Thermochimica Acta 557 (2013) 44–49

Contents lists available at SciVerse ScienceDirect

Thermochimica Acta

journal homepage: www.elsevier.com/locate/tca

Thermodynamics of inclusion complexes of natural and modified cyclodextrins with acetylsalicylic acid and ibuprofen in aqueous solution at 298 K

Giuseppina Castronuovo*, Marcella Niccoli

Department of Chemistry, University Federico II of Naples, Complesso Universitario a Monte S. Angelo, via Cintia, 80126 Naples, Italy

ARTICLE INFO

Article history:
Received 15 November 2012
Received in revised form 21 January 2013
Accepted 25 January 2013
Available online xxx

Keywords:
Cyclodextrins
Acetysalicylic acid (aspirin)
Ibuprofen
Inclusion complexes
Calorimetry

ABSTRACT

Thermodynamic parameters for the association of natural and substituted α-, β-, and γ-cyclodextrins with acetylsalicylic acid, salicylic acid and ibuprofen have been determined by isothermal titration calorimetry. Analysis of the data shows that complexes form, all having 1:1 stoichiometry. The shape-matching between the host and guest is the factor determining the values of the thermodynamic quantities. In the case of the smallest cyclodextrin interacting with acetylsalicylic acid and salicylic acid, the parameters indicate that hydrophobic interactions play the major role. Association occurs through the shallow inclusion of the benzene ring into the cavity. In the case of substituted β-cyclodextrins, instead, inclusion of the benzene ring is deeper and the tight fitting of the guest molecule to the cavity makes the enthalpy and entropy to be both negative. Ibuprofen interacts through its isobutyl group: the values of the association constants are very high for β-cyclodextrins as determined by the large and positive entropies due to the relaxation of water molecules from the cavity and the hydration spheres of the interacting substances. For all systems, a compensatory enthalpy–entropy relationship exists unless for those involving β-cyclodextrins and ibuprofen.

1. Introduction

Natural cyclodextrins (CDs) are cyclic oligomers of α-D-glucose characterized by a fairly polar exterior and by a relatively nonpolar cavity. The most important property of CDs is their ability to form complexes with a great variety of organic substances in solution and in the solid state [1–5]. The host–guest chemistry of inclusion complexes of cyclodextrins has been thoroughly studied, especially in relation to their most common pharmaceutical applications. The physicochemical properties of the included substances are altered upon complexation and cyclodextrins are widely used to enhance the aqueous solubility, stability and bioavailability of apolar drug molecules [6–9]. Besides, toxicity tests have demonstrated that orally administered CDs are essentially nontoxic, largely because they are not absorbed in the gastrointestinal tract. In the attempt to improve the properties of the natural macrocycles as drug carriers [10,11], many cyclodextrin derivatives have been prepared in the last years to modify their inclusion ability

Complexation processes result from the contribution of a series of noncovalent intermolecular forces: hydrophobic interactions, hydrogen bonds, van der Waals interactions, conformational energy, dipole–dipole and ion–dipole interactions and the rearrangement of water molecules originally surrounding both cyclodextrin and guest molecule [1,12–20]. The weight of every one of these interactions depends on the substituent groups on both the interacting molecules and on the dimensions of the cyclodextrin cavity. Preceding studies on the complexes of various cyclodextrins with different substances have allowed us to examine the factors which are necessary for a complex to form. The aim of the present contribution is to have the complete thermodynamic framework characterizing the inclusion process between natural and modified cyclodextrins and substances of pharmacological interest in aqueous solution. To that, the interaction of α-cyclodextrin (α-CD), 2-hydroxypropyl-α-cyclodextrin (HP-α-CD), methyl-α-cyclodextrin (M-α-CD), β-cyclodextrin (β-CD), 2-hydroxypropyl-β-cyclodextrin (HP-β-CD), methyl-β-cyclodextrin (M-β-CD) and γ-cyclodextrin with some drugs is investigated by a calorimetric method at 298 K. The drugs used in this study are: acetylsalicylic acid (aspirin, p*K*a = 3.5; Fig. 1), salicylic acid (pKa = 2.97) and ibuprofen (pKa = 4.4, Fig. 1), which belong to a group of medications called nonsteroidal, anti-inflammatory drugs (NSAIDs), pH-dependent and practically insoluble in water. Aspirin is one of the most widely used medications in the world. Its effects as an analgesic, antipyretic, anti-inflammatory and antithrombotic agent are widely known. Unfortunately, its use, especially in higher doses, can cause severe side effects as gastrointestinal ulcers, stomach bleeding, and tinnitus. Aspirin-CD inclusion complexes were devised to increase the solubility and reduce the concentration of free drug, with the consequent reduction of side effects. Ibuprofen (BF, see Fig. 1b) is used primarily for fever, pain, dysmenorrhoea and

* Corresponding author. Tel.: +39 081674239; fax: +39 081674091.
E-mail address: giuseppina.castronuovo@unina.it (G. Castronuovo).

0040-6031/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.tca.2013.01.037

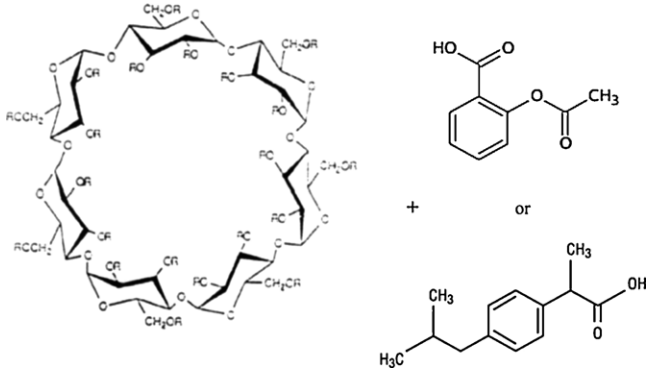

Fig. 1. Scheme of the interaction between a modified β-cyclodextrin and (upper) acetylsalicylic acid (aspirin) or (down) ibuprofen.

inflammatory diseases such as rheumatoid arthritis. Its pharmaceutical applications, however, are limited because it is only slightly soluble in water, has a bad taste and can have serious effects on the gastro-intestinal apparatus. The formation of inclusion complexes with cyclodextrins improves both its solubility and taste [21,22].

Microcalorimetry is the technique chosen to carry out this kind of study: through the thermal effect detected, it is possible to evaluate the association constant, and from that the Gibbs energy and entropy of the process. Knowing the values and signs of the thermodynamic parameters makes possible proposing a hypothesis about the forces involved in the interaction between CD and the examined guest molecules. That can be particularly useful for designing new modified cyclodextrins having more suitable characteristics to include specific drug.

2. Experimental

2.1. Materials

Natural α-, β-, and γ-cyclodextrin, as well as acetylsalicylic acid, salicylic acid and ibuprofen, were purchased from Sigma. Methyl-α-cyclodextrin, 2-hydroxypropyl-α-cyclodextrin, methyl-β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin and 2-hydroxypropyl-γ-cyclodextrin were purchased from Cyclolab: it is reported that the mean substitution degree has been determined by NMR. All substances were used as received, without further purification. The optical rotations of CDs were in agreement with those reported in the literature. Solutions of natural and modified cyclodextrins, of known molalities, were prepared by mass, using 0.05 mol kg^{-1} buffer phosphate, pH 7.4 or 9.3. Solutions of ibuprofen, acetylsalicylic acid and salicylic acid were, then, prepared using the same phosphate buffer as solvent.

2.2. Calorimetry

Measurements of the experimental heats of mixing, ΔH_{mix}, of two binary solutions containing any one of the solutes, were determined at 298 K using a thermal activity monitor (TAM) from Thermometric, equipped with a titration vessel. A microcomputer controlled the injections and collected the titration data. Approximately 30 injections of the titrating solution were made in each experiment, and at least two experiments were performed for each substance. Enthalpies of dilution of the added substance in the appropriate solvent were determined, using the same number of injections and concentrations as in the titration experiments, and were subtracted from the enthalpies of the mixing process. The dilution of the component present in the cell (usually the drug) was considered to be negligible. The estimated uncertainties in the molalities and the heat effects are 1% and 2%, respectively.

2.3. Treatment of the data

Assuming that a 1:1 complex is formed when mixing two binary solutions, the association process can be represented as follows:

$$CD + L = CD - L \tag{1}$$

where CD indicates a cyclodextrin and L a guest (drug) molecule.

The enthalpy of mixing two binary solutions, ΔH_{mix}, is related to the enthalpy of formation of a complex, or in general to the enthalpy of interaction between solutes, ΔH^*, and to the heats of dilution experienced by the two solutes, ΔH_{dil}, [23–25]

$$\Delta H_{mix}[(m^i_{CD})(m^i_L) \rightarrow m^f_{CD}, m^f_L] = \Delta H^* + \Delta H_{dil}(m^i_{CD} \rightarrow m^j_{CD}) + \Delta H_{dil}(m^i_L \rightarrow m^f_L) \tag{2}$$

where m^i_{CD}, m^i_L, m^f_{CD}, and m^f_L are the initial and final molalities of the cyclodextrin and drug. ΔH^*, normalized to the total molality of the guest, m_L, can be related to the actual molality of the cyclodextrin host molecule, m^f_{CD}, to the standard molar enthalpy of association, ΔH°_a, and to the apparent association constant, K'_a, as follows [26]:

$$\frac{m_L}{\Delta H^*} = \frac{1}{\Delta H^\circ_a} + \frac{1}{\Delta H^\circ_a K'_a m^f_{CD}} \tag{3}$$

For each value of ΔH^*, the actual concentration of the host molecule is given by:

$$m^f_{CD} = m_{CD} - \left(\frac{\Delta H^*}{\Delta H^*_{sat}}\right) m_L \tag{4}$$

where m_L is the total stoichiometric molality of the host molecule. The standard enthalpy and the constant are obtained from Eqs. (3) and (4) by an iterative least-squares fitting. The iterations are continued until two successive values of ΔH°_a differ by less than 2%. The values of the free energy and entropy are obtained through the usual thermodynamic relations. The absence of any information about the activity coefficients leads to the evaluation of association parameters thermodynamically not exactly defined. Only an apparent constant, K'_a, can be determined, and consequently the standard free energy and entropy, $\Delta G^{\circ\prime}_a$ and $\Delta S^{\circ\prime}_a$, suffer of the same limitations

3. Results

The thermodynamic association parameters for the formation of the drug/CD complexes were determined at 298 K. In Tables 1–3, the association constant, standard Gibbs energy, enthalpy and entropy are reported for the complexation of natural and modified cyclodextrins with acetylsalicylic acid, salicylic acid and ibuprofen, in aqueous phosphate buffer, pH 9.3 or 7.4.

Table 1 shows the thermodynamic parameters, obtained in phosphate buffer, pH 9.3, for the formation of inclusion complexes between natural and modified cyclodextrins and acetylsalicylic acid. The standard molar enthalpies of association, ΔH°_a, are negative for all employed cyclodextrins: those relative to natural and modified β-cyclodextrins are larger, in absolute value, than those for α-cyclodextrins, being intermediate that for γ-CD. The unsubstituted CDs are characterized by a less negative standard molar enthalpy compared to the respective modified ones. The enthalpies become more negative at increasing hydrophobicity of the modified β-CDs: in fact, enthalpy for the modified hydroxypropyl-cyclodextrin having DS = 6,3 is larger than that for

Table 1
Thermodynamic parameters for the association of various cyclodextrins with acetyl salicylic acid in 0.05 mol kg^{-1} buffer phosphate, pH 9.3, at 298.15 K.

System	ΔH_a° [a,b]	K'_a [a,c]	$\Delta G_a^{\circ\prime}$ [b,d]	$T\Delta S_a^{\circ\prime}$ [b,e]
α-CD	−2.2 ± 0.9	110 ± 70	−12 ± 2	10 ± 3
Methyl-α-CD (DS[f] = 11)	−2.7 ± 0.1	150 ± 10	−12.4 ± 0.2	9.7 ± 0.3
2-Hydroxypropyl-α-CD (DS[f] = 4.5)	−7 ± 1	105 ± 30	−11.5 ± 0.9	5 ± 2
β-CD	−7.5 ± 0.8	210 ± 30	−13.2 ± 0.4	6 ± 1
2-Hydroxypropyl-β-CD (DS[f] = 3)	−12 ± 1	55 ± 10	−9.9 ± 0.5	−2 ± 1
2-Hydroxypropyl-β-CD (DS[f] = 6.3)	−15.8 ± 0.9	100 ± 10	−11.4 ± 0.3	−4 ± 1
Methyl-β-CD (DS[f] = 12)	−24 ± 2	145 ± 20	−12.3 ± 0.3	−12 ± 2
γ-CD	−4.9 ± 0.6	45 ± 10	−9.4 ± 0.6	5 ± 1
2-Hydroxypropyl-γ-CD (DS[f] = 4.5)		N.A.[g]		

[a] Errors reported are the standard deviations as obtained by fitting the data to Eqs. (3) and (4).
[b] kJ/mol.
[c] kg/mol.
[d] Errors are half the range of $\Delta G_a^{\circ\prime}$ calculated from the upper and lower error in K'_a.
[e] Errors are the sum of the errors on free energy and enthalpy.
[f] Degree of substitution.
[g] N.A. means that experiments have been performed, but no association was detected.

Table 2
Thermodynamic parameters for the association of various cyclodextrins with salicylic acid in 0.05 mol kg^{-1} buffer phosphate, pH 9.3, at 298.15 K.

System	ΔH_a° [a,b]	K'_a [a,c]	$\Delta G_a^{\circ\prime}$ [b,d]	$T\Delta S_a^{\circ\prime}$ [b,e]
α-CD	−2.4 ± 0.6	90 ± 30	−11 ± 1	9 ± 2
β-CD	−12 ± 1	120 ± 10	−11.9 ± 0.3	0 ± 1
Methyl-β-CD (DS[g] = 12)	−16.3 ± 0.8	110 ± 10	−11.7 ± 0.3	−5 ± 1

[a] Errors reported are the standard deviations as obtained by fitting the data to Eqs. (3) and (4).
[b] kJ/mol.
[c] kg/mol.
[d] Errors are half the range of $\Delta G_a^{\circ\prime}$ calculated from the upper and lower error in K'_a.
[e] Errors are the sum of the errors on free energy and enthalpy.

DS = 3, while the largest value characterizes the interaction with methyl-β-CD. Entropies for α-CDs and γ-CD are positive while negative for β-CDs. Despite the great variability in the values of the enthalpies and entropies of association, the values of $\Delta G_a^{\circ\prime}$ vary in a limited range, showing a relationship between the enthalpy and entropy change, *i.e.* the enthalpy–entropy compensation. That leads to very similar and low values of the association constants, which fall in the 50/200 kg/mol range. For the propyl substituted γ-CD, association was not detected.

Table 2 shows the thermodynamic parameters, obtained in phosphate buffer at pH 9.3, for the formation of inclusion complexes between natural and modified cyclodextrins and salicylic acid., The values of the thermodynamic parameters for the unsubstituted α-CD and β-CD are similar to those obtained for the complexes with acetylsalicylic acid.

The data for ibuprofen, reported in Table 3, indicate that the complexation with α-CDs is very different from that with β-CDs. For both cyclodextrins the inclusion processes are exothermic, and entropies are positive. The values of inclusion enthalpies for natural cyclodextrins are more negative than the corresponding modified ones, those relative to β-CDs (except methyl-β-CD) being much larger as respect to the α-CDs. The standard molar entropies are positive and very different for the various α-CDs, while they are large and positive and approximately invariant for all the examined β-CDs. Gibbs energy distinguishes very well the two CDs: in fact, for β-CDs it almost doubles that for α-CDs. For α-CDs, the association constants increase at increasing hydrophobicity of the cyclodextrin: they are very large for β-CDs, as determined by the very high and positive entropic contribution. In particular, for the natural β-CD, the large and negative value of enthalpy determines that the complex is characterized by an association constant larger than that involving modified β-CDs.

Fig. 2 shows the complete thermodynamic framework for the association of acetylsalycilic acid and ibuprofen with the natural and modified cyclodextrins. Enthalpies and Gibbs energies are reported *vs* 3N-DS, where N is the number of glucopyranose rings forming the cyclodextrin, and DS is the substitution degree. Reporting the only DS as the independent variable would not allow to distinguish between α-CDs and β-CDs having the same substitution degree, but different number of glucose units, hence different residual hydrophilicity.

4. Discussion

According to the commonly accepted view, complexation of a hydrophobic guest molecule with a cyclodextrin occurs through the inclusion of the alkyl portion into the prevailingly hydrophobic cavity. The functional group forms hydrogen bonds with the

Table 3
Thermodynamic parameters for the association of various cyclodextrins with ibuprofen in 0.05 mol kg^{-1} buffer phosphate, pH 7.4, at 298.15 K.

System	ΔH_a° [a,b]	K'_a [a,c]	$\Delta G_a^{\circ\prime}$ [b,d]	$T\Delta S_a^{\circ\prime}$ [b,e]
α-CD	−8.5 ± 0.4	99 ± 8	−11.4 ± 0.2	2.9 ± 0.6
Methyl-α-CD (DS[f] = 11)	−5.2 ± 0.1	720 ± 30	−16.3 ± 0.1	11.1 ± 0.2
2-Hydroxypropyl-α-CD (DS[f] = 4.5)	−5.3 ± 0.7	100 ± 20	−11.6 ± 0.4	6 ± 1
β-CD	−9.24 ± 0.06	(5.0 ± 0.1)10^4	−26.7 ± 0.7	17.5 ± 0.8
2-Hydroxypropyl-β-CD (DS[f] = 3)	−8.16 ± 0.09	(2.9 ± 0.1)10^4	−25.5 ± 0.1	17.3 ± 0.2
2-Hydroxypropyl-β-CD (DS[f] = 6.3)	−7.87 ± 0.08	(3.2 ± 0.3)10^4	−25.7 ± 0.3	17.8 ± 0.3
Methyl-β-CD (DS[f] = 12)	−4.92 ± 0.05	(7.6 ± 0.7)10^3	−22.2 ± 0.2	17.2 ± 0.3

[a] Errors reported are the standard deviations as obtained by fitting the data to Eqs. (3) and (4).
[b] kJ/mol.
[c] kg/mol.
[d] Errors are half the range of $\Delta G_a^{\circ\prime}$ calculated from the upper and lower error in K'_a.
[e] Errors are the sum of the errors on free energy and enthalpy.
[f] Degree of substitution.

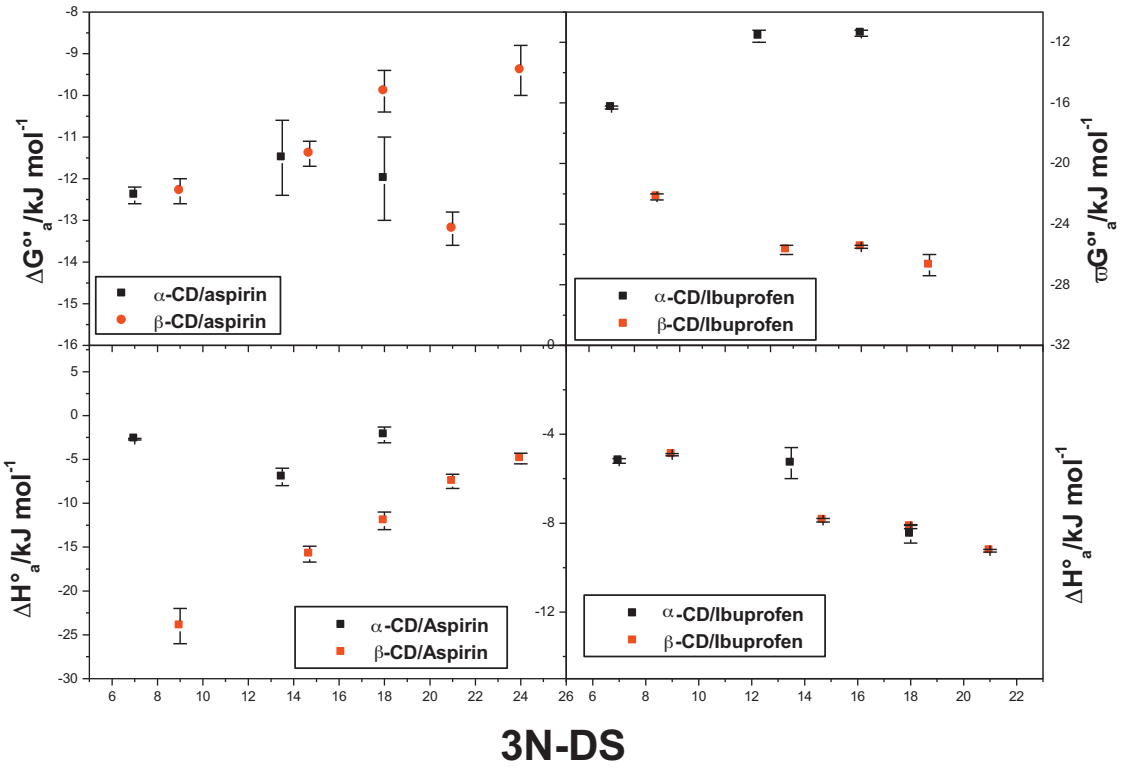

Fig. 2. Enthalpies and Gibbs energies for aspirin and ibuprofen interacting with natural and modified α-CDs or β-CDs as a function of 3N-DS, where N is the number of glucopyranose rings forming cyclodextrins and DS is the degree of substitution.

external hydroxyl groups on the rim of the macrocycle cavity, thus preventing the further penetration of the alkyl chain [27,28]. The present data relative to the interaction of natural or modified α-, β-, and γ-cyclodextrins with some drugs as guest molecules show that association occurs through the same mechanism. However, the presence of external methyl or propyl groups in the substituted CDs causes the balance of the forces upon association to be different from that acting when the natural cyclodextrins are involved. In all cases, the association is characterized by negative enthalpies. The value of enthalpy is the result of several factors, among them the endothermic contribution due to the disruption of hydrogen bonds between water molecules in the cavity, the endothermic dehydration of the including hydrophobic guest molecule, and the exothermic contribution stemming from the van der Waals interactions between the guest and the cyclodextrin cavity. For the last interactions, the dimensions of the cyclodextrin cavity play the major role. The α-CD cavity has the best dimensions to include an alkyl chain, while β-CD can accommodate a benzene ring at the best. In the case of a loose adaptation of the guest molecule upon formation of a complex, contributions stemming from the interactions with the cavity will be negative, but smaller, as in the case of γ-CD. Also entropy is a complex quantity whose value is the result of several contributions. Upon inclusion, water molecules relax from an ordered microenvironment, namely the cavity, and from the ordered hydrophobic hydration shells of the guests to a more disordered bulk. In the case of modified (alkylated) cyclodextrins, another additional effect must be taken into account: the dehydration of the external alkyl groups, an endothermic process. In those cases, the very large and positive values are determined by the relaxation to the bulk of water molecules from the hydrophobic hydration shells of the external alkyl groups and from the cavity. For natural and modified β-CDs the last contribution can be assumed to be the predominant one [12,29].

Acetylsalycilic acid has three possible points to include within the cavity of a cyclodextrin: the carboxylic group, the acylic group and the benzene ring (Table 1). At pH 9.3, the carboxyl group is ionized in solution: hence, as reported in the literature, carboxylate ion cannot enter into the hydrophobic cavity because of its extended hydration [27]. Then, inclusion could occur or through the benzene ring or through the acylic group. Calorimetric titrations of the two natural cyclodextrins and of methyl-β-cyclodextrin with salicylic acid lead to inclusion parameters (Table 2) which describe the penetration of benzene into the cavity of the CDs, since no other part of the molecule can be included. The similarity of the binding parameters for the interaction of aspirin and salicylic acid with the same cyclodextrins, makes to infer that, at the pH used, the interaction of cyclodextrins with aspirin occurs through the inclusion of the benzene ring into the cavity. For α-CDs, the values of the association constants indicate the formation of rather weak complexes, thus underlining that the fitting of the guest molecule to the cavity is rather superficial. That is in agreement with literature data which report that the benzene ring penetrates shallowly into the narrower α-CD cavity, whose diameter (about 5 Å) is too small to give a deep and tight inclusion of the guest molecule [13,30,31]. Instead, the fitting of benzene is deeper into the wider cavity of β-CD, whose internal diameter is about 7 Å, the best dimensions for the association with a benzene ring. The values of enthalpies for α-CDs are small and negative, while those for modified β-CDs are negative and large, an indication that van der Waals interactions between the guest molecule and the cavity are much more significant. The last effect determines the entropy to be negative for the reduced motion of the guest molecule. Consequently, the Gibbs energy is rather small and the constants as low as those for the smaller cyclodextrin. These conclusions are in agreement with the findings from NMR studies on unionized aspirin, that has been found to form stable inclusion complexes with various β-cyclodextrins: the benzene ring is located inside the cavity while

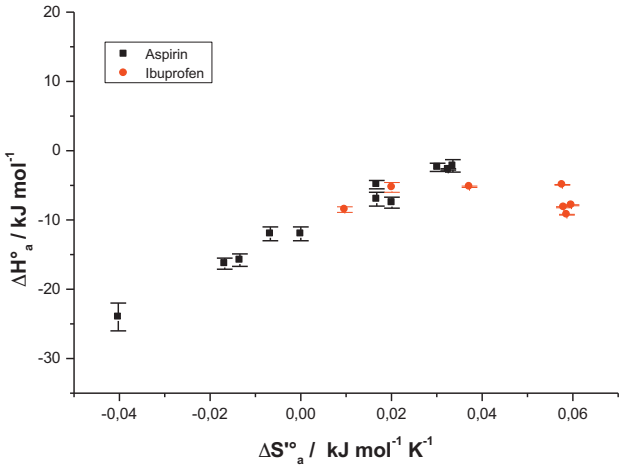

Fig. 3. Enthalpy–entropy compensation plot for the formation of the complexes of natural and modified α-CDs or β-CDs with aspirin or ibuprofen.

the acetyl ester group protrudes from it. The same studies indicated that the ionized aspirin does not form complexes with the examined β-cyclodextrins. Loftsson et al. carried out a structural analysis of the inclusion complex between β-CD and aspirin by NMR [32]. They concluded that the phenyl ring of the guest is completely included into the cavity and the ester group stands somewhat out of it. In contrast, the ionized aspirin molecule is, to a certain degree, pulled out from the β-CD cavity so that the included portion of the aspirin molecule should be smaller than that under acidic conditions [33]. IR studies, too, evidentiate the formation of inclusion complexes stabilized by van der Waals interactions of aromatic rings of salycilic acid molecules with the hydrophobic cavities of CD molecules. The stabilization inside β-cyclodextrin is supported by the formation of weak hydrogen bonds between phenyl hydroxyls of salicylic acid and glycoside oxygens of cyclodextrin molecules [34,35].

Ibuprofen includes into the cavity of cyclodextrins probably through its isobutyl group. The ΔH_a° values for α-CDs are negative and smaller than those for β-CDs. That is not unexpected probably because, beyond the isobutyl group, also the benzene ring enters partially into the cavity of CDs. This hypothesis is confirmed by NMR literature data [36], which suggest that only the isobutyl group of the BF molecule is included in the cavity of α-CD, while the β-CD cavity accommodates, beyond the isobutyl, part of the aromatic ring of the BF molecule, too [37]. The association constants and then the values of the Gibbs energy depend on the cavity size of cyclodextrins, being those for α-CDs much smaller than those for β-CDs. The values of entropies are positive for both cyclodextrins: they originate from the dehydration of the isobutyl part of ibuprofen upon inclusion and from the relaxation of water molecules from the cavity. However, for β-CDs, the entropic term is large, positive and almost invariant. The complexes formed are characterized by large association constants, for the favorable, concurrent contribution of both enthalpy and entropy, being the former negative and the latter positive (see Fig. 3). Given the dimensions of β-cyclodextrins, the association occurs through the inclusion of the isobutyl group together with the aromatic ring. The suitable fit between host and guest determines the values of the thermodynamic parameters. Hence, the values of the entropic contribution are determined by the relaxation to the bulk of water molecules from the hydrated interacting groups and from the cavity. The last effect appears to be predominant, as detected by the invariance of entropy whatever the cyclodextrin, natural, modified or having different substitution degree (see Table 3). In the literature there are structural [38–41] and thermodynamic [36] studies on ibuprofen–cyclodextrin complexes. Our data are in good agreement with calorimetric data, showing similar trend of the thermodynamic parameters: any differences can be attributed to the different solvent and pH of measurement.

5. Conclusion

The formation of a complex between a cyclodextrin and a prevailingly hydrophobic guest molecule is a process ruled by the changes experienced by the solvent water upon association: dehydration of the guest molecule, desolvation of the cavity, formation of a hydration shell for the complex.

The complete thermodynamic framework reported in Fig. 2 is a good synthesis of the association of acetylsalycilic acid and ibuprofen with natural and modified cyclodextrins. The 3N-DS abscissa takes into account the number of hydroxyl groups substituted by an alkyl group, hence it is bound to the residual hydrophilic character of the examined cyclodextrins. For aspirin, it comes out that the Gibbs energy varies in a small range because of the enthalpy–entropy compensation. That leads to rather weak complexes, described by small association constants. For ibuprofen, enthalpies vary in a limited range for both α- and β-cyclodextrins. Hence, the very different association constants characterizing the formation of the complexes with the two types of differently sized cyclodextrins are determined by entropy, which is positive in both cases, but very large for the larger macrocycle. For most complexes reported in the literature, a roughly linear trend is obtained when reporting ΔH° *vs* ΔS°': this compensatory enthalpy–entropy relationship exists [1,12,42–44] for all processes dominated by equation phenomena and ascribed to the modifications experienced by the solvent in the hydration cospheres of the interacting substances. Fig. 3 is very descriptive of the processes examined. In fact, the plot is roughly linear, whatever the cyclodextrin or the guest molecule, with the exception of the last five points referring to the systems involving β-CD interacting with ibuprofen. Then, for those systems enthalpy–entropy compensation does not operate and the large values of the association constants, among the highest found for cyclodextrin complexes, are determined prevailingly by entropy.

References

[1] M.V. Rekharsky, Y. Inoue, Complexation thermodynamics of cyclodextrins, Chem. Rev. 98 (1998) 1875–1918.
[2] M.V. Rekharsky, Y. Inoue, Chiral recognition thermodynamics of β-cyclodextrin: the thermodynamic origin of enantioselectivity and the enthalpy–entropy compensation effect, J. Am. Chem. Soc. 122 (2000) 4418–4435.
[3] R.J. Clarke, J.H. Coates, S.F. Lincoln, Inclusion complexes of the cyclomalto-oligosaccharides (cyclodextrins), Adv. Carbohydr. Chem. Biochem. 46 (1988) 205–249.
[4] A. Connors, The stability of cyclodextrin complexes in solution, Chem. Rev. 97 (1997) 1325–1358.
[5] W. Saenger, Cyclodextrin inclusion compounds in research and industry, Angew. Chem. Int. Ed. Engl. 19 (1980) 344–362.
[6] F. Bellia, D. La Mendola, C. Pedone, E. Rizzarelli, M. Saviano, G. Vecchio, Selectively functionalized cyclodextrins and their metal complexes, Chem. Soc. Rev. 38 (2009) 2756–2781.
[7] E. Junquera, D. Ruiz, E. Aicart, Role of hydrophobic effect on the noncovalent interactions between salicylic acid and a series of β-cyclodextrins, J. Colloid Interface Sci. 216 (1999) 154–160.
[8] E. Junquera, V.G. Baonza, E. Aicart, Energetics of the encapsulation of *o*-, *m*-, and *p* hydroxybenzoic acids by β-cyclodextrin and its methylated and hydroxypropylated derivatives in aqueous solution, Can. J. Chem. 77 (1999) 348–355.
[9] E. Junquera, E. Aicart, Potentiometric study of the encapsulation of ketoprophen by hydroxypropyl-β-cyclodextrin. Temperature, solvent, and salt effects, J. Phys. Chem. B 101 (1997) 7163–7171.
[10] K. Uekama, F. Hirayama, T. Irie, Cyclodextrin drug carrier systems, Chem. Rev. 98 (1998) 2045–2076.
[11] A.R. Hedges, Industrial applications of cyclodextrins, Chem. Rev. 98 (1998) 2035–2044.

[12] G. Castronuovo, M. Niccoli, L. Varriale, Complexation forces in aqueous solution. Calorimetric studies of the association of 2-hydroxypropyl-β-cyclodextrin with monocarboxylic acids or cycloalkanols, Tetrahedron 63 (2007) 7047–7052.
[13] G. Castronuovo, M. Niccoli, Thermodynamics of inclusion complexes of natural and modified cyclodextrins with propranolol in aqueous solution at 298 K, Bioorg. Med. Chem. 14 (2006) 3883–3887.
[14] L. Liu, Q.-X.J. Guo, The driving forces in the inclusion complexation of cyclodextrins, J. Inclusion Phenom. Macrocycl. Chem. 42 (2002) 1–14.
[15] M.V. Rekharsky, M.P. Mayhew, R.N. Goldberg, P.D. Ross, Y. Yamashoji, Y. Inoue, Thermodynamic and nuclear magnetic resonance study of the reactions of α- and β-cyclodextrin with acids, aliphatic amines, and cyclic alcohols, J. Phys. Chem. 101 (1997) 87–100.
[16] M.F. Brewster, T. Loftsson, Cyclodextrins as pharmaceutical solubilizers, Adv. Drug Deliv. Rev. 59 (2007) 645–666.
[17] P.D. Ross, M.V. Rekharsky, Thermodynamics of hydrogen bond and hydrophobic interactions in cyclodextrins complexes, Biophys. J. 71 (1996) 2144–2154.
[18] G. Barone, G. Castronuovo, P. Del Vecchio, V. Elia, M. Muscetta, Thermodynamics of formation of inclusion compounds in water. α-Cyclodextrin–alcohol adducts at 298.15 K, J. Chem. Soc. Faraday Trans. I 82 (1986) 2089–2101.
[19] D. Hallén, A. Schön, I. Shehatta, I. Wadsö, Microcalorimetric titration of α-cyclodextrin with some straight-chain alkan-1-ols at 288.15, 298.15, and 308.15 K, J. Chem. Soc. Faraday Trans. 88 (1992) 1859–2853.
[20] N.A. Todorova, F.P. Schwarz, The role of water in the thermodynamics of drug binding to cyclodextrin, J. Chem. Thermodyn. 39 (2007) 1038–1048.
[21] M. di Cagno, P.C. Stein, N. Skalko-Basnet, M. Brandl, A. Bauer-Brandl, Solubilization of ibuprofen with β-cyclodextrin derivatives: energetic and structural studies, J. Pharm. Biomed. Anal. 55 (2011) 446–451.
[22] L.J. Waters, S. Bedford, G.M.B. Parkes, J.C. Mitchell, Influence of lipophilicity on drug–cyclodextrin interactions: a calorimetric study, Thermochim. Acta 511 (2010) 102–106.
[23] W.G. Mc Millan, J.E. Mayer, The statistical thermodynamics of multicomponent systems, J. Chem. Phys. 13 (1945) 276–306.
[24] J.J. Kozak, W.S. Knight, W. Kauzmann, Solute-solute interactions in aqueous solutions, J. Chem. Phys. 48 (1968) 675–691.
[25] H.L. Friedman, C.V. Krishnan, Studies of hydrophobic bonding in aqueous alcohols: enthalpy measurements and model calculations, J. Solution Chem. 2 (1973) 119–140.
[26] M. Eftink, R. Biltonen, in: E. Beezer (Ed.), Biological Microcalorimetry, Academic Press, London, 1980.
[27] G. Castronuovo, V. Elia, M. Niccoli, F. Velleca, G. Viscardi, Role of the functional group in the formation of the complexes between α-cyclodextrin and alkanols or monocarboxylic acids in aqueous solutions. A calorimetric study at 25, Carbohydr. Res. 306 (1998) 147–155.
[28] S. Andini, G. Castronuovo, V. Elia, E. Gallotta, Inclusion compounds in water: calorimetric and spectroscopic studies of the interaction of cyclomaltohexaose (α-cyclodextrin) with alkanols at 25°, Carbohydr. Res. 217 (1991) 87–97.
[29] G. Castronuovo, M. Niccoli, Solvent effects on the complexation of 1-alkanols by parent and modified cyclodextrins. calorimetric studies at 298 K, J. Therm. Anal. Calorim. 103 (2011) 641–646.
[30] Y. Inoue, Y. Miyata, Formation, Molecular dynamics of cycloamylose inclusion complexes with phenylalanine, Bull. Chem. Soc. Jpn. 54 (1981) 809–816.
[31] M. Cervero, F. Mendicuti, Inclusion complexes of dimethyl 2 6-Naphthalenedicarboxylate with α- and β-cyclodextrins in aqueous medium: thermodynamics and molecular mechanics studies, J. Phys. Chem. B 104 (2000) 1572–1580.
[32] T. Loftsson, E.M. Brewster, Pharmaceutical applications of cyclodextrins. 1. Drug solubilization and stabilization, J. Pharm. Sci. 85 (1996) 1017–1025.
[33] T. Fukahori, M. Kondo, S. Nishikawa, Dynamic Study of interaction between β-cyclodextrin and aspirin by the ultrasonic relaxation method, J. Phys. Chem. B 110 (2006) 4487–4491.
[34] L.A. Belyakova, A.M. Varvarin, D. Yu Lyashenko, O.V. Khora, E.I. Oranskaya, Complexation in a β-cyclodextrin-salicylic acid system, Colloid J. 69 (2007) 546–551.
[35] L.A. Belyakova, D.Yu. Lyashenko, Complex formation between benzene carboxylic acids and β-cyclodextrin, J. Appl. Spectrosc. 75 (2008) 314–318.
[36] S. Xing, Q. Zhang, C. Zhang, Q. Zhao, H. Ai, D. Sun, Isothermal titration calorimetry and theoretical studies on host–guest interaction of ibuprofen with α-, β- and γ-cyclodextrin, J. Solution Chem. 38 (2009) 531–543.
[37] I. Oh., M.Y. Lee, Y.B. Lee, S.C. Shin, I. Park, Spectroscopic characterization of ibuprofen/2-hydroxypropyl-β-cyclodextrin inclusion complex, Int. J. Pharm. 175 (1998) 215–223.
[38] B. Rossi, P. Verrocchio, G. Villani, I. Mancini, G. Guella, E. Rigo, G. Scarduelli, G. Mariotto, Vibrational properties of ibuprofen–cyclodextrin inclusion complexes investigated by Raman scattering and numerical simulation, J. Raman Spectrosc. 40 (2009) 453–458.
[39] V. Crupi, D. Majolino, V. Venuti, G. Guella, I. Mancini, B. Rossi, P. Verrocchio, G. Villani, R. Stancanelli, Temperature effect on the vibrational dynamics of cyclodextrin inclusion complexes: investigation by FTIR-ATR spectroscopy and numerical simulation, J. Phys. Chem. A 114 (2010) 6811–6817.
[40] J.L. Manzoori, M. Amjadi, Spectrofluorimetric study of host–guest complexation of ibuprofen with β-cyclodextrin and its analytical application, Spectrochim. Acta A 59 (2003) 909–916.
[41] V. Crupi, G. Guella, D. Majolino, I. Mancini, B. Rossi, R. Stancanelli, V. Venuti, P. Verrocchio, G. Villani, T-dependence of the vibrational dynamics of IBP/diME-β-CD in solid state: a FT-IR spectral and quantum chemical study, J. Mol. Struct. 972 (2010) 75–80.
[42] R. Lumry, S. Rajender, Enthalpy–entropy compensation phenomena in water solutions of proteins and small molecules: a ubiquitous properly of water, Biopolymers 9 (1970) 1125–1127.
[43] E. Grunwald, C. Steel, Solvent reorganization and thermodynamic enthalpy–entropy compensation, J. Am. Chem. Soc. 117 (1995) 5687–5692.
[44] P. Lo Meo, F. D'Anna, M. Gruttadauria, S. Riela, R. Noto, Thermodynamics of binding between α- and β-cyclodextrins and some p-nitro-aniline derivatives: reconsidering the enthalpy–entropy compensation effect, Tetrahedron 60 (2004) 9099–9111.