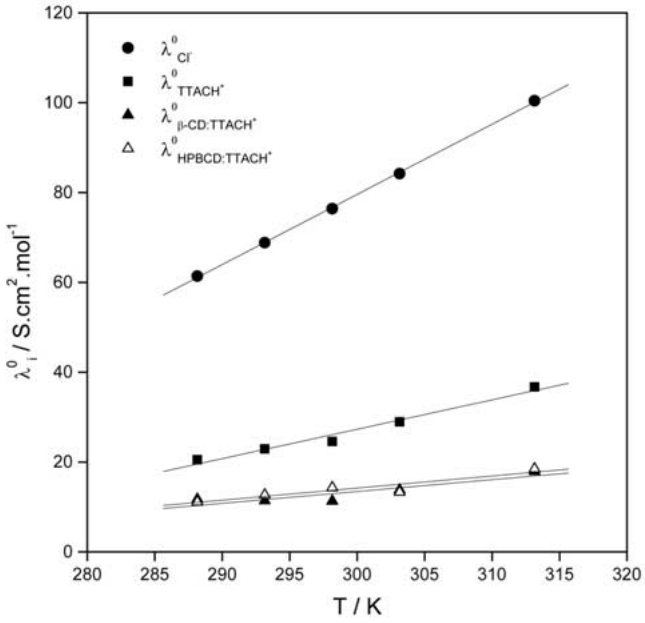

Figure 4. Plot of the ionic molar conductivities at infinite dilution of the free, $\lambda^0_{TTACH^+}$, and complexed drug, $\lambda^0_{CD:TTACH^+}$, and of Cl^-, λ^0_{Cl}, as a function of temperature.

which indicates that the mobilities of both complexes are very similar and seem to be unaffected by the substitution of an hydrogen atom by an hydroxypropyl group in the C_6 of the parent β-cyclodextrin.

The results for $K_{CD:TTACH^+}$ reported on Table 1 for the complexes studied herein reveal a moderate affinity of the drug by both β-CD and HPBCD, which is favorable from a pharmaceutical point of view [23], since it is known that a high affinity between the drug and the CD implies a difficult delivery of the active principle to the organism, while, in the case of very weak associations, there are no significative differences between the administration of the CD:Drug complex and of the drug alone [6]. The dependence of these affinities, $K_{\beta-CD:TTACH^+}$ and $K_{HPBCD:TTACH^+}$, with the temperature can be also noticed in Table 1, where a decrease on the affinity of both cyclodextrins for the drug decreases as long as the temperature increases. Figure 5 shows the van't Hoff plots of both association processes.

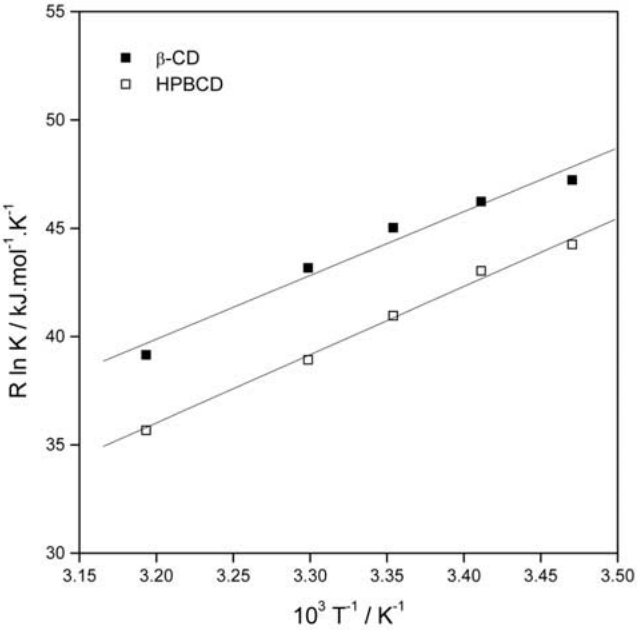

Figure 5. van't Hoff plot for the association of $TTCAH^+$ with β-CD and HPBCD.

Although van't Hoff analyses assume that ΔC_p is zero, which is not always true for this kind of processes [24–26], they are useful to have at least a qualitative information about the enthalpic or entropic character of the process. Linear relationships have been found within the uncertainty of the K values in both cases, revealing an independence of both the ΔH^0 and the ΔS^0 of the association processes with $T(\Delta C_p^0 \sim 0)$, along the range of temperatures studied herein. Values of $\Delta H^0 = (-29 \pm 3)$ kJ mol^{-1} and $\Delta S^0 = (-54 \pm 9)$ J K^{-1} mol^{-1} for the β-CD:$TTACH^+$ complex, and $\Delta H^0 = (-31 \pm 3)$ kJ mol^{-1} and $\Delta S^0 = (-65 \pm 9)$ J K^{-1} mol^{-1} for the HPBCD:$TTACH^+$ complex have been obtained from the slopes and the intercepts, respectively, of the linear fits of the data to the classical van't Hoff equation ($R \ln K = -\Delta H^0/T + \Delta S^0$).

Although the uncertainty in these results is high, as usual for van't Hoff analyses, it can be observed that $TTCAH^+$ species bind to β-CD and/or HPBCD with a favorable enthalpic term ($\Delta H^0 < 0$) and an unfavorable entropic term ($\Delta S^0 < 0$). Both processes are exothermic and enthalpy driven ($|\Delta H^0| > T|\Delta S^0|$), as usually found [26–33] for associations between small guest molecules and an apolar cavity in water. However, this is not what is to be expected for a typical hydrophobically driven process, where positive change in entropy and close to zero enthalpy change are observed [34]. A combination of hydrophobic effect ($\Delta H^0 \sim 0$; $\Delta S^0 > 0$), van der Waals forces ($\Delta H^0 < 0$; $\Delta S^0 < 0$) and and solvent reorganization could account for the thermodynamic parameters of $TTCAH^+$ binding to β-CD and/or HPBCD. Within the uncertainty surrounding these parameters, it can be concluded that the enthalpic term is similar in both associations, while the entropic term seems to be more unfavorable for the association of HPBCD with $TTCAH^+$. Thus, the responsible of the higher affinity of β-CD by $TTCAH^+$ could be the difference between the entropic terms. It looks like the contribution of van der Waals interactions and hydrophobic effect could be similar in both inclusion processes, while the contribution of solvent reorganization could be the factor that makes the binding of β-CD and $TTCAH^+$ energetically more favorable than that of HPBCD and $TTCAH^+$.

Conclusions

This paper constitutes a physicochemical characterization of the interaction of β-CD and its hydroxypropylated derivative with the anesthetic drug, tetracaine hydrochloride. By means of conductometric measurements, it has been found that the drug penetrates the CD cavities, forming 1 : 1 inclusion complexes with moderate affinities at temperatures going from 15 °C to 40 °C. Both associations have been found to be exothermic and enthalpic driven processes, with favorable enthalpic terms dominant above unfavorable entropic terms. These results could point to the contribution of van der Waals interactions, hydrophobic effect, and solvent reorganization, as the main driven forces governing the interaction between the CD and the drug.

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References

1. D.O. Thompson: *Crit. Rev. Therap. Drug Carrier Syst.* **14**, 1 (1997).
2. D. Duchene and D. Wouessidjewe: *Drug Develop. Ind. Pharm.* **16**, 2487 (1990).
3. R.A. Rajewski and V.J. Stella: *J. Pharm. Sci.* **85**, 1142 (1996).
4. J. Szejtli: *Carbohydr. Polym.* **12**, 375 (1990).
5. J. Szejtli: *Med. Res. Rev.* **14**, 353 (1994).
6. J.L. Atwood, J.E.D. Davies, D.D. MacNicol, and F. Vögtle: *Comprehensive Supramolecular Chemistry*, Pergamon, Oxford (1996).
7. I. Orienti, V. Zecchi, V. Betasi, and A. Fini: *Arch. Pharm. (Weinheim)* **324**, 943 (1991).
8. V.T. D'Souza and K.B. Lipkowitz: *Chem. Rev.* **98**, 1741 (1998).
9. P. Jarho, A. Urtti, and T. Jarvinen: *Pharm. Res.* **12**, 1371 (1995).
10. T. Loftsson, H. Fridriksdottir, B.J. Olafsdottir, and O. Gudmundsson: *Acat. Pharm. Nord.* **3**, 215 (1991).
11. D. Duchene, D. Wouessidjewe, and G. Ponchel: *J. Control. Release* **62**, 263 (1999).
12. K. A. Connors: *Binding Constants: The Measurement of Molecular Complex Stability*, John Wiley & Sons, New York (1987).
13. W.C. Bowman and M.J. Rand: *Textbook of Pharmacology*, Blackwell, Cambridge (1990).
14. C. Avendaño: *Introducción a la Química FarmacéUtica*, McGraw-Hill-Interamaricana, Madrid (1993).
15. E. Junquera and E. Aicart: *Rev. Sci. Instrum.* **65**, 2672 (1994).
16. D.A. Deranleau: *J. Am. Chem. Soc.* **91**, 4044 (1969).
17. E. Junquera and E. Aicart: *J. Phys. Chem. B* **101**, 7163 (1997).
18. R.A. Robinson and R.H. Stokes: *Electrolyte Solutions*, Butterworth, London (1965).
19. U. Tinner: *Electrodes in Potentiometry*, Metrohm, Herisau (1989).
20. L. Brüll: *Gazz. Chim. Ital.* **64**, 624 (1934).

21. E. Junquera, M. Martin-Pastor, and E. Aicart: *J. Org. Chem.* **63**, 4349 (1998).
22. E. Junquera, L. Peña, and E. Aicart: *J. Incl. Phenom. Mol. Recogn. Chem.* **24**, 233 (1996).
23. E. Junquera, L. Peña, and E. Aicart: *J. Pharm. Sci.* **87**, 86 (1998).
24. S.J. Gill, S.F. Dec, G. Olofsson, and I. Wadso: *J. Phys. Chem.* **89**, 3758 (1985).
25. S. Sprang, R. Fletterick, M. Stern, D. Yang, N. Madsen, and J. Sturtevant: *Biochemistry* **21**, 2036 (1982).
26. D.A. Stauffer, R.E. Barrans, and D.A. Dougherty: *J. Org. Chem.* **55**, 2762 (1990).
27. F. Diederich, D.B. Smithrud, E.M. Sanford, T.B. Wyman, S.B. Ferguson, D.R. Carcanague, I. Chao, and K.N. Houk: *Acta Chem. Scand.* **46**, 205 (1992).
28. M.R. Eftink, M.L. Andy, K. Bystrom, H.D. Perlmutter, and D.S. Kristol: *J. Am. Chem. Soc.* **111**, 6765 (1989).
29. Y. Inoue, Y. Liu, L. Tong, B. Shen, and D. Jin: *J. Am. Chem. Soc.* **115**, 10637 (1993).
30. Y. Inoue, T. Hakushi, Y. Liu, L.H. Tong, B.J. Shen, and D. S. Jin: *J. Am. Chem. Soc.* **115**, 475 (1993).
31. M.V. Rekharsky, F.P. Schwarz, Y.B. Tewari, R.N. Goldberg, M. Tanaka, and Y. Yamashoji: *J. Phys. Chem.* **98**, 4098 (1994).
32. M.V. Rekharsky, F.P. Schwarz, Y.B. Tewari, and R.N. Goldberg: *J. Phys. Chem.* **98**, 10282 (1994).
33. M.V. Rekharsky, R.N. Goldberg, F.P. Schwarz, Y.D. Tewari, P.D. Ross, Y. Yamashoji, and Y. Inoue: *J. Am. Chem. Soc.* **117**, 8830 (1995).
34. C. Tanford: *The Hydrophobic Effect: Formation of Micelles and Biological Membranes*. Wiley & Sons, New York (1980).