Pergamon

Tetrahedron 57 (2001) 6823–6827

TETRAHEDRON

Spectrophotometric determinations of binding constants between cyclodextrins and aromatic nitrogen substrates at various pH values

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Received 14 February 2001; revised 11 May 2001; accepted 7 June 2001

Abstract—The inclusion capacity of native β-cyclodextrin (**1**) and mono-(6-amino-6-deoxy)-β-cyclodextrin (**2**) versus aromatic compounds having a nitro or an amino group or both has been investigated at three different pH values. Molecular interactions in inclusion complexes have also been investigated by means of molecular mechanics (MM2/QD) models. Electrostatic and van der Waals interactions and the formation of a hydrogen bond between the donor amino group and the oxygen atom of the secondary hydroxyl group seem to be the more important contributions in determining complex stability.

1. Introduction

Cyclodextrins (CDs) are widely used as hosts to form inclusion complexes with small- and medium-sized organic molecules.[1] Complexation reactions involving cyclodextrins are highly important to drug delivery systems and also to the separation and food industries.[2] These reactions also serve as excellent models for understanding general inclusion phenomena, as well as enzyme–substrate interactions.[3] Despite the enormous amount of experimental and theoretical work, the analysis of the ultimate factors governing inclusion phenomena has even been the object of intense debate in recent years.[4]

From a thermodynamic point of view it has been proposed to dissect the inclusion process in a series of ideal steps which can be summarized as: (i) desolvation of the guest; (ii) internal desolvation (partial or total) of the host cavity; (iii) inclusion of the guest; (iv) reorganization of the solvent pool.[5] This scheme provides the general basis to discuss the role of a given effect in the process. Furthermore the linear relationship empirically found between enthalpy (ΔH°) and entropy ($T\Delta S^\circ$) variations ('enthalpy–entropy compensation' effect)[4,6] has been recently interpreted in terms of a main role assumed by the host cavity desolvation and by the conformational changes induced on inclusion for the host itself.[6a,e]

The relative importance of different steps of the above scheme can be changed by modifying one or more functional groups (hydroxyl groups). At present, only a limited number of systematic thermodynamic studies using modified cyclodextrins has been reported.[6f,g,7]

We have therefore collected data for a comparative study of the formation of inclusion complexes between two different hosts as native β-cyclodextrin (**1**) and the mono-(6-amino-6-deoxy)-β-cyclodextrin (**2**) and some benzene derivatives (Fig. 1); aniline derivatives (**A**–**F**), and for comparison nitrobenzene (**G**), *p*-nitroethylbenzene (**H**) and *p*-nitroisopropylbenzene (**I**). The guests were chosen in such a way to have variations in molecular properties such as, for example, dipole moment, molecular volume, ability to act as hydrogen bond donor/acceptor, solvation. Binding constants were measured spectrophotometrically at 298 K in phosphate buffer aqueous solution at pH 6, 8 and 11. Such values were chosen in order to avoid acid catalyzed hydrolysis of the host, and because **2** is allowed to pass from a medium in which it is present almost as free base to a medium in which it is present almost as its conjugate acid ($\mathbf{2}H^+$). We have also used molecular mechanics (MM2/QD) models in order to investigate molecular interactions in inclusion complexes of cyclodextrins.

2. Results and discussion

In Table 1 we report the values of the binding constants for the different possible complexes between hosts **1** and **2** and the guests **A**–**G**. Binding constants are not particularly high, compared to literature reports for similar guests.[4] Furthermore, in some cases binding is so weak that we were not able to determine a true constant with the adopted method. In these cases we indicate generically that the constant is

Keywords: cyclodextrins; inclusion; molecular mechanics.

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0040–4020/01/$ - see front matter
PII: S0040-4020(01)00635-4

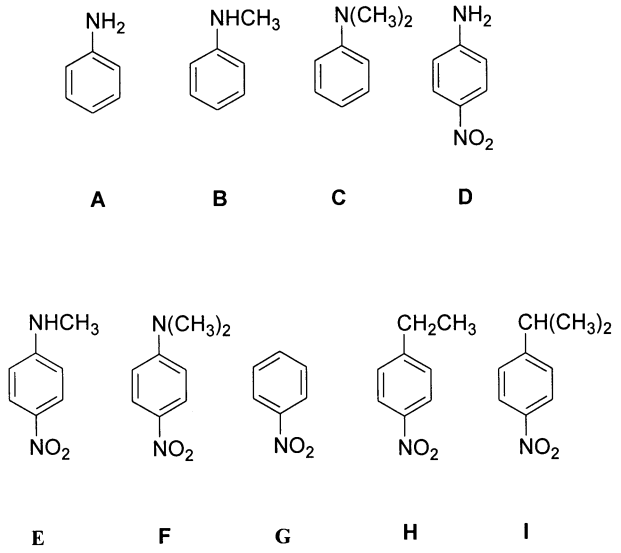

Figure 1. Guest molecules.

presumably less than the lowest value determined, i.e. 30 M^{-1}.

The inclusion constant values show that native cyclodextrin **1** is on the whole a better host than the aminocyclodextrin **2**. In fact, only at pH=11 do the two hosts have similar binding ability whereas for the other pH values, irrespective of the guest, **1** shows *K* values higher than **2**. Binding constants of **A**–**G** are influenced by medium acidity but different trends have been observed for **1** and **2**. In fact, the ability of **1** to include a guest seems to increase with medium acidity whereas **2** has the opposite trend. We can suppose that protonation of amino group in the cyclodextrin **2** causes negative host–guest interactions. On the other hand the lower values for **1** at pH=11 could be attributed to a partial deprotonation of secondary hydroxyl groups. The reduced binding ability of electrically charged cyclodextrins has been already noticed, and it has been attributed to a lack of desolvation of the host.[8] Recently, an active role for the buffer in this sense has also been pointed out; in fact anionic buffers (such as phosphate buffers) have been found effective in decreasing binding with cationic cyclodextrins (differently from non anionic buffers).[9]

With regard to the structure of the guest, data in Table 1 indicate that *p*-nitro-anilines **D**–**F** and -alkylbenzenes **H**–**I** are included more efficently than the other compounds. This seems to indicate that an increase in dipolar character of substrate causes a more favorable inclusion. However, also the different ability of guests to form hydrogen bonds with cyclodextrin and water, respectively, as well as the hydrophobic properties of alkyl group of guests, seem to have a role in determining the strength of complexation. For cyclodextrin **2** these factors seem to compensate each other so, with the exception of pH 11, inside each of two series of amino derivatives **A**–**C** and **D**–**F** a similar tendency to inclusion is observed. For cyclodextrin **1** the binding constant values indicate a more complex situation. Aniline (**A**) and *p*-nitroaniline (**D**) seem to prefer, with respect to *N*-alkyl derivatives, the aqueous phase, this is probably a consequence of substrate–water hydrogen bonds being stronger than those substrate–cyclodextrin. The ability to form hydrogen bonds, as well as the different hydrophobicity could explain the different inclusion of **B** and **C**, the latter being more strongly bonded than the former. In order to explain the trend of binding constants of **E** and **F** with cyclodextrin **1** it is necessary that both formation of hydrogen bond and hydrophobic interactions are responsible for the inclusion process. The behavior of *p*-nitroalkylbenzenes **H** and **I** (for which the substitution pattern on the benzyl carbon atom is similar to one on the nitrogen amino atom in **E** and **F** respectively) indicates that, lacking the possibility of hydrogen bond interactions, the affinity for inclusion increases regularly with the hydrophobicity. A comparison among the binding constants of guests **E**, **F**, **H** and **I** points out the major role played by hydrogen bond donation in the inclusion process. Indeed, the host–guest complex is more stable for **E**, as a consequence of hydrogen bond formation, than **H**, vice versa, **I**, according to its higher hydrophobic character, gives a more stable complex than **F**, substrate lacking acidic hydrogen

Table 2. Calculated free energies of desolvation (HF/3-21G/COSMO) hydrophobic substituent constants for guests **A**–**I**

Guest	ΔG_{desolv} (kJ mol^{-1})	π
A	22.1	−1.23
B	21.0	−0.47
C	15.4	0.18
D	37.6	−1.51
E	36.5	−0.75
F	28.7	−0.10
G	17.2	−0.28
H	15.9	0.74
I	15.3	1.25

Table 1. Binding constants for cyclodextrins **1** and **2** at various pH values

Guest	*K* (mol dm^{-3})					
	1 at pH			**2** at pH		
	6	8	11	6	8	11
A	<30	<30	<30	<30	<30	<30
B	60±20	40±10	<30	<30	<30	<30
C	150±30	85±40	100±15	<30	<30	100±15
D	380±40	350±30	340±30	160±25	250±30	330±30
E	1080±80	800±80	560±60	190±80	210±80	510±60
F	710±50	660±70	580±40	180±50	240±50	550±40
G	40±10	30±10	30±10	30±10	40±10	68±16
H	400±160	240±40	400±160	170±35	170±35	300±100
I	1450±65	1100±250	1100±130	600±120	660±50	780±90

atoms. In order to have further insights into the relative importance of different factors implied in the inclusion process, we used computational tools.

In the first instance we paid attention to the guest–solvent interactions. In Table 2 we report the free energies of solvation energies for our guests, calculated by means of ab initio HF/3-21G/COSMO[10] method, as well as hydrophobic substituent constants π.[11]

We can immediately notice a substantial lack in correlation between solvation energies and binding constants: despite their higher solvation energies *p*-nitroanilines **D**–**F** are better included than anilines **A**–**C**; *p*-nitroalkylbenzenes **H**–**I** appear to be less solvated than the corresponding *p*-nitroanilines, but are more solvated than anilines **A**–**C**, and show about the same solvation energy, in disagreement with the very favorable inclusion of **I**. Furthermore, both *p*-nitroaniline **D** and nitrobenzene **G** are more strongly solvated than dimethylaniline **C**, but binding constants, for cyclodextrin **1**, increase in the order **G**<**C**<**D**. Alternatively we tried to evaluate the interactions between guests and their environment by means of the hydrophobic substituent constants. This approach should have the advantage of considering the different behavior of the guest within the water pool and the hydrophobic host environment. No significant correlation between binding constants and hydrophobic substituent constants may be found; in particular the model fails in predicting the correct affinity order for *p*-nitroanilines, and also binding towards dimethylaniline **C** and nitrobenzene **G** is uncorrectly predicted to be too favorable. We may conclude that desolvation of the guest alone is unable to explain the relative stability of our complexes.

We attempted to rationalize the data collected in Table 1 correlating the logarithms of binding constants by means of single (π) or dual parameters (π and $\Delta G^{\circ}_{\mathrm{desolv}}$) relationships but bad results were obtained in both cases.

Nevertheless, desolvation also concerns the host. The extent of its internal desolvation is a function of the volume actually occupied by the guest and its hydrophobic properties. Molecular dimensions are a factor which has been claimed in order to rationalize the behavior of homologous series of linear guests (such as aliphatic alcohols or carboxylic acids[12]), whose binding constants approximately triple for the addition of a methylene group in the structure. For compounds **A**–**I** a similar trend is observed only for **H** and **I** and in some cases for anilines **A**–**C**. By contrast the behavior of nitroanilines is not so simple. The binding constant for **E** is actually about three times as much as that for **D**, but a similar increase is not found on passing from **E** to **F**. It should also be noticed that the enormously increased affinity of **D** with respect to **G**, cannot be clearly attributed to an increase of guest dimensions related to the introduction of the amino group on the guest structure. Indeed, the amino group cannot be compared to a methyl (or better a methylene) group because it is less effective in expelling water molecules from the CD cavity, owing to its polarity and its possibility to act as a hydrogen bond donor/acceptor. In other words the effects on guest binding deriving from the amino and the nitro groups do not seem simply 'additive', but reinforce each other as they act synergically on the electronic distribution of the molecule giving rise to a high dipole moment.

Thus polar effects seem better candidates to explain our data. The 'polarity' of the CD cavity has been claimed and predicted theoretically for almost a decade.[13] Polarity is oriented in such a way to have its positive side corresponding to the zone of the primary hydroxyl groups, and the negative side at the level of the secondary hydroxyl groups. In response, a suitable polarity in the guest molecule seems an important requisite for binding. This idea poses a question about the possibility of quantitative evaluation of specific host–guest interactions. It must be stressed that protonation of the amino group of **2** or deprotonation of secondary hydroxyl groups causes an increase in the polarity of host, therefore the more polar guests should be included more efficiently unless the charged group binds more strongly the water molecules of cavity. In order to evaluate quantitatively the host–guest interactions, we used molecular mechanics calculations based on the MM2[14] force field to elaborate suitable models of our complexes as isolated species in the gas phase. We took into account three possible hosts, namely **1**, **2**, and $\mathbf{2}H^{+}$. From a structural point of view, models predict (in agreement with the above discussion) that the guests accomodate themselves in the host cavity in such a way to bear the negatively polarized nitro group towards the primary rim of the host, while the amino group (positively polarized) prefers the opposite side. In this manner the amino group of **A** (**D**) and **B** (**E**) can act: as hydrogen bond donor towards the secondary hydroxyl groups; as hydrogen bond acceptor through the nitrogen atom. This latter interaction is the only one possible for amino group of **C** (**F**). Furthermore, the nitro group can easily act as a hydrogen bond acceptor toward the primary hydroxyl groups of the host.

In Table 3 the energies associated with the binding interaction are reported.

Quantitative correlation between calculated energies and experimental data is questionable. Actually we find fair 'by-group' linear correlations if we take into consideration each log *K* series for a given neutral host and pH value. Models predict quite correctly the observed inclusion trends, but strangely seem to overstimate the stability of complexes with nitrobenzene **G**. A more detailed analysis reveals that van der Waals and electrostatic interactions (hydrogen bond contributions are not explicitly considered by the method used but we think that the electrostatic interactions reflect although approximately the ability of a group to form hydrogen bond) are the more important contributions to complex stability. In particular van der Waals interactions appear much more important (by about 60 kJ mol^{-1}) for anilines **A**–**C** than for other guests; different dipolar and electrostatic contributions are predicted to be destabilizing for anilines and strongly stabilizing for *p*-nitro-anilines/alkylbenzenes. The particularly high electrostatic contribution for the interaction of **E** with neutral guests should be noticed.

However no general correlation can be constructed. In particular, examining data for **2** we find that the complexes with

Table 3. Calculated MM2 energies for inclusion complexes between hosts **1**, **2**, and $\mathbf{2}H^+$ and guests **A–I**

Host	Guest	$E_{ster.}$[a] (kJ mol^{-1})	$\Delta E_{ster.}$[b] (kJ mol^{-1})	ΔE_{strain}[c] (kJ mol^{-1})	ΔE_{vdW}[d] (kJ mol^{-1})	$\Delta E_{est.}$[e] (kJ mol^{-1})
1	**A**	264.7	−92.2	−12.6	−118.1	38.7
	B	275.6	−96.5	−3.9	−123.0	30.6
	C	286.2	−109.2	14.0	−141.6	18.5
	D	255.1	−112.0	−5.9	−48.3	−57.6
	E	251.5	−129.7	−1.4	−59.9	−68.2
	F	264.3	−139.3	−0.2	−70.6	−68.2
	G	260.2	−117.3	−1.6	−46.0	−68.1
	H	244.1	−135.2	−2.6	−67.1	−65.3
	I	240.7	−143.9	−2.7	−75.0	−65.8
2	**A**	257.9	−95.0	−19.3	−114.8	39.0
	B	257.1	−111.1	−20.6	−128.9	38.4
	C	274.7	−116.7	−13.7	−133.9	30.8
	D	242.8	−120.3	−15.6	−52.4	−48.4
	E	249.4	−127.7	−8.7	−72.7	−46.3
	F	260.9	−138.8	−17.9	−80.7	−40.2
	G	257.2	−116.3	−17.5	−36.1	−62.7
	H	245.6	−129.7	−10.6	−73.5	−45.2
	I	235.6	−144.9	−19.3	−69.8	−55.8
$\mathbf{2}H^+$	**A**	210.5	−87.9	21.4	−119.6	10.3
	B	207.0	−106.7	16.5	−136.3	13.1
	C	214.5	−122.5	16.0	−153.3	14.7
	D	115.2	−193.4	23.1	−88.4	−128.3
	E	157.8	−164.9	29.3	−71.8	−110.0
	F	168.9	−176.4	19.2	−64.6	−131.0
	G	128.1	−190.9	24.2	−101.9	−125.8
	H	160.1	−160.8	26.3	−73.0	−114.1
	I	155.5	−170.6	18.8	−73.5	−115.9

[a] MM2 steric energy of the inclusion complex.
[b] Stabilization energy of the inclusion complex. Calculated as $\Delta E_{ster.}=E_{ster.}(cplx)-E_{ster.}(guest)-E_{ster.}(host)$.
[c] Contribution to $\Delta E_{ster.}$ relative to steric (bond length, angle and dihedral) strain.
[d] Contribution to $\Delta E_{ster.}$ relative to van der Waals interactions.
[e] Contribution to $\Delta E_{ster.}$ relative to electrostatic (dipole and charge) interactions.

the protonated host $\mathbf{2}H^+$ are predicted to be more stable than those with **2**, in striking disagreement with experimental findings. Actually our models, elaborated as isolated molecules, allow us to evaluate only the interaction between 'naked' host and guest, and suffer for the absence of any explicit solvent environment. Indeed the slopes of the correlations show clearly a sort of 'levelling effect' attributable to the medium. It should be also noticed that no entropic effect is kept into account by calculations. However, this could be unimportant simplification if 'enthalpy–entropy compensation' effect is operative. Indeed, in this case the entropic term is linearly correlated to binding energy.[6] The entropic term has also been found unimportant for several classes of compounds when very similar averaged unit variations in ΔG° and ΔH° have been calculated by effect of adding a methylene to guest. For example,[4] in the case of β-cyclodextrin, the averaged unit increments in ΔG° and ΔH° are -2.8 and -3.3 kJ mol^{-1}, respectively. This clearly indicates that entropic term can control the ultimate stability of the complex but the effect should be nearly constant for similar compounds. When it is not possible to neglect the entropic term, only the Gibbs energy values can give the correct indication of relative stability of adducts. Our results also show how the subtle interplay of different and contrasting effects concurs in determining the effective stability of the inclusion complex. Anyway, specific interaction effects related to the structure and the electronic properties of the guest are quite well reproduced by MM2 calculations and appear, at least within homogeneous series of complexes, the main source of thermodynamic stability.

3. Conclusions

Data reported in this work show that the inclusion process depends strongly on the host structure, in our case substitution of a primary hydroxyl group for an amino group decreases the ability of host to include a guest. Finally, it seems that for the substrates examined there is no obvious hierarchy among the factors (except for the not very important steric strain) that govern inclusion process.

4. Experimental

4.1. Materials

Mono(6-amino-6-deoxy)-β-CD **2** was prepared according to literature reports;[15] β-CD **1** (Fluka) was used as such without further purification. Samples of **1** and **2** for binding constant measurements were dried before use, keeping them for three days in desiccator in vacuo over phosphorus pentoxyde at 65°C, and were then stored in the same apparatus at 40°C. Commercial products **A**, **B**, **C**, **G**, **H**, and **I** (Aldrich, Fluka) were purified by distillation immediately before use. Commercial **D** (Aldrich) was purified by crystallization; **E** and **F** were prepared and purified according to literature reports.[16] Stock phosphate buffer solutions were prepared according to literature reports and used within a few days, after checking the real pH value with a PHM82 Radiometer equipped with a GK2401C combinated electrode. Freshly double-distilled decarbonated water was

used for the preparation of the buffers, which were used as solvents for the preparation of the measurement solutions.

4.2. Measurement of binding constants

Solutions for measurements were prepared at a fixed concentration of guest (usually about 20 μM) and at a concentration of host ranging from 0 to about 6 mM. UV–vis spectra were recorded at 298±0.3 K on a Beckmann DU-7 spectrophotometer, and presented good isosbestic points. A suitable wavelength was chosen after recording a 'difference spectrum' by comparison of the samples without cyclodextrin and with the highest cyclodextrin concentrations. The absorbances of the different solutions at the work wavelength were processed by the method reported by Benesi–Hildebrand.[17]

4.3. Calculations

HF/3-21G/COSMO calculations were performed by means of the Gaussian 98[18] software from the Gaussian Inc.; MM2 calculations were performed by means of the CS Chem3D Pro™ 5.0 software package from CambridgeSoft Corporation. Models of the hosts and of their complexes were elaborated with the aid of the 'Quenched Dynamics' (QD) method as reported by Lipkowitz.[19] The behavior of a suitable starting model of the complex at 300 K is simulated by molecular dynamics for a period of 1200 ps. Structures are sampled from the simulation pool and left to undergo full geometry optimization. In this way, only a limited number of energy minima are found. Data in Table 3 refer to the absolute minimum found for each complex.

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