BIOORGANIC CHEMISTRY **12**, 130–140 (1984)

Binding to Cyclodextrins: An Interpretive Model

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Received July 18, 1983

A model is presented for the interpretation of cyclodextrin inclusion complex binding constants. The binding process is broken down into several steps and various aspects of the process are examined, the importance of nonbonded interactions and solvation processes being reiterated. In the context of the breakdown given here, mass differences in the guest molecule are shown to affect significantly the contributions from several of the steps. In addition, the importance of the "tightness" of the guest–host fit is illustrated. Estimates of the various contributions to the value of the binding constant are given for complexes of α-cyclodextrin with an azo dye and with methanol.

INTRODUCTION

Cyclodextrins have been the subject of so much active investigation that they hardly need introduction (*1*). Their utility as artificial enzymes is quite apparent and has been well documented by Breslow (*2, 3*). Their ability to mimic enzymes, of course, is due to the presence of a cavity of appropriate size in the sugar and the presence of hydroxyl groups on the periphery of the cyclodextrin, which can serve as catalytic groups or as points of attachment for catalytic groups or orienting groups. The presence of the cavity allows the formation of inclusion complexes, some of which have commercial potential (*4*).

The majority of the studies of the cyclodextrins have been directed toward an understanding of their catalytic ability, including efforts to modify the sugar chemically to improve catalytic power. The nature of the binding process itself has received less attention. The process has been described as including conformational changes, hydrophobic interactions, and Van der Waals interactions (*4*), but these descriptions have largely been inferred from the nature of the complexes formed and the geometries adopted by the complexes in the solid state as deduced from crystalographic studies (*5*). A more rigorous attempt to examine the binding process (*6*), which is flawed by an erroneous estimate of the change in the number of vibrational degrees of freedom during the complexation process, illustrates the difficulties involved and the assumptions needed to account for the role of the solvent. In this paper a breakdown of the binding process is presented which clearly isolates terms which are readily calculated (or at least estimated) and which clearly define the solvation part of the process, allowing the free energy contribution for the solvation term to be estimated from equilibrium constant data. The separation into individual contributions has some similarity to the one already

0045-2068/84 $3.00

given (*6*), since both depend on statistical mechanical formalisms. However, the approach presented here differs in many details and isolates the solvation aspect of the binding process from all other contributions. By avoiding a too detailed description of solvation, a picture emerges which allows a more ready comparison with experimental results.

THE STATISTICAL THERMODYNAMICAL MODEL

Consider the reaction for the formation of a cyclodextrin complex, that is

$$CD + X \rightleftharpoons CD \cdot X \qquad [1]$$

where CD represents cyclodextrin, X the included molecule, and CD · X the complex. (While the description being developed here is aimed at a discussion of the formation of cyclodextrin complexes, the procedure can be applied to other similar equilibria.) The criterion for equilibrium is

$$\mu_{CDX} - \mu_{CD} - \mu_X = 0 \qquad [2]$$

where μ_i is the chemical potential of species i. Now, the expression for the chemical potential of a solute in a very dilute solution can be obtained from Hill's treatment of the McMillan–Meyer solution theory (*7*), namely

$$\mu_i = RT(V\gamma_i^0/Q_i) + RT\ln C_i - RT\ln(1000/N_0). \qquad [3]$$

Here C_i represents the molarity of species i, N_0 represents Avogadro's number, and the third term on the right arises from a conversion from density units to molarity units. Q_i is the gas-phase partition function for an isolated molecule of type i. γ_i^0 is given by

$$\gamma_i^0 = Q_i\psi_0/\psi_1, \qquad [4]$$

where ψ_0 is a grand partition function, the sum being over solvent molecules and refering to pure solvent; and ψ_1 being the same except that it refers to solvent containing one solute molecule.

The use of a model involving grand partition functions seems to lead to an insuperable computational obstacle given the current status of aqueous solution theory. However $1/\gamma_i^0$ has an additional interpretation (*7*), namely, it is the equilibrium constant for the process

$$\text{solute in gas} \rightleftharpoons \text{solute in solution.} \qquad [5]$$

Thus

$$\Delta G_i^0(\text{solvation}) = RT\ln\gamma_i^0. \qquad [6]$$

(The original definition of γ_i^0 as included in Eq. [3] was based on standard states of unit density (*7*) for both phases. This is important when it is realized that γ_i^0 is a Henry's law constant, the latter often being defined in other units.) Thus, while γ_i^0 may not be readily estimable, it at least has a simple interpretation.

Substituting from Eq. [3] into Eq. [2] leads to, after some rearrangement,

$$RT\ln K_A = -RT\ln(1000/N_0) - RT\ln(\gamma_{CDX}{}^0/\gamma_{CD}{}^0\gamma_X{}^0) - RT\ln(Q_{CD}Q_X/VQ_{CDX}). \quad [7]$$

Here K_A is the equilibrium constant for Eq. [1] using molarity concentration units.

Now Q_i, as noted earlier, is the gas-phase partition function of species i and can be given by

$$Q_i = Vq_i^{\text{int}}/\Lambda_i^3, \quad [8]$$

where V/Λ_i^3 is the translational partition function. Λ_i^3 is given by

$$\Lambda_i^3 = (h^2/2\pi mkT)^{3/2}. \quad [9]$$

q_i^{int} is the partition function for internal motion, including rotational, vibrational and electronic motion. To a fair approximation, q_i^{int} can be factored into terms for each of the motions, under the assumptions that they are independent. Thus

$$q_i^{\text{int}} = q_i^{\text{rot}}q_i^{\text{vib}}q_i^{\text{elec}}. \quad [10]$$

Expressions for each of these can be obtained from any standard text of statistical thermodynamics (*7*). We have

$$q_i^{\text{rot}} = (\sqrt{\pi}/\sigma)(8\pi^2kT/h^2)^{3/2}\sqrt{I_AI_BI_C} \quad [11]$$

$$q_i^{\text{vib}} = \sum_{i=1}^{3N-6} e^{-\theta/2T}/(1 - e^{-\theta/T}) \quad [12]$$

and

$$q_i^{\text{elec}} = e^{D/RT} \quad [13]$$

Here σ is the symmetry number of the molecule, I_A, I_B, and I_C are the principle moments of inertia; θ is proportional to the normal vibrational frequency; and D is the (positive) energy required to dissociate a molecule into its constituent atoms. In adopting Eq. [12], harmonic behavior is being assumed. As will be clear further on, this will be adequate for the purposes at hand, although Eq. [12] can be replaced by a more accurate expression if this is warranted. After suitable substitution one arrives at

$$RT\ln K_A = -RT\ln(1000/N_0) - \Delta\Delta G^0(\text{solv}) - \Delta G^0(\text{trans}) - \Delta G^0(\text{rot}) - \Delta G^0(\text{vib}) - \Delta G^0(\text{elec}), \quad [14]$$

where

$$\Delta\Delta G^0(\text{solv}) = RT\ln(\gamma_{CDX}{}^0/\gamma_{CD}{}^0\gamma_X{}^0) = \Delta G_{CDX}{}^0(\text{solv}) - \Delta G_{CD}{}^0(\text{solv}) - \Delta G_X{}^0(\text{solv}) \quad [15]$$

and

$$\Delta G^0(\text{trans}) = RT\ln(\Lambda_{CDX}{}^3/\Lambda_{CD}{}^3\Lambda_X{}^3) \quad [16]$$

The expressions for ΔG^0 for rotational, vibrational, and electronic motion can be expressed in terms of Eqs. [11]–[13], but the latter two can be somewhat simplified given certain assumptions.

First consider the vibrational motion of the molecules involved. In the separate reactants, CD and X, there are $3N_{CD} - 6$ and $3N_X - 6$ normal modes. In the complex, there are a total of $3(N_{CD} + N_X) - 6$ normal modes, so that, in going to the complex, an additional six vibrational modes are gained. These clearly come from the three translational and three rotational modes lost on complex formation. In the formation of the complex, no covalent bonds are formed or broken. As a working hypothesis it can be assumed that the vibrations existing in the separated molecules will also exist in the complex, and terms arising from these vibrations will cancel out when calculating contributions to K_A. The six "vibrations" remaining then refer to the motion of the guest relative to the host. The vibrational contribution then becomes

$$\Delta G^0(\text{vib}) = -RT \sum_{i=1}^{6} \ln q_i^{\text{vib}}, \qquad [17]$$

where the sum is only over the six special guest–host vibrations.

The electronic motion term is better considered as a dissociation energy term. It can be treated in the same way as the vibrational term. Since the dissociation energy refers to the energy it takes to remove all of the atoms to infinity, and since there are no covalent bonds in the complex which are not present in the separate molecules, the only contribution to K_A from dissociation energy will be due to the energy required to separate the guest from the cavity of the host. After consideration of the location of zero point energy one has,

$$\Delta G^0(\text{elec}) = -D \qquad [18]$$

where D is the (positive) energy required to separate the guest from the cavity of the host.

EVALUATION OF TERMS

Having set down expressions for the various contributions to $RT\ln K_A$, there remains the task of estimating each of the terms.

The translational term contains only the masses of the species involved and can be evaluated with little difficulty.

In order to evaluate the rotational contribution, the principal moments of inertia are needed. In order to obtain these, the geometries of the cyclodextrin, guest, and complex are required. In this work, geometries are obtained as follows. For the cyclodextrin, the geometry of the acetate complex (*8*) as determined by X-ray methods is adopted. Missing hydrogen atoms are placed on the hydroxyl groups in a fashion consistent with acceptable bond angles and bond lengths (*9*). In cgs units, the moments turn out to be 3.93×10^{-36}, 2.6×10^{-36}, and 2.47×10^{-36}. For comparison, the moments obtained using the geometry of the hydrate (*10*), which is considerably distorted from that of the more symmetrical acetate complex, are 4.12×10^{-36}, 2.74×10^{-36}, and 2.31×10^{-36}. The geometries of the guest molecules considered here, namely an azo-dye and methanol, were built up from

acceptable literature values of bond angles and bond lengths (*9*). In the case of the dye, the structure of azobenzene (*9*) was used to define the skeleton of the dye. In order to calculate the moments for the complex, it was necessary to insert the guest in the cavity of the cyclodextrin, the latter assumed to have the geometry of the acetate complex. A procedure (to be described further on) designed to calculate the energy of interaction between the guest and host yielded the geometry of most favorable energy. In the case of the dye as guest, the fit was "tight" so that there was little flexibility as to possible orientations of the guest within the cavity. In the case of the smaller methanol molecule, the moments were largely determined by the large cyclodextrin and were relatively insensitive to the placement of the guest.

The energy of interaction of the guest within the cyclodextrin included a contribution from van der Waals forces and a contribution from electrostatic forces. The potential function was

$$D = \sum (A_{ij}/r_{ij}^{12}) - \sum (B_{ij}/r_{ij}^{6}) + c \sum z_i z_j / r_{ij}. \qquad [19]$$

The interaction between every atom on the guest and every atom on the host was included. The parameters A_{ij} and B_{ij} describing the van der Waals interactions were taken from the literature (*11*). The partial charges, z_i and z_j, were calculated using the program CNDO (*12*). In the case of cyclodextrin, the large number of atoms caused computer usage time to be excessive so that partial charges were calculated for glucose and these, after a slight fractional adjustment to maintain an overall charge of zero, were applied to the cyclodextrin. Determining the charges for the two-unit sugar, maltose, in the configuration that it would have as part of the cyclodextrin molecule, gave the same charges.

The energy was calculated by orienting the cyclodextrin such that its glycosidic oxygens were in the x–y plane with opposite glycosidic oxygens on the x axis and the sixfold rotation axis corresponding to the z axis. The guest was placed at various positions on the z axis and rotated about the y axis until an angle of rotation giving the lowest energy was found. While this procedure does not sample all possible geometries, it is expected to give a reasonable estimate of the minimum energy in the case of dyes as guests for the following reasons. The initial placement of the guest orients the aromatic rings such that the planes of the rings are on the line connecting opposite glycosidic oxygens. This orientation gives the fit with the least steric interactions. A rotation of the aromatic rings by 15° points them toward methylene hydrogens within the cavity of the cyclodextrin, these latter protruding into the cavity more than the glycosidic oxygens. Although the steric requirements are less stringent in the case of methanol, no attempt was made to search all possible geometries in view of the fact that the calculation of the vibrational contribution described next has a high uncertainty.

An accurate calculation of the vibrational contribution from vibrational frequencies demands knowledge of the interaction energy between the guest and host as a function of the six coordinates describing the relative motion of the guest and host. The examination of this relative motion has not been extended far enough to allow this calculation. It is recognized that the motion can be far from harmonic

and may really involve what might better be described as hindered rotation. However, in order to illustrate the utility of the model proposed here and to draw some tentative conclusions about the binding process, one proceeds by making some assumptions. First, one assumes that Eq. [12] can be used in Eq. [17], i.e., that the motion is harmonic. Then it is assumed that, for a given complex, all six frequencies are the same and low (of the order of a few wavenumbers) and then makes reasonable guesses of their values. Here one is guided by what one already knows about vibrational frequencies from infrared spectroscopy. In the two cases considered here, a frequency of about 1 cm^{-1} was assumed for methanol and 10 cm^{-1} was assumed for the azo dye. Although these values are admittedly guesses of the desired quantities, they are reasonable. First, the values are characteristic of weak interactions. (Note that the vibrational frequency of the I_2 molecule is 215 cm^{-1}.) Second, the value for methanol should be lower than that for the dye since methanol, because of its small size, is expected to have a greater range of motion within the cavity than the dye. However, frequencies do depend upon both force constants (that is, the curvature of the potential function in the vicinity of its minimum) *and* the masses of the moving species. Thus, although methanol is expected to have a lower value for the force constant because of its relatively larger range of motion compared with that of the dye, its lower mass would tend to offset this, drawing the two frequencies toward each other. In order to test the sensitivity of the conclusions to the guessed frequencies, results for a second guess will also be calculated. In this second case, a higher frequency of 100 cm^{-1} will be assumed, and it will be further assumed that it is the same for both the dye and the methanol. The two sets of guesses will be refered to as case 1 and case 2. The value of 100 cm^{-1} can safely be taken as an upper limit. Since the main thrust of this work is to illustrate the factors that are important in analyzing the binding process, and not to calculate any of the terms with great precision, it will be seen that no significant differences in conclusions will arise in going from case 1 to case 2.

DISCUSSION

The azo dye studied here is depicted in Fig. 1. The results of the calculation are given in Table 1. Association constants were taken from the literature (*13, 14*) and refers to α-cyclodextrin.

The results presented here can be applied to two different types of questions. The first question, which views the binding process in an absolute sense, is, Why do complexes form at all? What is the nature of the "bond" holding the complexes together? The second question is a relative one, that is, Why is this complex more stable than that one?

In attempting an answer to either sort of question, a dissection of the process under study is necessary. The one given here, being supported by well-established statistical thermodynamic theory, is convenient in that it isolates for discussion two aspects of the binding process currently considered important, namely solvation effects and nonbonded interactions. Consider first that the question of why

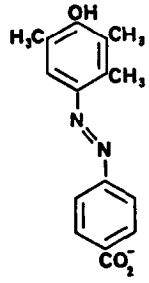

FIGURE 1

complexes are formed at all. An examination of Table 1 for either guest shows that the overall ΔG^0 (the sum of the five energy terms given and the constant term, $RT\ln(1000/N_0)$) is a combination of large terms with opposite signs. No one term can be isolated as the "cause" of the binding process. Attention may be called, perhaps, to the relatively large nonbonded energy, −47.63 kcal/mol, in the case of the dye and ascribe the strength of the binding to this force. But such a statement can only be made in the context of the breakdown given here, and one then could be tempted to ascribe a significant, favorable contribution to binding from merely using molarity units simply because the last entry in the table is significant and favorable! (Actually, the last contribution can be discussed in terms of entropy changes in converting from one standard state to another. The intent here is simply to call attention to the pitfalls existing in a breakdown like the one given here.)

What role does solvation play in the binding process? The values of $\Delta\Delta G^0$(solv) given in the table suggest that changes in solvation work *against* the binding process. In fact, for case 1, the stability constant for the formation of the dye–α-cyclodextrin complex in the gas phase is a factor of 1.5×10^{26} times greater than that in water. For case 2, the factor is 2.6×10^{13}. Of course, $\Delta\Delta G^0$(solv) was

TABLE 1

	Dye	Methanol
K_A	1.24×10^3	9.31×10^{-1}
ΔG^0(tran)	37.51	35.77
ΔG^0(rot)	9.27	4.83
ΔG^0(vib)	−10.72(−2.41)	−18.96(−2.41)
$-D$	−47.63	−11.51
$\Delta\Delta G^0$(solv)	35.70(27.39)	18.29(1.71)
$RT\ln(1000/N_0)$	−28.35	−28.35

Note. K_A for the dye (units, M^{-1}) was taken from Ref. (*13*) and that for methanol was taken from Ref. (*14*). All other units are in kcal/mol. The last entry is included to allow comparison of terms. The entries in parentheses for vibrational and solvation terms refer to the case 2 choice of vibrational frequencies.

calculated using the experimental stability constant and the evaluated partition functions. The most uncertain term is ΔG^0(vib), based as it is on guesses of vibration frequencies. But in order for $\Delta\Delta G^0$(solv) to have come out equal to zero, a frequency greater than 3000 cm^{-1} would have been required in the case of the dye and one greater than about 300 cm^{-1} in the case of methanol, both values seeming more appropriate for stiff covalent bonds than for the loose oscillations expected in the cavity. (Recall the value of 215 cm^{-1} for the I_2 vibrational frequency.) Also, care must be exercised because $\Delta\Delta G^0$(solv) compares the free energy change occurring when 1 mol of guest *and* 1 mol of host are solvated with that occurring when only 1 mol of complex is solvated. The value of $\Delta\Delta G^0$(solv) thus reflects the disparity in the number of moles in the initial and final states.

A description of the solvation effect in terms of a hydrophobic effect can take place only if a definition of the hydrophobic effect is available. One such definition has been given by Ben-Naim (*15*), and can be adopted here and expressed in terms of quantities defined above. One has for ΔG^0(HI) (HI = hydrophobic interaction)

$$\Delta G^0(\text{HI}) = \Delta\Delta G^0(\text{solv}) - D. \qquad [20]$$

Using the data from Table 1 for case 1, one has ΔG^0(HI) = −11.93 kcal/mol for the dye and 6.78 kcal/mol for methanol. For case 2 one has −20.24 and −9.8 kcal/mol, respectively. To the extent that Ben-Naim's equation is applicable (he talks in terms of spherical molecules in contact and not inclusion complexes), the results are inconclusive because of the uncertainty from the unknown, and therefore guessed at, vibrational frequencies. However, it is quite possible that case 2 represents an overestimate of these frequencies and that case 1 is closer to the truth. If that were the case, then there is a favorable effect for the dye but not for the methanol. At any rate, that the binding to cyclodextrin is caused by hydrophobic interactions is not at all clearly established.

It has been said that the binding process is aided by the expulsion of high-energy water from the cavity and the release of bond angle strain that exists in the hydrated cyclodextrin. The description given here cannot confirm or deny these assertions for the simple reason that any contribution to the free energy of binding from these sources is buried within $\Delta\Delta G^0$(solv). An estimate of the importance of these effects demands a calculation of the individual solvation energies of the three species involved.

In view of all of the above, there seems to be no more reason to talk about a "bond" between guest and host than there is to say a "bond" is formed when a nonpolar molecule is extracted from water to a nonpolar solvent.

When it comes to comparing two complexes and deciding what makes one complex more stable than another, one again is confronted with the fact that no one factor is overwhelming in deciding stabilities. If one uses a scheme in which solvation and nonbonded interaction terms are isolated, then mere mass differences can be viewed as having a significant effect on determining the relative stabilities. Thus, for the complexes examined here, the two terms directly related to mass, that is, the translational and rotational terms, favor the methanol complex by a factor of 18.9 and 1.80×10^3 for each contribution. If the "size" of a molecule can be further considered roughly proportional to the mass, then the

vibrational part of the breakdown can be included in the mass effect. Note, in case 1, that ΔG^0(vib) for methanol is more negative than that for the dye. The smaller molecule has more freedom to move in the cavity. Thus, by means of the vibrational term, a decrease in the size of the molecule leads to an increase in the stability of the complex. Since the translational, rotational, and vibrational terms all work in the same direction, their effects can be lumped together, favoring the methanol complex over the dye complex by a factor of 3.7×10^{10} in the stability constants. Even in case 2, however, where the vibrational frequencies are assumed to be the same, the smaller molecule is still favored by a factor of 3.4×10^4.

Now, since the mass effects favor the smaller molecule, and since the experimental data shows the larger molecule to have the greater stability, one must look to the other terms for the reversal in order. Since the solvation term also favors the methanol complex in the two cases considered, the differences in stability clearly lies in the nonbonded interactions which, in this case, favor the dye by a factor of 3.0×10^{26}. One can conclude that differences in nonbonded interactions have a significant role in deciding the differences in stability. Even here one must be cautious because the Van der Waals term increases as the number of atoms in the guest increases. Thus, even this term can be considered a function of the size of the molecule yielding a contribution to the stability in a direction to cancel the earlier discussed mass effects. The solvation effects can also be considered a function of size if one realizes that the free energy of solvation includes a contribution to the creation of a cavity within the solvent. However, in view of the large number of polar groups involved and in view of the need to include possible conformational changes and high-energy water within the cavity of the cyclodextrin, one hesitates to relate the mass to the solvation term by any sort of proportionality. In any case, given all of the cancelling tendencies, it is no wonder that many cyclodextrin complexes have stability constants spanning a rather limited range of values.

Water is unique among solvents as being the medium in which complexation is principally observed. Its exceptional character can only be explained by an examination of the solvation terms with the realization that an increase in $\Delta\Delta G^0$(solv) by 5 kcal/mol is sufficient to reduce a stability constant by a factor of 2.2×10^4 which, in turn, is sufficient to cause a "nonbonding" situation experimentally. Strictly speaking, since $\Delta\Delta G^0$(solv) contains contributions from the solvation of all three species, it is not logically possible to ascribe the reduction of stability to a change in the solvation of the cyclodextrin alone. However, when one realizes that water retains its unique position among solvents in spite of the fact of the wide variety of guests studied, one is tempted to impute to the ΔG^0(solv) for cyclodextrin a large unfavorable change on going from water to any other solvent, large enough to counteract any favorable changes in the ΔG^0(solv) for the guest and complex that one might expect to encounter occasionally for some of the many guests studied. And this may well arise from the expulsion of high-energy water and a significant conformational change, but confirmation of this will require extensive analysis of the data by means of a model such as the one presented here.

Attention is called to what appears to be a miscount of vibrational degrees of freedom in an earlier paper (*6*). In the first step of their hypothetical process, two

water molecules are released from the cavity with accompanying gains of translational and rotational motion and loss of van der Waals and hydrogen bonding energy. Vibrational freedom of both water molecules was assumed constant. In fact, a total of 12 vibrational motions, which the included water molecules executed relative to the host, were lost upon removing them from the cavity. These overlooked degrees of vibrational freedom are not compensated for in the second step of the cycle, which brings two water molecules back into the solvent, nor are they compensated for by the inclusion of the guest, since the inclusion of the guest only involves six degrees of freedom. In the inclusion of the guest only a one-dimensional rotation is allowed, there being five vibrations not accounted for, and, as the entry in Table 1 shows, these motions can make a significant contribution to the binding free energy.

CONCLUSION

The intent of the analysis given here has been to point out factors that have to be considered in explaining the binding process. It has been shown that factors previously held to be important are important but only in the context of all of the steps that the binding process is factored into. Especially of note is the relatively uninteresting contribution to stability differences due to mass differences as contained in the translational and rotational terms. And while no one would want to explain stabilities in terms of "lightness" or "heaviness" in the same way as one would in terms of "hydrophobicity" or "polarity," it should be clear that any breakdown of the binding process into steps that reflect the latter will also include steps that reflect the former mass effects. Furthermore, whether or not these mass effects are cancelled partially or completely in other terms when considering the entire binding process, it should be clear that, given the artificiality of any breakdown of the binding process, no one step or collection of steps should be considered in isolation from the others. While the model confirms the importance of solvation and nonbonded interactions, it has also called attention to the importance of the fit between the guest and host as reflected in the vibration term. Although a reliable calculation of the latter may prove difficult, there exists the possibility of confirming the direction of trends by comparing calculated estimates of the vibrational term with experimentally determined "dynamic coupling coefficients" (*16*) and with results of Monte Carlo-type simulations. It is hoped that the steps outlined here can serve as a basis for continued analysis of the differences in stabilities of cyclodextrin complexes.

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