The Stability of Cyclodextrin Complexes in Solution

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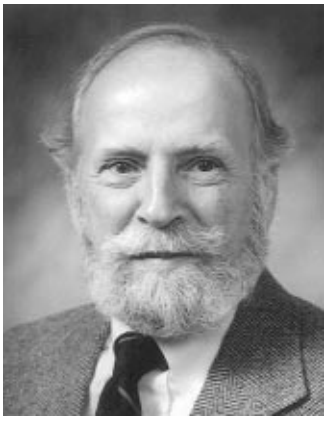
Contents



Kenneth A. Connors, a native of Torrington, CT, received the B.S. in pharmacy in 1954 from the University of Connecticut and the Ph.D. in pharmacy in 1959 from the University of Wisconsin, where he worked with Takeru Higuchi. After postdoctoral study with Myron L. Bender at Illinois Institute of Technology and Northwestern University, in 1962 he joined the faculty of the School of Pharmacy at the University of Wisconsin—Madison, where he has made his professional career. He has written the books *A Textbook of Pharmaceutical Analysis* (third edition 1982), *Reaction Mechanisms in Organic Analytical Chemistry* (1973), *Chemical Stability of Pharmaceuticals* (second edition 1986, with G. L. Amidon and V. Stella), *Binding Constants* (1987), and *Chemical Kinetics* (1990). From 1991 to 1993 he served as acting dean of the School of Pharmacy.

I. Introduction

A. The Cyclodextrins

A cyclodextrin (CyD) is a cyclic oligomer of α-D-glucose formed by the action of certain enzymes on starch. Three cyclodextrins are readily available: α-CyD, having six glucose units (and also named cyclohexaamylose or cyclomaltohexaose); β-CyD (seven units, cycloheptaamylose, cyclomaltoheptaose); and γ-CyD (eight units, cyclooctaamylose, cyclomaltoheptaose). CyDs with fewer than six glucose residues are too strained to exist, whereas those with more than eight residues are very soluble, difficult to isolate, and hardly studied to date. α-CyD, β-CyD, and γ-CyD are commonly referred to as the native CyDs. Very many covalently modified CyDs have been prepared from the native forms.

Compounds **1**−**3** are the chemical structures of α-, β-, and γ-CyD, respectively. The glucose units are connected through glycosidic α-1,4 bonds, as illustrated in **4**. The structural consequence of this bonding mode is the formation of a doughnut-shaped molecule having (for n glucose residues) one rim lined with n primary hydroxy groups, the other rim lined with $2n$ secondary hydroxy groups, and the interior of the cavity lined with (from the secondary hydroxy rim inwards) a row of CH groups (the C-3 carbons), then a row of glycosidic oxygens, and then a row of C-5 CH groups. The CyD molecule is often described as a torus, but is somewhat more realistically pictured as a shallow truncated cone, the primary hydroxyl rim of the cavity opening having a somewhat reduced diameter compared with the secondary hydroxy rim. (In some cases the torus may depart significantly from perfect symmetry.)

It is, of course, the possession of this cavity that makes the CyDs attractive subjects for study. The

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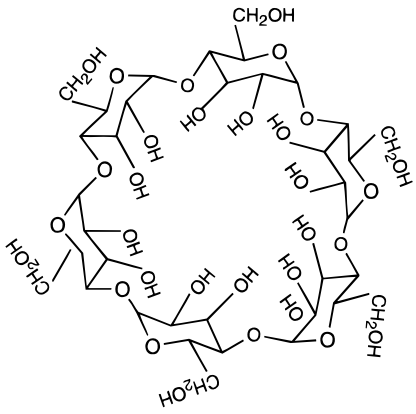

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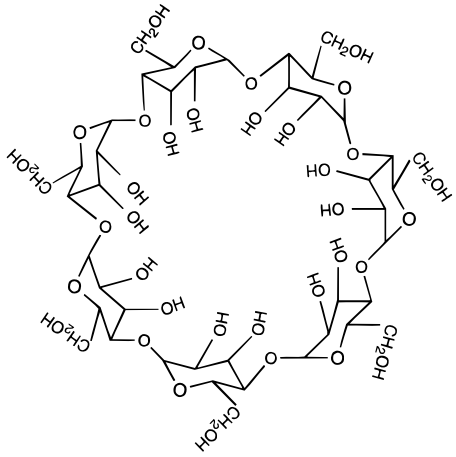

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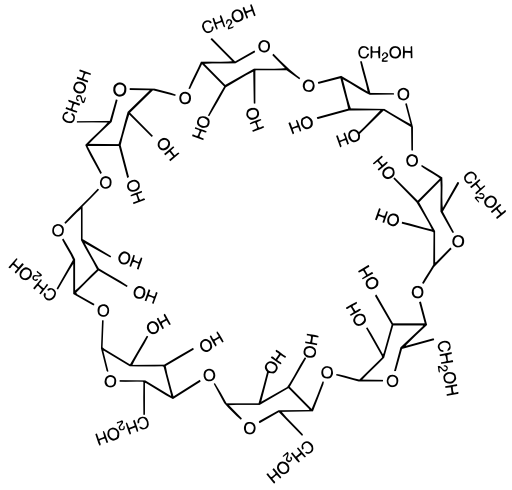

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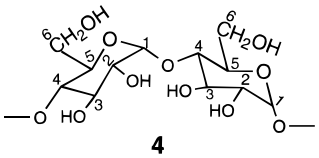

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CyD exterior, bristling with hydroxy groups, is fairly polar, whereas the interior of the cavity is nonpolar relative to the exterior and relative to the usual external environments, water in particular. These compounds have therefore been studied as "hosts" for "guest" molecules capable of entering (in whole or in part) the cavity and forming noncovalent host−guest inclusion complexes. (At one time there was resistance to the idea that one molecule might enter another molecule, but this issue has long been settled and it is now known that most, although not all, CyD complexes are appropriately described as inclusion complexes.)

Many questions have arisen about the complexing behavior of the CyDs, and this article deals with some of them. At the outset we present this question: do the three native CyDs constitute a monotonically graded series, whose behavior simply varies in quantitative ways as a consequence of their different cavity sizes; or are they so substantially different that they cannot usefully be regarded as closely analogous? Many authors have published studies on the CyDs on the premise that the CyDs constitute simple but realistic models of more complicated processes such as macromolecular hydration, hydrophobic protein interactions, and so on. It is therefore amusing that this "simple" model system is not yet well enough understood to provide much confident guidance for the interpretation of macromolecular phenomena.

B. Scope of This Review

This article treats the title subject, with attention given to other topics only to the extent that they are helpful to the central issue. Among the subjects not dealt with are the history, production, structure determination, conformational analysis, chemical modifications, and applications of the CyDs. Their uses as enzyme models will not be covered, nor will experimental methods for measuring complex stability. The citations to the literature support the subject of the title, but are not uniformly comprehensive throughout the review inasmuch as some supporting topics (such as complex structures and association−dissociation rates) could themselves form the subjects of comprehensive reviews. Only the three native CyDs, α-, β-, and γ-CyD, are included in the discussion, except as information on chemically modified CyDs may be pertinent to our subject.

Cyclodextrin chemistry has been repeatedly reviewed, so further reading in the topics not covered here is readily available. Book-length treatments have appeared at intervals,[1−6] and many shorter and more specialized reviews have been published.[7−25]

II. The Nature of Cyclodextrins

A. Physicochemical Properties

Table 1 lists some interesting properties of the native CyDs. The cavity dimensions given in the table are approximate, being composites resulting from a molecular modeling treatment of nearly 100 published X-ray structures of CyD hydrates and other complexes;[26] recall that the cavity diameter narrows on proceeding from the secondary hydroxyl rim to the primary hydroxyl rim, and of course within the cavity the van der Waals radii of the oxygens and hydrogens contribute further variability. Other properties have been measured, such as rate of acid hydrolysis,[31] molar volumes,[32] activity coefficients,[32] diffusion coefficients,[33] and solubility in dimethylformamide.[34]

Table 1. Some Physicochemical Properties of the Cyclodextrins

property	cyclodextrin α	cyclodextrin β	cyclodextrin γ	ref
no. glucose units	6	7	8	
empirical formula (anhydrous)	$C_{36}H_{60}O_{30}$	$C_{42}H_{70}O_{35}$	$C_{48}H_{80}O_{40}$	
mol wt (anhydrous)	972.85	1134.99	1297.14	
cavity length, Å	8	8	8	26
cavity diameter, Å (approx)	~5.2	~6.6	~8.4	26
α_D, deg	+150.5	+162.0	+177.4	8
heat capacity (anhyd solid), J mol^{-1} K^{-1}	1153	1342	1568	27
heat capacity (infinite diln), J mol^{-1} K^{-1}	1431	1783	2070	27
pK_a (25°)	12.33	12.20	12.08	28, 29
$\Delta H°$ (ionization), kcal mol^{-1}	8.36	9.98	11.22	28, 29
$\Delta S°$ (ionization), cal mol^{-1} K^{-1}	−28.3	−22.4	−17.6	28, 29
solubility (water, 25°), mol L^{-1}	0.1211	0.0163	0.168	30
$\Delta H°$ (solution), kcal mol^{-1}	7.67	8.31	7.73	30
$\Delta S°$ (solution), cal mol^{-1} K^{-1}	13.8[a]	11.7[a]	14.7[a]	30

[a] Mole fraction standard state.

Many of the quantities in Table 1 show an apparently regular trend in the series α-CyD, β-CyD, γ-CyD; the pK_a, enthalpies and entropies of ionization, and heat capacities behave in this way. The solubility behavior, however, is very different, with all of the CyDs being less soluble than are acyclic saccharides, and β-CyD being (apparently) an anomaly among the CyDs. The thermodynamics of solution show that the relatively low solubility of β-CyD is associated with both a less favorable $\Delta H°$ and a less favorable $\Delta S°$. These solubility results are one piece of information suggesting that the CyDs may not universally behave as a monotonically graded series.

The native CyDs all apparently undergo self-association in aqueous solution,[32,35] and Coleman et al.[35] have attributed the low solubility of β-CyD to the interruption by aggregated β-CyD, with its 7-fold symmetry, of the hydrogen-bond structure of water, the even symmetries of α-CyD and γ-CyD not behaving in this way. This explanation may not account for the relatively high solubility of δ-CyD, which contains nine glucose units.[8] Szejtli[36] proposes that the intramolecular hydrogen bonds of the β-CyD rim are responsible for its low solubility. Alkylation of β-CyD hydroxyls leads to increases in solubility, and this phenomenon has constituted one motivation for carrying out such chemical modifications.

The solubilities of most solid solutes in binary aqueous−organic solvent mixtures reveal a monotonic dependence on solvent composition, but several reports describe the appearance of maxima in the solubility of β-CyD in mixed solvents.[37−40] This phenomenon has been attributed to solvent−solute interactions or to inherent solvent behavior, for properties such as excess partial molar volume, ultrasonic absorption, and dielectric relaxation of the solvent mixtures themselves often show maxima. (Okada et al.[41] find apparently monotonic decreases of solubility of α-CyD, β-CyD, and γ-CyD in water−methanol solutions, and in this solvent system anomalous behavior, if present, is subtle.) It has recently been shown[42] that α-CyD exhibits solubility maxima in several water−cosolvent mixtures. Study of the solid phase in equilibrium with the solution phase revealed (in the water−2-propanol mixture) that, in the solid, the mole ratio of water to α-CyD changes from 6:1 in pure water to 3:1 in water−2-propanol mixtures, the attainment of the 3:1 ratio coinciding with the composition at which the solubility maximum was seen. Leiterman et al.[42] proposed that the unusual solubility behavior is the result of a change in the composition of the stable solid phase in these mixed-solvent systems.

Measured dipole moments of the CyDs have not been reported, but several calculated values are available. The results are highly variable. Kitagawa, Sakurai, and co-workers[43−45] based their calculations on published X-ray crystal structures of CyD complexes, and the resulting dipole moments are influenced by the guest. Very large moments, in the range 10−20 D, were obtained for the CyDs. These workers find that the CyD cavity is highly polarized. In the α-CyD:4-nitrophenol complex, the narrow (primary hydroxyl) end of the cavity possesses a positive potential, the secondary hydroxyl end a negative potential; yet the opposite polarity is found for the α-CyD:2 H_2O system.[44] Bakó and Jicsinsky[46] used AM1 calculations to find the CyD structure, deriving dipole moments of 7.06, 2.03, and 2.96 D for α-CyD, β-CyD, and γ-CyD, respectively; their calculated structures were similar to X-ray results, although some disagreement was noted in orientation of glucose units. Botsi et al.[47] calculated the dipole moment of β-CyD, obtaining 2.9 D when the primary hydroxy groups are perpendicular to the cavity axis and 14.9 D when they are parallel to the axis. In solution the orientation of these groups will be influenced by interaction with the solvent, so an intermediate value may be expected. (The dipole moment of D-glucose itself is quite large, experimental values of 8.0, 12.1, and 14.1 having been reported).[48]

B. Hydration

The CyDs crystallize from water as hydrates of variable composition. α-CyD is usually encountered as the hexahydrate, α-CyD·$6H_2O$, which can exist in crystal forms I and II,[49−52] but a third form, α-CyD·7.57 H_2O, has been crystallized from aqueous $BaCl_2$.[53] β-CyD exists as the undecahydrate, β-CyD·$11H_2O$, and as the dodecahydrate, β-CyD·$12H_2O$;[54,55] but these integral ratios are idealizations, the actual composition depending upon the relative humidity.[56,57] γ-CyD is sometimes described as an octahy-

drate, but it can crystallize with from 7 to 18 molecules of water.[26,37,58−61] δ-CyD has been crystallized as δ-CyD·13.75H_2O.[62]

α-CyD·6H_2O (Form I) has two water molecules in the CyD cavity and four molecules outside the cavity;[49,50] the positions of the two included molecules are fixed by hydrogen bonding to each other and to O(6) hydroxy groups. Form II of α-CyD·6H_2O has one water molecule inside the cavity.[52] In Form III, 2.57 molecules of water are found in the cavity, distributed statistically over four sites, with an occupancy of 0.64 per site.[53] The fixed location of cavity-bound water in α-CyD·6H_2O is unusual, the other CyD hydrates having their included water statistically distributed among alternate sites. Thus β-CyD·12H_2O has 6.5 water molecules distributed among eight sites,[54] and γ-CyD·13.3H_2O has 5.3 waters distributed among 13 sites.[58] A consequence of the hydrogen-bonding arrangement in α-CyD·6H_2O is that the α-CyD ring does not possess 6-fold symmetry, being "puckered", and therefore having a higher conformational strain energy than the hexagonally symmetrical conformation. The "relief of strain energy" accompanying the process of guest inclusion has been proposed as a driving force for complex formation; this hypothesis is treated in section VI.E. Form III is nearly symmetrical, so it is considered not to possess excess conformational strain energy.[53] The β-CyD and γ-CyD molecules are also close to symmetrical in their hydrate forms.

Table 1 shows that the enthalpies of solution of the CyD hydrates are endothermic; these values were obtained from measurements of the dependence of solubility on temperature. Calorimetric measurements of the enthalpies of solution of the anhydrous CyDs have been reported;[34,63,64] these are exothermic. (Such measurements must contend with the rate of hydration compared with the calorimetric time scale.) Combination of the two kinds of quantities yields the enthalpy of hydration,[63,64] which is exothermic. The energy of hydration per molecule of water for β-CyD appears to be a constant quantity for each molecule added (or lost in dehydration).[57,64] This seems remarkable considering that there are two "types" of water in the crystal structure, namely included water and interstitial water, and there is evidence that the cavity-bound water is lost first upon dehydration.[56,60] DTA thermograms[30] of β-CyD and γ-CyD hydrates give undifferentiated peaks beginning at 30 and 50 °C, respectively; α-CyD hydrate shows three endothermic peaks centered at 80, 106, and 129 °C.

NMR studies on hydrates of β-CyD and γ-CyD show that the ^2H exchange rates of water molecules and hydroxy groups are greater than 10^6 s^{-1} (the NMR time scale).[57,61] A neutron scattering study of β-CyD·11H_2O revealed two jump distances for H atom reorientation;[65] one of these describes jumps of hydroxy groups and water molecules over distances of about 1.5 Å, the other constitutes diffusive motion of water within the cavity over distances of about 3.0 Å. At room temperature both motions have rates of 2×10^{10} to 2×10^{11} s^{-1}.

Miyajima et al.[32] have concluded, on the basis of the sign of the temperature dependence of the viscosity *B* coefficients, that α-CyD and γ-CyD are both "structure-makers" in aqueous solution. Linert et al.[66] carried out Monte Carlo calculations on α-CyD and β-CyD (each with 503 water molecules) and, based on the resulting radial distribution functions, concluded that α-CyD leaves the water structure unaffected whereas β-CyD is a "structure-breaker". They suggest this as a reason for the peculiar solubility behavior of β-CyD.

C. Conformational Flexibility

Even a hard plastic space-filling molecular model of a CyD has some flexibility, and we may expect a real molecule to be yet more flexible and yielding, inasmuch as the plastic spheres representing van der Waals contacts are arbitrarily drawn cutoffs of a continuously graded electron density, so that the demarcation between molecule and not molecule is ill-defined. Of course the primary structure of a CyD (that is, the covalent bonding pattern), being essentially a cycle of cycles, imparts considerable rigidity to these molecules. But within the motional limitations imposed by this cyclic scheme of bonds there may be scope for significant conformational mobility, which is pertinent to the possible capability of a CyD cavity to accommodate itself to the spatial and electronic character of a wide variety of guests.

Saenger[67] has discussed conformational studies of the CyDs. The glucose units appear always to exist in the C1 chair conformation. The formation of a ring of hydrogen bonds between O(2)···O(3) tends to stabilize the CyD cycle. For a long while the CyDs were considered to be conformationally quite rigid, but this view is undergoing revision. Lichtenthaler and Immel[26] based molecular modeling studies on published solid-state structures of CyD hydrates, concluding that the solid-state conformations can be viewed as "snapshots of their overall shape in aqueous solution..." They find that γ-CyD forms almost perfectly symmetrical structures, whereas α-CyD and β-CyD have more flexibility.

It was pointed out in section II.B that α-CyD·6H_2O does not possess hexagonal symmetry in the solid state, one of the glucose units being tilted relative to the other five.[49,50] ^{13}C NMR[68] and calculational results[69] now suggest that in solution α-CyD is essentially symmetrical, at least on average. Molecular dynamics simulations on α-CyD[70] indicate considerable flexibility, with the possibility that the α-CyD may, to some limited extent, adapt its shape to the requirements of a substrate.[70b] Lipkowitz[71] and Wertz et al.,[72] with gas-phase calculations, find that the CyDs are conformationally flexible and that the most stable conformations are not highly symmetrical. The present position seems to be that in the solution phase the CyDs are fairly flexible molecules and explore a significant range of conformations, some of which depart considerably from the highly symmetrical extreme.

D. Polarity of the Cyclodextrin Cavity

In 1967 van Etten et al.[73] showed that the ultraviolet absorption spectrum of 4-*tert*-butylphenol in an aqueous solution of α-CyD closely matches its spectrum in dioxane. These authors did not explicitly

conclude that the polarity of the α-CyD cavity is similar to that of dioxane; rather they took the spectral coincidence as evidence that the aromatic chromophore was included in the ether-like cavity of the α-CyD. Uno et al.[74] concluded, on the basis of blue shifts in the spectra of amine *N*-oxides in the presence of CyDs, that the cavity environment is like methanol or ethanol, depending upon the probe. A series of 1,4-disubstituted benzenes gave no consistent spectral shifts in α-CyD solutions compared with spectra of these compounds in pure solvents, and it was decided that UV spectral probes cannot provide unambiguous evidence of the cavity polarity.[75] The spectrum of 1,4-dimethoxybenzene in 0.1 M aqueous α-CyD exhibits fine structure closely mimicking its spectrum in cyclohexane, and quite different from the nearly featureless bands in water or in dioxane.[75]

Many workers have relied on fluorescence spectroscopy to study CyD complexing, because fluorescence quantum yields are sensitive to the polarity of the probe's environment. Cramer et al.,[76] in an important paper in the CyD field, showed an enhancement in the fluorescence intensity of 1-anilino-8-naphthalenesulfonate in solutions of CyDs, with β-CyD and γ-CyD having more profound effects than α-CyD; this difference was attributed to the relative sizes of the guest and the CyD cavities and was consistent with inclusion of the probe molecule. Later authors have related fluorescent probe behavior in the presence of CyDs to cavity polarity,[77,78] in some cases comparing the cavity environment with that of a pure organic solvent, in other cases attempting to attach a quantitative measure of polarity to the CyD cavity. Thus Ramamurthy and Eaton[79] found that the excited-state lifetime of β-naphthol is 7.2 ns in the presence of β-CyD, to be compared with lifetimes of 5.9 ns in methanol, 8.9 ns in ethanol, and 13.3 ns in cyclohexane; they conclude that the β-CyD cavity environment is like that of an alcohol solvent. Cox et al.[80] correlated the longer wavelength emission band (assigned to a twisted internal charge-transfer structure) of (dimethylamino)benzonitrile (DMABN) and (diethylamino)benzonitrile with $E_T(30)$ (the transition energy of the Dimroth−Reichardt betaine, widely used as an empirical measure of solvent polarity[81]) and with the dielectric constant ϵ, and estimated the effective $E_T(30)$ of α-CyD to be 45 (like that of *tert*-butyl alcohol) using DMABN as the probe; the other three combinations yielded effective $E_T(30)$ values of 57−58 (like ethylene glycol). Once again it is found that the estimated polarity of the CyD cavity depends upon the compound used to probe it.

Heredia et al.[82] developed correlations of diphenylamine fluorescence energy with $E_T(30)$ and with Kosower's *Z* value;[83] they assign a *Z* value of 88 (similar to ethanol) to the cavity of β-CyD. Street and Acree[84] related the emission wavelength of pyrene-3-carboxaldehyde to solvent dielectric constant, concluding that $\epsilon = 55$ for α-CyD and $\epsilon = 48$ for β-CyD. (The dielectric constant of dimethyl sulfoxide acid is 49; that of formic acid is 58.) Fluorescence enhancement studies are not unambiguous routes to estimating effective CyD polarity because the fluorescence quantum yield is subject not just to the polarity of the environment, but also to restrictions on the motional freedom or collisional probability of the fluorescent probe.[85−87] The effect of a CyD on fluorescence efficiency may be a consequence of both factors, as discussed by several authors.[85−90]

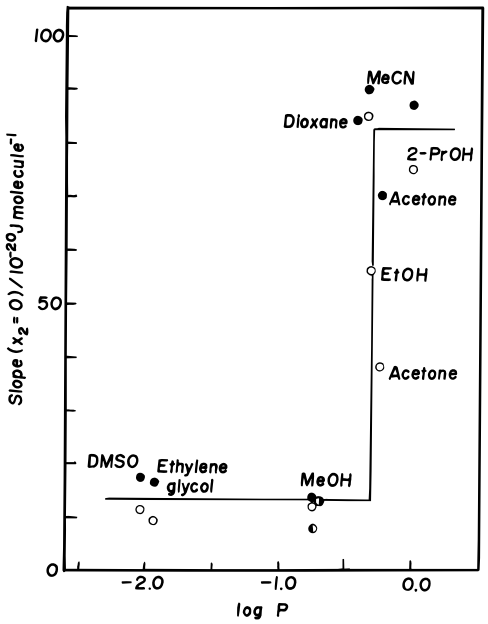


Figure 1. Plot of initial slope of the solvent effect (see text) against log *P* of the organic cosolvent, for some α-CyD complexes: (○) 4-nitroaniline; (●) methyl orange zwitterion; (◐) 4-nitrophenol; (◑) 4-nitrophenolate.

Some calculational studies have led to inferences about the environment within the cavity. Linert et al.[66] concluded that the β-CyD cavity is hydrophobic, but that the α-CyD cavity cannot clearly be placed in this category. Lichtenthaler and Immel[26] developed "lipophilicity patterns" based on solid-state complex structures, concluding that the three CyD's are quite similar, the wider (secondary hydroxyl) end of the cavity being hydrophilic, the narrower end hydrophobic.

A different approach has been taken in our laboratory by making use of solvent effects on α-CyD complex stability.[92−93] Let ΔG^*_{comp} be the free energy change for complex formation, calculated from the binding constant. This quantity is measured as a function of x_2, the mole fraction of organic cosolvent in binary aqueous−organic solvent mixtures. The slope of a plot of ΔG^*_{comp} against x_2 at $x_2 = 0$ (the initial slope) is one measure of the sensitivity of the complex stability to the solvent change. (In section VI.D a quantitative description of this effect is given.) Figure 1 shows a plot of this initial slope against log *P* of the organic cosolvent, for several α-CyD complexes. (*P* is the 1-octanol/water partition coefficient, a widely used measure of hydrophobicity.) The line segments drawn in the figure convey the inference that the experimental points describe a practically discontinuous function, the discontinuity appearing at the value log $P \approx -0.3$. The chemical interpretation of this observation is that the cosolvents can be divided into two classes, those more polar than log $P = -0.3$, and those less polar than this. At a next level of inference we have suggested[92] that log $P = -0.3$ corresponds to the effective polarity of the

α-CyD cavity. Those solvents less polar than this can partition effectively into the cavity, whereas more polar solvents are less effective in competing for the interior of the CyD. It is interesting to observe that the discontinuity in Figure 1 practically coincides with the polarities (according to this measure) of ethanol and dioxane. The dielectric constant is often used as a quantitative measure of polarity, but the dielectric constant of dioxane (about 2, very similar to that of cyclohexane) is misleading; after all, dioxane is infinitely miscible with water.

III. Binding Equilibria and Kinetics

A. Equilibria

1. Stoichiometric Ratios

For consistency the following symbolism is used throughout: S represents the *substrate*, or guest; L represents the *ligand*, which is the host (cyclodextrin). Stoichiometric ratios are always stated in the order S:L, so that a 1:2 ratio signifies the complex SL_2 and so on.

It is not surprising that the most commonly claimed stoichiometric ratio for CyD complexes is 1:1, and this claim is usually justified. Nevertheless, other ratios are known, the most common of these probably being 1:2. The ratios 2:1 and 2:2 have also been reported. Some representative studies are cited.[94−110]

Three-component CyD complexes are known. Several workers have investigated ternary complexes composed of a CyD, a guest, and an alcohol that seems to function as a "space-regulator" by optimizing the fit of the guest to the CyD cavity. In many cases these seem to be 1:1:1 complexes. This phenomenon has been observed with (as guests) pyrene,[111−114] α-naphthyloxyacetic acid,[115] acridine,[116−117] fluorene,[118] acenaphthene,[119] and coronene.[120] Nitriles[118] and amines[121] can also serve as the "filler" component. Hashimoto and Thomas[122] have described a 1:1:1 complex of pyrene:a surfactant: *β*-CyD. Even more unusual stoichiometries have been reported: Hamai[123] described a complex of 2-methoxynaphthalene:*o*-dicyanobenzene:*β*-CyD with 1:1:2 stoichiometry; and Herkstroeter et al.[124] observed this 1:1:2 combination of 1-pyrene butyrate: *n*-hexanesulfonate:*γ*-CyD. Giorgi and Tee[125] have proposed a ternary complex consisting of a single guest complexed with two different cyclodextrins; the interactants are 4-nitrophenyl octanoate, dimethyl-*β*-CyD, and *γ*-CyD.

2. Stepwise Binding Constants

We can expect complexes to be formed as a result of bimolecular processes, so the three simplest complexes are formed according to these equilibria:

$$S + L \rightleftharpoons SL$$

$$SL + L \rightleftharpoons SL_2$$

$$S + SL \rightleftharpoons S_2L$$

(It is also possible for, as an example, SL_2 to be formed from S and the dimer L_2.) The stepwise binding constants for these equilibria, denoted K_{11}, K_{12}, and K_{21}, are defined by eqs 1−3.

$$K_{11} = \frac{[SL]}{[S][L]} \tag{1}$$

$$K_{12} = \frac{[SL_2]}{[SL][L]} \tag{2}$$

$$K_{21} = \frac{[S_2L]}{[S][SL]} \tag{3}$$

In these equations, brackets signify molar concentrations, and each of these constants has the unit M^{-1}. (Of course these are really concentration quotients, not thermodynamic constants, but with the usual level of experimental accuracy and precision, and the uses to be made of the results, the much greater effort required to extract thermodynamic constants seldom can be justified. A few such quantities have, however, been reported.)

Any complex S_mL_n can be written as if formed directly from the unassociated substrate and ligand according to

$$mS + nL \rightleftharpoons S_mL_n$$

with overall binding constant β_{mn}:

$$\beta_{mn} = \frac{[S_mL_n]}{[S]^m[L]^n} \tag{4}$$

The overall constant can always be written as a product of stepwise constants. In cyclodextrin studies the usual practice is to express complex stabilities in terms of the stepwise binding constants (although some authors define a dissociation constant, which is the reciprocal of a binding constant). It sometimes happens, however, that measurement of an overall constant is possible, whereas the stepwise constants of which the overall constant is composed cannot be separately determined. For example, in the system 4,4′-dicarboxybiphenyl:α-CyD, $\beta_{12} = K_{11}K_{12} = 2.91 \times 10^7\ M^{-2}$; it was not possible to estimate K_{11} or K_{12} individually.[105]

3. Thermodynamic Quantities

Inasmuch as the stepwise binding constants are not thermodynamic constants, it is somewhat misleading to use the symbolism $\Delta G°$ for the free energy change calculated from the binding constant, but this is usually done. Enthalpy and entropy changes can be obtained from the temperature dependence of the equilibrium constant or from calorimetric measurements.

An important issue, often overlooked in the cyclodextrin field, is that the magnitudes of the standard free energy and entropy changes (not the enthalpy change) are dependent on the standard state chosen by the experimentalist. In practical terms, this comes down to a choice of concentration scales. The usual practice is to measure concentrations in molar units, giving binding constants in M^{-1} units, and leading to entropy changes based on the 1 M standard state. Arguments have been given[126−129] that

the mole fraction standard state (yielding "unitary" free energy and entropy changes in Gurney's terminology[126]) provides thermodynamic quantities better suited to chemical interpretation; the essence of the argument is that the unitary quantities do not contain the mixing contribution. This is especially important in solvent effect studies. To interconvert equilibrium constants on the molar (c) and mole fraction (x) scales eq 5 can be used, where Δq is the change in number of particles as reactants are converted to products, M^* is the number of moles of solvent in 1 kg of solvent, and ρ_1 is the solvent density.

$$K_c = K_x(M^*\rho_1)^{\Delta q} \quad (5)$$

For all stepwise binding constants $\Delta q = -1$. Applied to measurements made at 25 °C in dilute aqueous solution, the unitary free energy and entropy changes are given by eqs 6 and 7.

$$\Delta G_x^\circ/\text{cal mol}^{-1} = -1364.4 \log K_c - 2379.5 \quad (6)$$

$$\Delta S_x^\circ/\text{cal mol}^{-1}\,\text{K}^{-1} = \Delta S_c^\circ + 8.0 \quad (7)$$

Since the sign of the entropy change is thought by many workers to have great mechanistic significance, eq 7 is not a trivial relationship.

4. Quantitative Binding Models

A helpful systematization can be achieved with the aid of a simple model relating the equilibria in a typical CyD system. A CyD may be thought of as possessing two *binding sites*, namely portions of the CyD at, on, or in which a guest may bind; these are the two ends of the cavity. Let us also consider a guest molecule that possesses two potential binding sites. Though somewhat limiting, this description still includes a large fraction of the substrates that have been studied. The essential point is that most substrate molecules are too large to be completely engulfed by the CyD; instead there exist (sterically or electronically) preferred moieties on the substrate that enter the CyD cavity. In a system as described there may exist four possible isomeric 1:1 (SL) complexes, four 1:2 (SL_2) complexes, and four 2:1 (S_2L) complexes. Now, if 2:1 complexes are absent, it is a reasonable inference that the CyD actually possesses only a single binding site, which presumably is the wider (secondary hydroxyl) end; this seems to be the case for α-CyD, but is less assured for the larger hosts. If only one end of the CyD can be entered, there can form only two 1:1 complexes and one 1:2 complex.[130] (Some authors call a two-site substrate a "ditopic" guest, and the notion of isomeric 1:1 complexes has been referred to as "bimodal binding". The "direction of binding" is another term used by some as synonymous with choice of binding site.)

Figure 2 shows how these three complexes are related. In this figure XY is the substrate, X and Y representing its two binding sites. A primed site

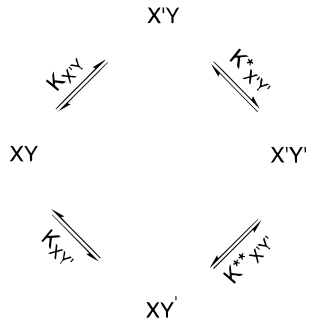


Figure 2. Binding site model for a two-site substrate XY. A primed site represents binding by a ligand site.

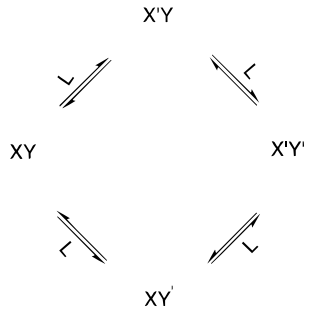


Figure 3. Binding site model for a two-site substrate XY and a one-site ligand L. A primed site represents a substrate site bound by an L.

indicates that a CyD is bound at that site, so X′Y and XY′ are isomeric 1:1 complexes, whereas X′Y′ is the 1:2 complex, which can be formed by two routes. The four equilibrium constants (only three of which are independent) are *microscopic binding constants*. We now apply this binding site model to some interesting cases.

a. Simple One-Site Ligand.[104] This case is exemplified by α-CyD. Figure 2 is now modified, in Figure 3, to show explicitly how the CyD molecules enter the equilibria. For this model the stepwise constants are related to the microscopic constants by eqs 8 and 9,

$$K_{11} = K_{X'Y} + K_{XY'} \quad (8)$$

$$K_{12} = \frac{a_{XY}K_{X'Y}K_{XY'}}{K_{11}} \quad (9)$$

where $a_{XY} = K^*_{X'Y'}/K_{XY'} = K^{**}_{X'Y'}/K_{X'Y}$. The dimensionless quantity a_{XY}, which is called the interaction parameter, is itself the equilibrium constant for this reaction:

$$X'Y + XY' \rightleftharpoons X'Y' + XY$$

If the binding sites are independent, it is energetically immaterial how the ligands are distributed, so $a_{XY} = 1$ if the sites are independent. (It does not necessarily follow that if $a_{XY} = 1$ the sites are independent.)

The two equations, eqs 8 and 9, contain three unknown quantities (K_{11} and K_{12} being experimentally measured), so in general the microscopic constants and interaction parameter are not accessible. If, however, the two substrate binding constants

should be identical, then, labeling this substrate XX, eqs 8 and 9 become eqs 10 and 11.

$$K_{11} = 2K_{X'X} \tag{10}$$

$$K_{12} = a_{XX}K_{11}/4 \tag{11}$$

For such a substrate $K_{X'X}$ and a_{XX} can be determined. This has been done, with α-CyD as the ligand, for sym-1,4-disubstituted benzenes[104] and sym-4,4′-disubstituted biphenyls.[105] The interaction parameter was found to range between 0.07 and 33. The influences on the magnitude of a_{XX} have been analyzed as follows:[104]

i. The Electronic Effect of L Bound at Site X′ on the Nature of Site X. If the sites in XX are electron deficient, upon interaction of one of them with L to give X′X there will be a partial electron transfer from L to the binding site. This has the effect of increasing the charge density at site X in X′X relative to that at X in XX. Thus binding of the second ligand will be favored relative to that of the first one, and a_{XX} will be greater than unity through the operation of this effect. If the sites are electron rich the opposite drift of charge takes place, and a_{XX} will be less than unity. Thus a_{XX} may be expected to follow a Hammett plot with a negative slope.

ii. The Repositioning Effect. In the 1:1 complex the relative position of ligand and binding site is optimal with regard to lowering the total free energy of the system. Formation of the 1:2 complex will result in adjustment of all three molecules to minimize the total free energy, since in the 1:2 complex X′X′ the two bound sites are necessarily identical on average. This may require a repositioning of the substrate−ligand orientation that was reached in the 1:1 complex. Any such repositioning must therefore be destabilizing, since the orientation in the 1:1 complex is optimal, and will therefore lower a_{XX}.

iii. The Ligand−Ligand Interaction Effect. In a 1:2 complex there is a possibility that the facing rims of the two cyclodextrin molecules may interact attractively (a substrate-promoted ligand dimerization). Such an effect could only be manifested as 1:2 complex stabilizing (increasing a_{XX}), because any destabilizing repulsive interactions would be accounted for in terms of the repositioning effect.

It is possible for these effects to combine so as fortuitously to generate an a_{XX} value close to unity, so this result obviously does not imply that the sites are independent.

Let us return to eq 8. Some workers in the cyclodextrin field apparently do not accept this equation, because reports have been published in which separate constants are claimed to have been measured for binding at two sites on a substrate, that is, for isomeric 1:1 complexes. One of the circumstances in which this claim has been made invokes two experimental methods, such as the solubility and spectroscopic techniques, when it is supposed that one of the methods measures all binding, both "specific" and "nonspecific", whereas the other measures just "specific" binding. The other circumstance is exemplified by absorption or emission spectroscopy, in which the isomeric complexes may be identified as possessing different spectra (quite possible), so that measurements at two appropriate wavelengths are used to measure the individual microscopic constants.

All such approaches are illusory;[129] eq 8 cannot be evaded. This point is sufficiently important to make use of a specific experimental technique as an example. We bring in the widely applied absorption spectroscopic method to make the point, but any other method would give the same result. For a single 1:1 complex eq 12 is the binding isotherm.

$$\frac{\Delta A}{b} = \frac{\Delta\epsilon_{11}K_{11}S_t[L]}{1 + K_{11}[L]} \tag{12}$$

Here $\Delta A/b$ is the change in absorbance per centimeter when the free ligand concentration changes from zero to [L], S_t is the total substrate concentration, and $\Delta\epsilon_{11} = \epsilon_{11} - \epsilon_S - \epsilon_L$. The corresponding isotherm for a system containing two isomeric 1:1 complexes SL and LS is

$$\frac{\Delta A}{b} = \frac{(K_{SL}\Delta\epsilon_{SL} + K_{LS}\Delta\epsilon_{LS})S_t[L]}{1 + (K_{SL} + K_{LS})[L]} \tag{13}$$

Comparison of the equations leads to these identities:

$$K_{11} = K_{SL} + K_{LS} \tag{14}$$

$$\Delta\epsilon_{11} = \frac{K_{SL}\Delta\epsilon_{SL} + K_{LS}\Delta\epsilon_{LS}}{K_{SL} + K_{LS}} \tag{15}$$

Note that it is irrelevant that at the experimental wavelength one of the complexes may make no contribution to the signal; eq 14 still describes the result.

The physical basis for the generality of eq 8 is that these are reversible systems at equilibrium. The isomeric complexes necessarily possess the same functional dependence on the solution concentrations or activities. This coupling of the equilibria is reflected in eq 8, and is independent of the experimental technique. The only way to determine separately the two microscopic constants for the isomeric complexes is to provide a second independent equation. This is a classical problem in the field of acid−base equilibria, where the proton takes the role of L in Figure 3.[131]

b. Duplex Two-Site Ligand. The ligand in this case may be symbolized L−L, with each L representing a CyD, so the two (identical) ligand binding sites are covalently linked and we suppose that their spacing permits them both to bind to the sites on two-site substrate XY. The system is shown in Figure 4.

In this system X′Y, XY′, and X′Y′ are all 1:1 complexes, since each consists of one XY and one L−L. The complex X′Y′ is a chelate. Higher stoichiometric ratios are possible but will not be considered here. The development used for case (a)[130] leads to eq 16 for the stepwise constant K_{11},

$$K_{11} = K_{X'Y} + K_{XY'} + b_{XY}K_{X'Y}K_{XY'} \tag{16}$$

where $b_{XY} = K^*_{X'Y'}/K_{X'Y} = K^{**}_{X'Y'}/K_{X'Y'}$. Equation 16 is very interesting, especially in those instances in

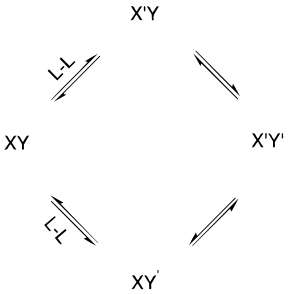


Figure 4. Binding site model for a two-site substrate XY and a duplex two-site ligand L−L. A primed site indicates that an L is bound at that site.

which the microscopic constants are quite large, for then (provided b_{XY} is not extremely small) the sum $K_{X'Y} + K_{XY'}$ will be negligible relative to the product $b_{XY}K_{X'Y}K_{XY'}$, and we can write, approximately,

$$K_{11} = b_{XY}K_{X'Y}K_{XY'} \quad (17)$$

which is equivalent to

$$\Delta G^\circ_{11} = -RT \ln b_{XY} + \Delta G^\circ_{X'Y} + \Delta G^\circ_{XY'} \quad (18)$$

The free energy changes are additive, with the interaction parameter b_{XY} (which has the unit M) being a measure of deviation from simple additivity of the nonchelated contributions. Jencks[132] has given an empirical relationship having the form of eq 18.

Many duplex CyDs have been synthesized,[133−141] and quantitative studies have shown behavior consistent with eqs 17 and 18. Breslow and co-workers have thoroughly explored this type of chemistry.[136−141] In one example,[136] a β-CyD dimer β-CyD-CH_2SSCH_2-β-CyD gave with the one-site guest *t*-Bu-C_6H_4-OH $K_{11} = 1.6 \times 10^4$ M^{-1}, and with two-site guests *t*-Bu-C_6H_4-X-C_6H_4-*t*-Bu (X variable) K_{11} values ranging from 10^4 to 10^8 M^{-1}. Binding constants as large as 10^{11} M^{-1} have been observed.[141]

Some binding schemes other than those explicitly modeled by Figures 3 and 4 have been reported. Tabushi et al.[142] studied the ternary complex of a metal ion, a modified β-CyD, and an adamantane carboxylate, which yield a chelate whose stability satisfies eq 18. Veno et al.[143] complexed β-CyD with a naphthalene-appended γ-CyD. Petter et al.[144] observed cooperative binding of guests with large aggregates of chemically modified β-CyDs, these aggregates providing multiple binding sites. Protonic equilibria of acid−base guests create systems containing two or more conjugate species, each a potential guest with its own CyD binding constant. Such systems have been studied in many laboratories. They are conceptually quite straightforward, although they can present experimental difficulties. Somewhat more complicated behavior is shown by certain acid−base indicators that can exist in azonium and ammonium tautomeric forms; these have been exhaustively treated by Tawarah and coworkers.[145−148]

Takuma et al.[148] have claimed that their results on halo-substituted benzenes do not fit the model of Figure 3. This may be, but these authors have misinterpreted the model, as when they suppose that the model requires that K_{11} of monofluorobenzene be one-half that of 1,4-difluorobenzene. It does not; according to the model, K_{11} of fluorobenzene is the sum of constants for binding at the fluoro site and the phenyl site, each electronically modified by the *para* substituent. Thus it is consistent with the model that K_{11} for fluorobenzene is larger than K_{11} for difluorobenzene, the experimental result.

B. Kinetics of Complexation

Because the equilibrium constant of a reversible elementary reaction is equal to the ratio of rate constants, kinetic measurements of CyD complex association/dissociation rates should provide valuable mechanistic information beyond that available from equilibrium measurements alone. Cramer et al.[76] studied the kinetics of association and dissociation of a series of naphthylazobenzenes complexed with α-CyD. The binding constants (K_{11}) for eight of these guests showed little variation with guest structure, ranging from 270 to 1010 M^{-1}. In marked contrast to this insensitivity to structure of the equilibrium constants, the association rate constants varied from 2.8 M^{-1} s^{-1} to 5.2×10^7 M^{-1} s^{-1} and the dissociation rate constants ranged from 0.01 s^{-1} to 1.3×10^5 s^{-1}. The substrate specificity of the kinetics was interpreted to mean that desolvation of the substrate is probably a kinetically important step. After "threading" of the α-CyD onto the phenylazo moiety, resolvation occurs, accounting for the insensitivity of K_{11} to substrate structure, since the dissociation rate will then also be controlled by desolvation.

Most of the systems studied by Cramer et al.[76] required temperature-jump relaxation studies, but one reaction was slow enough (probably because of steric inhibition) to study by conventional spectrophotometry. The 2:1 and 2:2 complexes of pyrene with γ-CyD are said to require several hours to reach equilibrium,[99] but such slow CyD complexation rates are highly unusual.

The great range of time scales observed in the work of Cramer et al.[76] has since been found to be quite common, but the simple one-step kinetic scheme has had to be elaborated, with many workers proposing the two-step scheme of eq 19 to account for their observations.

$$S + L \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} SL^* \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} SL \quad (19)$$

The substrate and the CyD undergo reaction to form a transient complex SL*, which then relaxes to the isomeric complex SL.

If the first step of eq 19 is slow and the second step fast (in relative terms), then the first step is rate-determining. Under pseudo-first-order conditions (ligand concentration much greater than substrate concentration) a single exponential process will be observed with apparent rate constant given by

$$k_{obs} = k_1[L] + k_{-1} \quad (20)$$

If, however, the first step is fast and the second step is slow, more complicated behavior is possible. In some instances analytical signals can be seen for both

processes; then eq 20 describes the fast reaction and eq 21 describes the slow reaction (where $K_1 = k_1/k_{-1}$).

$$k'_{obs} = \frac{k_2 K_1[L]}{1 + K_1[L]} + k_{-2} \quad (21)$$

Equation 21 results from the application of the fast preequilibrium assumption to the first step in eq 19.

These equations have been used by many authors to interpret their data. Stopped-flow, temperature-jump, and ultrasonic absorption techniques have been applied to CyD systems. The most extensively studied substrates have been aromatic azo compounds, probably because of their interest as potential two-site substrates and also because their complexation is detectable by absorption spectroscopy.[76,149−159] Acid−base indicators have also been studied,[160−168] and a few miscellaneous systems have been examined kinetically.[169,174] Some workers have evaluated the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ as well as rate constants.

The only generalization that seems to emerge, to date, is that many CyD complexes form in the two-step scheme of eq 19, the first step constituting a hasty inclusion, with the second step a relaxation or accommodation to the final structure. This second step is thought to involve solvational and conformational changes. The more specific results of kinetic studies have been embodied in the additional information they provide, by correlating rates with structures, on preferred binding sites. The time scales of reactions vary from the second to the nanosecond range, with the largest rate constants approaching (but probably not reaching) the diffusion-controlled limit.

Kinetic studies of CyD complex formation have enormous potential for providing mechanistic insight, as rate measurements have done for so many other kinds of reactions. Before quantitative generalizations, mechanistic understanding, and predictive capability are achieved, however, it seems probable that a much wider range of substrate structures will have to be explored. It will then be possible to seek correlations (such as linear free energy relationships) and to examine phenomena (like catalysis and isotope effects) that have been very instructive in studying other reaction types.

C. Volume Changes

The usual method for measuring the molar volume change $\Delta V°$ of a reversible reaction is by determining the dependence of the equilibrium constant on external pressure, but this quantity is also accessible through density measurements or ultrasonic absorption studies. The activation volume $\Delta V^{\ddagger}$ is determined from the pressure dependence of a rate constant. Table 2 lists reported $\Delta V°$ values for CyD complex formation. $\Delta V^{\ddagger}$ values for CyD complex formation do not seem to have been reported. (Some $\Delta V^{\ddagger}$ estimates of chemical reactions catalyzed by CyDs are available[175−177]). The $\Delta V°$ estimates in Table 2 have experimental uncertainties in the range of 1−5 cm^3 mol^{-1}; most of the results have been obtained from pressure studies.

Table 2. Volume Changes on Cyclodextrin Complex Formation

host	guest	$\Delta V°$, cm^3 mol^{-1}	ref
poly(acryloyl)-β-CyD	8-anilinonaphthalene-1-sulfonate	+9.3	178
poly(acryloyl)-β-CyD	6-propionyl-2-(dimethylamino) naphthalene	+9.2	178
α-CyD	SCN^-	−4.2; −3.1	179
β-CyD	SCN^-	0; +1.5	179
α-CyD	ClO_4^-	−1.9; −1.4	179
β-CyD	ClO_4^-	+6.5; +8.0	179
α-CyD	I^-	−5.8; −7.0	179
β-CyD	I^-	0; +1.1	179
α-CyD	4-nitrophenyl acetate	0	177
β-CyD	4-nitrophenyl acetate	0	177
β-CyD	2-naphthyl acetate	+10	177
γ-CyD	2-naphthyl acetate	0	177
α-CyD	3-nitrophenyl acetate	−16	180
α-CyD	3-methylphenyl acetate	−10	180
α-CyD	4-methylphenyl acetate	−1	180
β-CyD	4-nitrophenyl ferrocenylacrylate[a]	−15	176
α-CyD	4-nitrotrifluoroacetanilide	−3	181
β-CyD	4-nitrotrifluoroacetanilide	−2	181
α-CyD	1-butanol	+1.5	171
α-CyD	1-pentanol	+3.1	171
α-CyD	dicyclomine cation	+6.3	172
α-CyD	chlorocyclizine cation	+5.6	174
β-CyD	di-*tert*-butylnitroxide	+5	182
γ-CyD	di-*tert*-butylnitroxide	+20	182

[a] In 50% ethylene glycol/water.

Several of the authors of the results shown in Table 2 have offered interpretations of their data, but these interpretations are not convincing, particularly when the variability of $\Delta V°$ is considered. Many of the $\Delta V°$ values are quite small, and interpretations of $\Delta V°$ as sums and differences of large numbers representing contributions from release of cavity-bound water, insertion of the substrate binding site, etc., necessarily leads to high relative uncertainties. Probably only after the collection of very many experimental $\Delta V°$ results for a wide range of substrate types, and for all three native CyDs, will patterns emerge. At the present stage, the only tentative pattern is that binding to α-CyD results in a $\Delta V°$ that may be more negative than does binding to β-CyD; from Table 2, the mean $\Delta V°$ for α-CyD is -2.4 ± 6.6 cm^3 mol^{-1}, whereas that for β-CyD is $+2.5 \pm 7.6$ cm^3 mol^{-1}.

IV. The Strengths of Cyclodextrin Complexes

A recent collection[183] of K_{11} values from the CyD literature is largely summarized in Table 3 and Figures 5−7. These systems are of the type shown in Figure 3, that is, the ligand is one of the three native CyDs, and only the formation of the 1:1

Table 3. Statistical Parameters for Cyclodextrin Complex Stabilities[a]

CyD	total no. of estimates	no. of systems (n)	μ	σ
α	960	663	2.11	0.90
β	1142	721	2.69	0.89
γ	188	166	2.55	0.93

[a] Population mean μ and standard deviation σ are expressed in log K_{11} units.

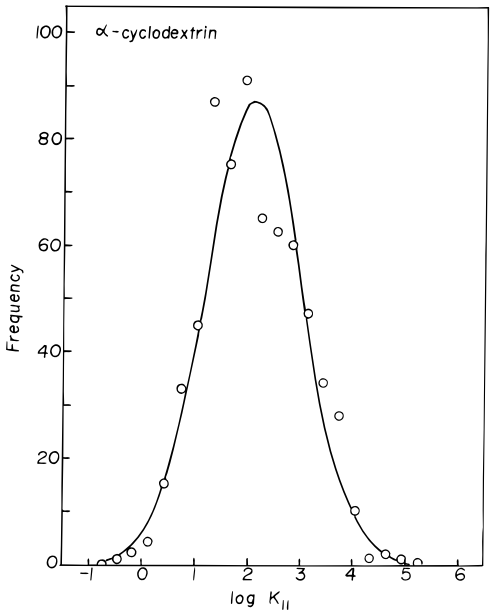


Figure 5. Frequency distribution (points) and normal distribution (curve) calculated with the parameters n = 663, μ = 2.11, and σ = 0.90 for α-CyD complex stabilities. (Reprinted from ref 183. Copyright 1995 American Pharmaceutical Association and American Chemical Society.)

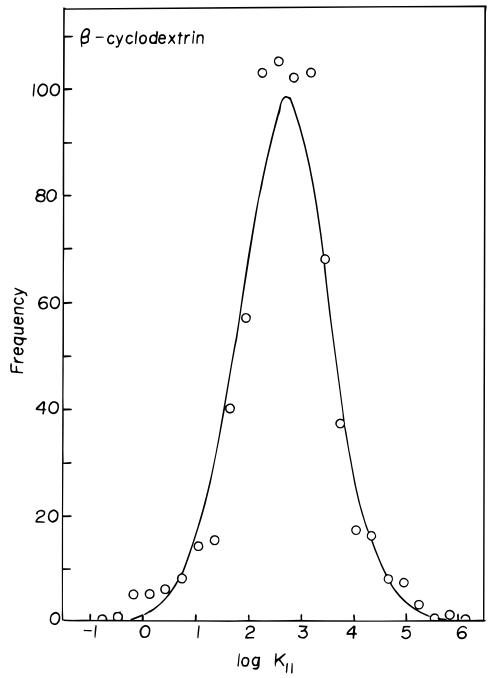


Figure 6. Frequency distribution (points) and normal distribution (curve) calculated with the parameters n = 721, μ = 2.69, and σ = 0.89 for β-CyD complex stabilities. (Reprinted from ref 183. Copyright 1995 American Pharmaceutical Association and American Chemical Society.)

complex is considered. For a given host−guest system studied by many different workers using different experimental techniques (exemplified by the α-CyD complexes of 4-nitrophenol and of 4-nitrophenolate) the standard deviation of log K_{11} is about 0.1 unit. However, a more realistic estimate of the usual reproducibility of these equilibrium constants is roughly a factor of 2 in K_{11}, or 0.3 in log K_{11}.

Treated as statistical populations, these complex stabilities appear to be reasonably described as normally distributed in log K_{11}; Table 3 lists the

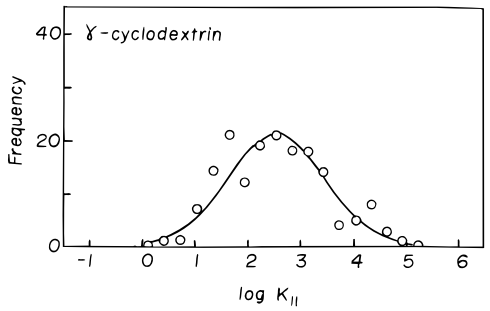


Figure 7. Frequency distribution (points) and normal distribution (curve) calculated with the parameters n = 166, μ = 2.55, and σ = 0.93 for γ-CyD complex stabilities. (Reprinted from ref 183. Copyright 1995 American Pharmaceutical Association and American Chemical Society.)

population means and standard deviations. Table 3 and Figures 5−7 combine all guests with a given CyD as a single population, although there is some indication that ionic guest−CyD complexes have, on average, slightly higher stabilities than do neutral complexes.[183]

These frequency distributions are useful in demonstrating the range of statistically expected stabilities for each CyD system, and they provide criteria for identifying outliers (on the high-stability tail of the distribution). The mean values of the populations may surprise some workers as being rather low, and the similarities among the three CyDs are apparent.

The CyD literature contains statements or implications to the effect that the CyDs are discriminating hosts (on the basis of their size-exclusion property); and contrary statements that they are not very discriminating hosts (on the basis that they form complexes with guests of a wide range of chemical structures). Although both statements have some support in experiment, neither is very useful. Let us consider the observation, provided in Table 3, that the standard deviation σ of log K_{11} is about 0.9 for all three native CyDs, and let us ask about σ for other populations of noncovalently interacting systems.

If we assume, reasonably enough, that such populations are normally distributed, their standard deviations may be roughly estimated as 1/5 to 1/6 of the observed range in the variable, which is $\Delta G°$ or log K. Consider acid−base strength.[184] The pK_a values of practically all carboxylic acids lie in the range 1−7; phenolic pK_a values (excluding evident outliers such as multiply substituted nitrophenols) fall between 7 and 11; aromatic amines from 1 to 6; and aliphatic amines from 8 to 12. log K for hydrogen bonding in solution (excluding some atypical donors, but without restriction as to structure type or solvent)[183] seems to lie in the range −1.7 to 3.9. That is, the ranges of all of these quantities are 4 to 6 log K units, corresponding to standard deviations of 0.7 to 1.0 unit, like σ for CyD complexes.

I am suggesting that any chemically reasonably defined population of a noncovalent association process will have a maximum typical stability range of 5−6 orders of magnitude in the equilibrium constant, resulting in a standard deviation of about one log K unit. The mean value of the distribution will be determined by the inherent defining features of the population; the standard deviation, however, is pre-

sumably controlled by the range of forces available from the noncovalent interactions. From this point of view, the behavior of the CyDs is completely normal.

Frequency distributions of the enthalpy change $\Delta H°$ for CyD complex formation have not been constructed. A casual survey of literature data suggests that nearly all (more than 95%) of $\Delta H°$ values for native CyD complexes lie in the range +1.0 to −12 kcal mol^{-1}.

V. The Structures of Cyclodextrin Complexes

This is a large subject that will be treated only to the extent that seems pertinent to our primary concern. The discussion is arranged by method of study.

A. X-ray Crystallography

The hydrated CyDs (see section II.B) can be regarded as aquo complexes; these have been well studied by X-ray crystallography: α-CyD,[49−53,186] β-CyD,[54,59,187] and δ-CyD.[62] Since X-ray diffraction does not directly yield hydrogen atom positions, neutron diffraction has been applied to the CyD hydrates,[188] providing the criterion that of O···O distances less than 3.0 Å virtually all represent O−H···O hydrogen bonds, whereas of O···O distances greater than 3.6 Å virtually none represent H-bonds; between these atomic separations a distribution exists.

How relevant to the dilute aqueous solution are crystalline complex structures? Some workers believe that a solid-state structure constitutes highly relevant information, this structure being construed as one among the many possible conformations that may exist.[26,189,190] Certainly the complex structure in the crystalline state demonstrates a possible conformation of the complex system, and is helpful to this extent. But there are orientation forces in the crystal that do not exist in the solution phase, or mutual interactions that are replaced by solute−solvent interactions, so some differences between solid and solution-phase complex structures can be expected. The crystal packing patterns of CyD complexes may provide environments or impose restrictions quite different from those in solution. These patterns comprise herringbone or brick work types of arrangements, or, especially common, endless channels formed by cavity-to-cavity alignment of CyDs. The role of the guest structure and size in determining the crystal packing pattern has been discussed.[191−194]

The earliest crystallographic studies on CyD complexes were dominated by Saenger in Germany and by Harata in Japan, but several other laboratories have contributed to the field.

Let us first consider the α-CyD complexes of aromatic compounds, substituted benzenes in particular. The α-CyD cavity dimensions allow the phenyl ring to be fully enclosed with quite a tight (van der Waals) contact. Figure 8 embodies the

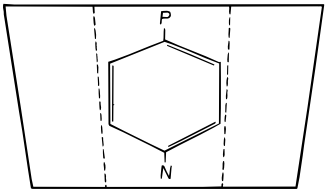


Figure 8. Depiction of a typical complex structure of α-CyD with a substituted benzene. N and P designate nonpolar and polar substituents, respectively. The wider end of the α-CyD is rimmed with secondary hydroxy groups, the narrower end with primary hydroxy groups.

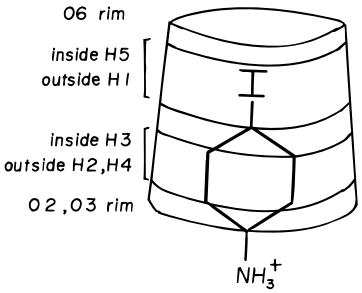


Figure 9. Structure of the 4-iodoaniline−α-CyD crystalline complex, showing the relationship of the guest to the host hydrogen atoms. (The wider, secondary hydroxyl, end of the cavity is the 0(2), 0(3) end.) (Adapted from ref 196b. Copyright 1977 American Chemical Society.)

results of many structural determinations. In this figure a 1,4-disubstituted benzene (or a monosubstituted benzene) is included in the α-CyD cavity, the phenyl ring essentially fully encapsulated. The letters N and P signify nonpolar and polar substituents, respectively, and their positions are as commonly (but not universally) observed, that is, the nonpolar group is deeply inserted (the direction of insertion presumably being from the wider, secondary hydroxyl, rim of the cavity), and the polar group is located near the secondary hydroxyls or it may even protrude from the cavity. Among the examples of this structural type are the α-CyD complexes of 4-iodoaniline,[195,196] 4-iodophenol,[197] the benzenesulfonate anion,[198] 4-nitrophenol,[199] and 4-hydroxybenzoic acid.[199] In the 4-hydroxybenzoic acid system, the carboxy group is inserted—that is, takes the role of group P in Figure 8—and the hydroxy group protrudes from the secondary hydroxyl end of the cavity. The 3-nitroaniline:α-CyD also adopts the Figure 8 structure.[200] Figure 9 shows more explicitly the mutual orientation of host and guest in the 4-iodoaniline:α-CyD crystalline complex; in this figure the locations of the α-CyD hydrogens are shown. 2-Fluoro-4-nitrophenol is inserted into α-CyD very much as is 4-nitrophenol, which places the fluorine atom slightly exterior to the secondary hydroxyl rim.[201] On the other hand, the α-CyD complexes of both 2-fluorophenol and 4-fluorophenol have the fluorine atom outside the cavity, apparently because the F atom can form an intermolecular hydrogen bond;[202] this has the result that in the 2-fluorophenol complex the phenolic hydroxy is also outside the cavity whereas in the 4-fluorophenol complex the phenolic hydroxy is inside the cavity. The aromatic rings of benzaldehyde[203] and benzyl alcohol[190] also are enclosed in the α-CyD cavity. In the α-CyD:methyl orange anion complex (methyl orange is 4-[[4-(dimethylamino)phenyl]azo]benzene-

sulfonic acid) the CyD cavity encloses the azo group and most of the sulfonate-substituted phenyl ring.[204]

Some of the structural features of these complexes may be, or clearly are, determined by crystal packing factors. Thus the solid-state methyl orange:α-CyD complex has 1:2 stoichiometry,[204] which could occur also in solution, although its presence will be concentration dependent. Another characteristic of the channel-type of crystal packing is that adjacent CyD molecules can be oriented head-to-head, tail-to-tail, or head-to-tail. (Most authors define the secondary hydroxyl rim as the head, but there is some disparity in usage of these terms.) A polar group on the guest can protrude from its host to interact with the hydroxy groups on an adjacent CyD, in this way creating a dimeric 2:2 structure that is not necessarily simply two identical 1:1 complexes. Examples of such dimeric 2:2 structures are the β-CyD complexes of 2,5-diiodobenzoic acid,[205] 4-ethylaniline,[206] and ethyl 4-aminobenzoate.[207] Some crystal structures do not seem to be pertinent to the solution state; for example, the 2:1 benzyl alcohol:α-CyD solid complex has one benzyl alcohol inserted in the CyD cavity and the other located in the interstitial space between CyD molecules.[190] The solid 1:1 complex between 1-phenylethanol and α-CyD does not seem to be an inclusion complex at all.[208]

The structures of β-CyD complexes of substituted benzenes show somewhat greater variability, probably because the larger β-CyD cavity allows the guest more possibilities for minimizing the energy of the system. Whereas α-CyD may, with respect to most guest molecules, be considered a one-binding site ligand (the secondary hydroxyl end of the cavity being this binding site), it is possible that the larger CyDs may sometimes function as two-site ligands. An interesting example of structural variability is provided by the β-CyD complexes of 4-*tert*-butyltoluene,[209] 4-*tert*-butylbenzyl alcohol,[194] and 4-*tert*-butylbenzoic acid.[210] All of these 1:1 complexes form head-to-head dimers in the crystal. In the 4-*tert*-butyltoluene complex, the *tert*-butyl group is inserted close to the primary hydroxyl rim, the phenyl ring in the cavity, and the methyl group at the secondary hydroxyl interface. In the other two complexes, however, the *tert*-butyl groups reside in the cavity near the secondary hydroxyl rim, the polar COOH or CH_2-OH groups being located at, or protruding from, the primary rim. Evidently the polar characteristics of these substituents are important in establishing the structures.

The benzyl alcohol:β-CyD complex has the Figure 8 structure,[211] as do the β-CyD complexes of some substituted benzoic acids and phenols;[212] the carboxy group in the benzoic acid series is inserted so that it lies near the primary rim. 4-Nitroacetanilide also adopts this structure, with the nitro group near the primary hydroxyl rim and the acetyl group level with the secondary hydroxyl;[213] this orientation is achieved by tilting of the guest molecule 30° to the axis of the β-CyD ring. The ethyl cinnamate:β-CyD complex forms a head-to-head dimer, each 1:1 unit having the olefinic double bond centered in the cavity, with the phenyl group toward the secondary (wider) rim and the ester group protruding through the primary rim, where it can hydrogen bond with a primary hydroxyl; this arrangement constitutes a reversal of the orientation shown in Figure 8.[214]

Aliphatic substrates form complex structures comparable in broad terms to the aromatic systems; that is, the hydrophobic portion of the guest tends to be enclosed within the CyD cavity, with polar groups positioned so as to interact with the rimming CyD hydroxy groups, or protruding from the cavity and interacting with an adjacent CyD molecule. Guest molecules substantially smaller than the host cavity are sometimes accompanied by space-filling water molecules. Among the systems conforming to this general picture are, with α-CyD, the guests methanol,[215] 1-propanol,[216] 1-propanesulfonate,[191] γ-aminobutyric acid,[217] (cyclobutane-1,1-dicarboxylato)-diammineplatinum(II),[218] and krypton;[219] with β-CyD, ethylene glycol,[189] glycerol,[189] 1,4-butanediol,[220] 3,3-dimethylbutylamine,[221] hexamethylenetetramine,[222] 1-adamantanecarboxylic acid,[223] and 1-adamantane methanol.[224] γ-CyD possesses a cavity large enough that it can enclose 12-crown-4,[225] and an even more elaborate complex is formed from γ-CyD, 12-crown-4, and lithium or potassium ion;[226] this constitutes a guest within a host within a host. The crystal structure is quite complicated, having four adjacent γ-CyD molecules oriented, in order, head-to-head, tail-to-tail, head-to-tail.

B. Nuclear Magnetic Resonance Spectroscopy

The study of CyD complexes by NMR was initiated by Demarco and Thakkar,[227] who observed ^{1}H chemical shift variations of CyD H(3) and H(5) in the presence of numerous substrates, and inferred that inclusion in the CyD cavity had taken place. This type of evidence has since been widely collected. In addition, nuclear Overhauser effects and relaxation and correlation time measurements have contributed to knowledge of CyD complex structures. Both ^{1}H and ^{13}C NMR have been applied. Inoue[24] has reviewed NMR studies of the CyDs.

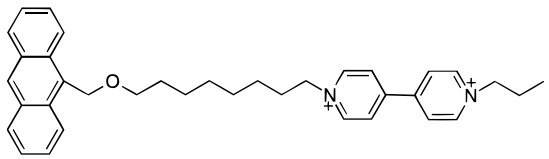
A typical structural inference is that if only H(3) undergoes a shift in the presence of substrate then the cavity penetration is shallow, whereas if H(5) also shifts the penetration is deep. (See Figure 9 for a pictorial description.) Some authors go further than structural inferences to draw conclusions about the nature of the binding forces. Despite the great power of NMR for structural investigation, its application to CyD complexes has led to some rather unconvincing energetic conclusions. Nevertheless, the general picture that results is congruent with Figure 8 and X-ray studies of the solid state: the wider (secondary hydroxyl end) rim of the CyD is the ligand binding site, and the nonpolar area of the substrate binding site is largely included within the CyD cavity, with polar portions either interacting with CyD hydroxyls or extending into the solvent phase. Of course, the identity of the CyD affects the structure of the complex and therefore the NMR signals, and a common finding, for a given substrate, is that penetration into the β-CyD cavity is deeper than into α-CyD. Among the substrates studied by NMR whose CyD complexes adhere reasonably to the picture developed above are many nitro-substituted

aromatics, particularly nitrophenols;[196b,228−236] the nitro group is inserted into the cavity, with any polar substituent protruding from the wider rim. It is especially important to note that, for both 4-nitrophenol and 4-nitrophenolate, it is the nitro end of the guest that enters the cavity.[296b,229,230] Many other guest molecules adopt orientations in the CyD cavity that are reasonably represented by Figure 8: *trans*-cinnamic acids;[237] some carboxylates;[238] azo dyes;[239−242] aromatic amino acids;[243] ephedrine;[244] anilinonaphthalenesulfonates;[245,246] azulene;[247] adamantanes;[248,249] a nonionic surfactant;[250] menthols;[251] and many drug molecules.[252−257] ^{13}C NMR has shown the structure of a 1:2 (SL_2) complex of 4-biphenylcarboxylate to possess a head-to-head relationship of the CyD rings, positioned so that hydrogen bonding of the O(2),O-(3) hydroxy group on the two CyDs is possible.[258a] NMR is capable of distinguishing between CyD complexes of enantiomers.[245,251,257,259] Gelb et al.[258b] have interpreted their ^{13}C NMR on the benzoic acid: α-CyD complex as showing that the acid (carboxy end first) enters the narrow (primary hydroxy) rim of the cavity; this interpretation differs from the prevailing view.

C. Optical Spectroscopy

1. Ultraviolet Absorption

van Etten et al.[73] argued that the close match of the UV spectra of 4-*tert*-butylphenol in dioxane and in an aqueous solution of α-CyD shows that the chromophore is included in the CyD cavity, which was considered to provide a molecular environment similar to dioxane. Toki et al.[260] interpreted the disappearance of the charge-transfer band of the anthracene−viologen **5** as evidence of interruption



5

of a donor−acceptor interaction between the two aromatic portions of the molecule, which in free solution takes place intramolecularly. (The α-CyD complex formation, incidentally, is unusually slow, having a half-life of about 500 s.) A modified β-CyD possessing a covalently attached chromophore as a "cap" exhibits blue shifts in the presence of guest molecules, indicative of the chromophore's displacement, upon guest binding, to a less hydrophobic environment.[261]

2. Circular Dichroism

Although most guest molecules are achiral, in the chiral environment of a CyD a guest chromophore may exhibit induced circular dichroism (ICD), and this phenomenon has been widely applied as a means for deducing complex structure. Zhdanov et al.[262] have reviewed this subject. The application to CyDs is based on the Kirkwood−Tinoco theory of polarizabilities, which, developed for the CyD case,[263−265] gives this rule: if the transition dipole moment of the guest chromophore is aligned parallel to the axis of symmetry of the CyD (that is, the axis of the CyD cavity), then the sign of the ICD Cotton effect for that transition will be positive, whereas if the moment axis is aligned perpendicular to the cavity axis, the ICD sign will be negative. This rule applies to a chromophore that resides inside the cavity; if the chromophore is located outside the cavity the signs of the ICD are opposite to this.[266,267] Although the theory allows the magnitude of the ICD to be calculated, it appears that deviations from radial symmetry of the CyD, and its conformational flexibility, can affect the strength of the ICD.[268,269]

Examples of the use of ICD to deduce the guest orientation in CyD complexes include naphthalene derivatives[263,270] (thus 2-substituted naphthalenes are "axially" inserted into the β-CyD cavity, meaning that the long axis of the naphthalene is parallel with the cavity axis),[263] benzophenone,[271] substituted benzenes,[272−275] cyclohexenones,[276] azo dyes[277−279] (azobenzenes, not surprisingly, are found to be axially included), azulene[280] (which is axially inserted in β-CyD but adopts an equatorial orientation in β-CyDs modified with lipophilic groups on the wider rim), and other substances.[266,281−286] The ICD of a series of 4-nitrophenyl alkanoates showed that those members of the series having short chains complexed by inclusion of the nitrophenyl moiety, whereas long-chain members inserted the alkyl chain in the CyD cavity, and this structural difference could be related to the catalytic effects on the ester hydrolysis.[287] 4-(Dimethylamino)benzoic acid and 2,6-dimethyl-β-CyD give markedly different ICD signals in water and in chloroform; Kobayashi[288] concludes that the guest is axially inserted in water but equatorially (or forms a lid-type complex) in chloroform.

Complex structural inferences from ICD are generally in agreement with the views developed on the basis of other experimental approaches, namely that the nonpolar portions of guest molecules are preferentially inserted in the CyD cavity. Exceptions to this behavior can be ascribed to steric factors, as in a series of methyl-substituted conjugated cyclohexenones studied by Bonora et al.,[276] who concluded that the more polar carbonyl group could be found in the CyD cavity when the substituent sterically prevented insertion of the nonpolar portion of the guest.

3. Fluorescence

The effects of CyD complexation on emission spectra include information about the structure of the complex, but interpreting the information may not be straightforward because of confounding effects. This difficulty was noted in section II.D, where fluorescence probes of the CyD cavity polarity were seen to be sensitive also to motional restrictions imposed by inclusion. Firm conclusions about the complex structure therefore may not emerge.[289] Nevertheless, certain types of systems can be very suggestive, as when intramolecular or intermolecular energy transfer processes are either enhanced or quenched by a CyD. For example, a series of polymethylene-bis-β-naphthoates, $C_{10}H_7COO(CH_2)_nOCOC_{10}H_7$ (n = 2, 3, 4, 5, 10) showed enhanced intramolecular eximer

fluorescence in the presence of β-CyD or γ-CyD,[290] indicating that the two naphthyl moieties are assisted in adopting a favorable orientation; in γ-CyD this could occur by inclusion of both naphthyls, whereas in β-CyD it may take place through inclusion of the methylene chain and association of the naphthyls "exo" to the cavity. It is consistent with this interpretation that γ-CyD protects against quenching of the fluorescence by sodium nitrite, whereas β-CyD does not.[290]

An intermolecular example is provided by triplet−triplet energy transfer from polynuclear aromatic compounds to biacetyl enhanced by CyDs, the size of the CyD cavity correlating with the size of the hydrocarbon.[291] The naphthalene−xanthone−γ-CyD system shows a similar effect, which suggests that the donor and acceptor are maintained in a fixed orientation within the γ-CyD cavity.[292] Other examples of such effects are some symmetrical protonated secondary amines $ArCH_2N^+H_2CH_2Ar$,[293] CyDs covalently modified with a 4-(dimethylamino)benzoyl cap,[294] and side-by-side double-stranded poly(ethyleneglycol) chains carrying terminal fluorophors.[295]

D. Structural Studies

The dependence of complex stability on guest structure (or the less frequently studied dependence of rate on structure) can provide easily accessible information about the structure of the complex. One advantage of such studies is that they can efficiently examine a wide range of structural alterations, whereas the more specific investigational tools, such as NMR or X-ray, are usually applied to a rather small sample of all possible structures.

The results in Table 4, from a study by Bergeron et al.,[230] exemplify this approach. These nitrophenols and nitrophenolates are potential two-site substrates in the terminology of section III.A.4, these binding sites being the nitro and the phenolic ends of the molecule. The comparison of the complexing behavior of 2,6-dimethyl-4-nitrophenol with 3,5-dimethyl-4-nitrophenol (and their conjugate bases) is definitive; the nitrophenyl site is the only site that

Table 4. Binding Constants of Nitrophenols and Nitrophenolates with α-Cyclodextrin[230]

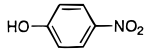
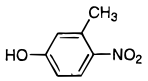
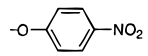
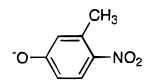
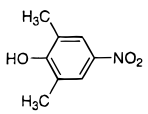
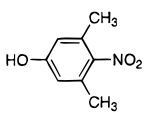
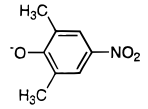
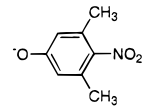
Substrate	K_{11}/M^{-1}	Substrate	K_{11}/M^{-1}
	190		0
	2130		26
	60		0
	1180		0

Table 5. Binding Constants for α-Cyclodextrin Complexes with Substrates Containing the *trans*-Cinnamoyl Group[130]

substrate	K_{11}, M^{-1}	K_{12}, M^{-1}
cinnamic acid	2260	60
cinnamate ion	110	15
3,5-dimethoxycinnamic acid	1965	0
benzalacetone	105	15
methyl cinnamate	1200	50

contributes significantly to the stability of such complexes. Molecular models show that di-*ortho* substitution at the binding site creates a guest moiety that is too large to enter the α-CyD cavity.

A similar demonstration is provided by the data in Table 5.[130] Two potential binding sites, the phenyl group and the side chain, are offered to α-CyD by these substrates, and indeed, most of the systems exhibit both 1:1 and 1:2 (SL_2) complexing. The phenyl site on 3,5-dimethoxycinnamic acid, however, is sterically blocked by the methoxy disubstitution, so this compound is a one-site substrate; accordingly, no 1:2 complex can be detected. Moreover, the magnitudes of the binding constants in Table 5 show that the side chain is the energetically preferred site. (The order-of-magnitude weaker binding of cinnamate ion and benzal acetone is attributed to the polarity of these substrates.[130])

The binding orientation of 1-substituted and 2-substituted naphthalenes in CyDs has been studied.[296−299] Fujita et al.[297] observed that α-CyD was a more effective catalyst of the hydrolysis of 1-naphthyl acetates than of 2-naphthyl acetates, whereas γ-CyD showed the reverse selectivity; β-CyD had effects intermediate to these. They concluded that the naphthyl function is axially included in α-CyD (that is, the long axis of the naphthyl is parallel to the long axis of the cavity), thus positioning the 1-substituent for catalysis by the hydroxy groups rimming the cavity. In γ-CyD, on the other hand, equatorial orientation of the naphthyl brings the 2-substituent into preferred relationship for catalytic effect. β-CyD could use either orientation, so does not show very selective behavior.

Several authors have studied substituted adamantanes and other alicyclics, drawn to these structures because the alicyclic function is close to spherical, rigid, and very nonpolar.[300−302] In carboxy-substituted substrates of this type two binding sites exist—the carboxylic acid and the alicyclic portion—and so both 1:1 and 1:2 binding can take place.[301] Some of the binding constants are very large, presumably as a result of a close match of the alicyclic group to the CyD cavity.[301] This is the Goldilocks effect: α-CyD is too small, γ-CyD is too big, but β-CyD is just right. (This close matching of binding site to cavity size to maximize complex stability may not be a general phenomenon, for Schneider et al.[245] have concluded, from studies of α-, β-, and γ-CyD with, for example, 1,8-anilinonaphthalenesulfonate, that a looser, not tighter, fit may result in stronger binding.)

Many systematic studies of substituted benzenes have been carried out.[104,105,148,303−313] These have been useful for identifying binding sites and assigning values to microscopic site binding constants.[104]

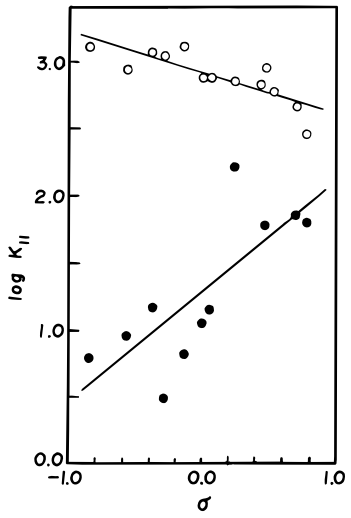


Figure 10. Hammett plots of log K_{11} against substituent constant for α-cyclodextrin complexes of 4-substituted benzoic acids (open circles) and their anions (filled circles).

Figure 10 presents a Hammett plot of log K_{11} against substituent constant for 4-substituted benzoic acids and their anions complexed with α-CyD.[304] (The data are drawn from numerous sources[73,303,304,307,315−319]—mainly ref 304—and some points are mean values.) These are two-site substrates. The pattern seen in Figure 10 is readily comprehensible on the hypothesis that, in the conjugate acid series, the −COOH site is the primary (energetically favored) binding site, and that binding at this site is enhanced by electron release from the *para* substituent. In the anion series, ionization of the primary site leaves only the 4-substituent site for binding, so K_{11} is smaller for the anion series; moreover, a greater electron density at the binding site leads to greater complex stability. Thus the negative slope in the acid series and the positive slope in the anion series are consistent results. The greater scatter observed with the anions is reasonable, for here the reaction site is not physically distant from the substituent site - in fact they are identical, hardly an optimal situation for a linear free-energy relationship. The 3-substituted substrates corresponding to the 4-substituted compounds in Figure 10 give α-CyD complex stabilities that fall, on the average, on the lines drawn in Figure 10. The reasonable inference is that the binding site assignments are the same in the two sets of substrates.[307,310]

4-Substituted phenols show behavior quite different from that seen for the benzoic acids.[306] In both the phenol and the phenolate series complex stability (with α-CyD) roughly increases in order of increasing Hammett substituent constant. The interpretation is that in both series the dominant (perhaps the sole) binding site is the 4-substituent. This generalizes the conclusion drawn for nitrophenols from the data in Table 4. For a given substituent, complex stability is greater with the phenolate substrate than with the phenol.

Anilines behave similarly to phenols, the substituent being the favored binding site. Moreover, since the electronic distribution in neutral phenols (acid form) and anilines (base form) is

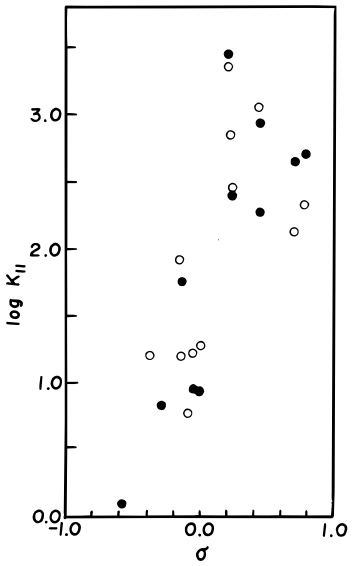
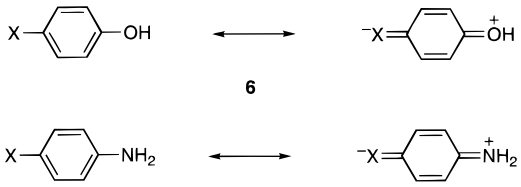


Figure 11. Plot of log K_{11} against substituent constant for 4-substituted phenols (open circles) and 4-substituted anilines (filled circles).

much alike as shown in **6** and **7**, we might expect their CyD complex stabilities to be similar.[305] This



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prediction is tested with the data shown in Figure 11[73,304−306,312,314,316,317,320−325] for their complexes with α-CyD. Evidently the result is as expected; there is, on average, no clear distinction between the complexing behavior of a substituted phenol and the corresponding aniline.

In recent work with substituted benzoic and perbenzoic acids and their conjugate basis, Davies and Savage[326] reach the same conclusions given above for the benzoic/benzoate series, but they find that for both the perbenzoic acid and perbenzoate series the −COOOH and −COOO− sites protrude from the secondary hydroxy rim of the CyD; thus the substituent is the primary binding site. A series of 1,4-disubstituted sulfur-containing benzenes introduces a steric element because of the dihedral angle at the sulfur atom, and this can limit the penetration depth into the CyD cavity.[327] Davies and Deary[327] invoke the dipole moment of the CyD (see section II.A for a discussion of dipole moment[43−45]) as the feature that controls guest orientation in the cavity.

If the cavity of a CyD is likened to the eye of a needle, then a long narrow substrate might be "threaded" through the CyD to give a thread-and-needle type of inclusion complex. This seems to happen with azo dyes, the CyD occupying a site approximately in the region of the azo group.[34,76,204] The effect is more pronounced in much longer guests, and many examples have been demonstrated. Viologens carrying long alkyl chains probably complex in this manner.[328] α-CyD does not complex with

polyisobutylene, β-CyD gives an insoluble complex whose yield decreases with molecular weight of the polymer, and γ-CyD gives a complex whose yield increases with polymer molecular weight.[329] Harada et al.[329] concluded that multiple γ-CyD molecules are threaded on the polyisobutylene chain. Wenz and Keller[330] observed very slow complexation of α-CyD with some iminopolymethylenes and inferred that threading was taking place. After completion of the threading step, they blocked the ends of the chain with covalent bond changes, thus "locking" the CyD molecules onto the chain; light scattering showed that 37 CyD rings were thus permanently threaded. Harada et al.[295] propose that two chains can be threaded side-by-side in the γ-CyD cavity. Much recent activity on catenanes and (especially) rotaxanes of the CyDs[331] suggests that new materials with unusual properties may emerge.

E. Calculational Methods

Theory has been extensively applied to the problem of predicting the structures of CyD complexes, that is, the mutual orientation of host and guest. Molecular mechanics calculations have found the greatest use. Very few calculational investigations have invoked the role of the solvent, a lack that renders (to an experimentalist interested in the solution phase) the results dubious. The usual approach is to compare the theoretical outcome with an experimental finding. The usual result is typically similar to what might be deduced from CPK molecular models together with conventional chemical concepts. Considerable variety in guest type has been studied.[34,47,248,249,257,269,332−345]

The approach of Lichtenthaler and Immel[332] is somewhat different in that they begin with the crystal structures of a number of complexes and conclude that the complementarity of hydrophobic and hydrophilic sites is important in determining host−guest orientation (this bears some relationship to the electrostatic arguments of Kitagawa et al.[43−45] and Davies and Deary[327]) and that flexibility of the CyD plays a role by allowing it to adapt, within limits, to the size and shape of the guest.

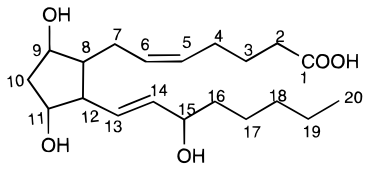
F. Molecular Dynamics

In section II.C the considerable conformational flexibility of the CyDs is discussed. Ultrasonic relaxation studies of the CyDs in aqueous solution show that α-CyD and γ-CyD (but perhaps not β-CyD) undergo conformational changes with relaxation times of 10^{-8} to 10^{-7} s.[170,346,347] Rauth and Knoche[346] and Kato et al.[347] observe two relaxations, accompanied by substantial volume changes. These effects may be the result of conformational or solvational changes.

X-ray crystal studies of CyD complexes have shown that guest molecules, or parts of them, may possess significant mobility.[209,215b,220] Fluorescence lifetime increases of substrates in the presence of CyDs are interpreted as evidence of inclusion[348,349] and, when two relaxations have been seen, of the presence of isomeric complexes[350] or of a distribution of structures.[351]

The most detailed information on the dynamics of CyD complexes has come from NMR spin−lattice relaxation times, which are related to correlation times. This approach was initiated by Behr and Lehn,[352] who examined complexes of the anions of 4-methylcinnamic acid, 3-methylcinnamic acid, and 4-*tert*-butylphenol with α-CyD. The correlation times of the free (uncomplexed) substrates were in the range 2 to 3.2×10^{-11} s, and these increased about 4-fold upon complexation with α-CyD. At the same time, τ_c for α-CyD increased by a factor of 25% to 85% upon complexation (from 34×10^{-11} s in the free state). The reorientation of the methyl groups is slowed 20-fold upon complexing. The very different overall correlation times of the guest and the host in the complexed state means that these entities are in relative motion; that is, the host and guest appear to be but weakly coupled. It is on this basis that Behr and Lehn propose that a description of complex formation should include, besides the thermodynamic stability and the association/dissociation kinetics, the extent of coupling of molecular motions of the interactants of which the complex is composed.

Similar observations have been made on other CyD complex systems, including as substrates sulfathiazole,[353] aromatic amino acids,[354] prostaglandin $F_{2\alpha}$,[355] substituted benzenes in the solid state,[356,357] di-*tert*-butylnitroxide,[358] 4-methylcinnamic acid (in modified β-CyDs),[359] *N*-(trifluoroacetyl)phenylalanine,[360] azo dyes,[361] and fenoprofen.[362] In this last case, the conclusion was reached that an independent motion of the guest exists relative to the CyD cavity.[362] Smith et al.,[360] on the other hand, conclude that there is little freedom of movement of the guest in the trifluoroacetylphenylalanine:α-CyD complex. Hirayama et al.[355] proposed quite different complex structures for the α-CyD and the β-CyD complexes of prostaglandin $F_{2\alpha}$ (**8**) on the basis of the internal correlation times of individual atoms. In the α-CyD



8

complex τ for C-19 and C-20 increased by over 3-fold upon complexing, whereas τ for C-2 and C-3 increased less than 2-fold, and τ for C-10 actually decreased slightly. It was suggested that the C-16 to C-20 alkyl chain is inserted in the α-CyD cavity, with some extracavity interaction of the COOH with the CyD reducing the mobility of the other side chain. In β-CyD, however, the dominant change was at C-10, and both side chains were postulated to protrude from the cavity.

G. Conclusions

A general statement, amounting to a prediction about the structures of CyD complexes, must be regarded as painting with a broad brush, the goal being a picture of the complex that is on average reasonable, but that may have exceptions caused by

unusual features of a guest molecule. The preceding review leads us to these statements:

(a) The CyDs usually function as one-site ligands, this site being the wider rim of the cavity, namely the rim carrying the secondary hydroxyl groups. This statement seems to be firmly based for α-CyD; the larger CyDs may, particularly with small substrates, permit both ends of the cavity to be entered.

(b) The substrate (unless it is so small a molecule as to permit its complete engulfment within the CyD cavity) possesses one or more binding sites, which are portions of the molecule sterically capable of insertion, whether shallowly or deeply, into the CyD cavity. Complexation by a CyD at more than one substrate binding site creates isomeric complexes having different structures.

(c) The structure of a complex is determined by an energetic balance between maximal inclusion, in the CyD cavity, of nonpolar surface area of the guest binding site and optimal mutual orientation of host and guest to permit interactions of polar portions of the guest with the CyD or the solvent.

We have long been guided by some simple postulates that, although formulated to account for complex stabilities, are pertinent also to complex structures,[104,305,310] namely: complex stability, at a binding site, is enhanced by an increase in binding site electron-density; it is enhanced by an increase in binding site polarizability; and it is decreased by an increase in binding site polarity. The influence of electron density in a reaction series is seen in Figure 10; the polarizability effect is responsible for the two highest points in Figure 11, which represent iodo-substituted substrates; and the comparison between benzalacetone ($C_6H_5CH{=}CHCOCH_3$) and methyl cinnamate ($C_6H_5CH{=}CH{-}COOCH_3$) in Table 5 is a polarity effect. Other workers have proposed different guidelines that may be useful as alternatives to, or in combination with, the above, to provide bases for complex structure predictions: Lichtenthaler and Immel[26,332] suggest that optimization of the complementarity of hydrophobic and hydrophilic sites on host and guest determines complex structure, their analysis subdividing the CyD cavity into zones of varying hydrophobicity and hydrophilicity; Davies and Deary[327] adopt a dominating dipole−dipole interaction as the main orienting feature.

VI. The Sources of Cyclodextrin Complex Stability

Much has been written about the forces responsible for the formation of CyD complexes, though some of that discussion is derivative and uncritical. Sections VI.A through VI.D review the evidence bearing on this matter, which is the central issue of this review. As an introductory basis for comprehending this material, the several hypotheses that have been proposed to account for CyD complex formation are listed here: (1) release of "high-energy" water from the CyD cavity; (2) relief of conformational strain energy possessed by the uncomplexed CyD; (3) the hydrophobic interaction; (4) electrostatic interactions, mainly dipole−dipole; (5) hydrogen bonding (which is largely of electrostatic origin); (6) induction forces, primarily dipole-induced dipole; (7) the London dispersion force. Not much seems to have been left out. In section VI.E these ideas are discussed more fully.

A. Empirical Structure–Stability Correlations

1. Univariate Correlations

a. Correlations With Structural Features. The CyD cavity dimensions impose a size exclusion restriction on complex formation, although this control is relaxed somewhat by the conformational flexibility of the CyD itself and by the possibility, which is often exercised, that only a portion of the substrate, which we have called the binding site, need enter the cavity. Most authors comment on this feature of inclusion complex formation, and some workers have designed studies to explore it; some work of this type was discussed in section V.D. The addition of a third space-filling component can enhance complex stability,[113,115,124] although destabilization has also been observed.[116] Although many workers believe that a tight fit of guest to host cavity conduces to strong binding, an argument has been made that a somewhat looser fit may be optimal.[245]

Correlations of complex stability (usually expressed as log K_{11}) with molecular size take several forms. Plots against the number of carbon atoms n_C in a chain or a substituent can be linear or curved; log K_{11} increases with n_C, but may reach a maximum value as n_C becomes large (in an alkyl chain). Such dependencies have been seen for surfactants,[363] alkanes,[364] alkanols,[365,366] nitrophenylalkanoates,[367,368] α,ω-diols[369] and α,ω-dicarboxylates,[370] polymethylene bis(1-pyridinium),[371] and barbiturates.[372] The enthalpy of complexation is a linear function of n_C for some alcohols,[366] and ΔC_P° for complexes of α-CyD with *n*-alkanols increases with n_C.[373] The behavior of α,ω-amino acid anions with α-CyD does not fit this pattern, and Castronuovo concludes that these substrates interact with the external surface of α-CyD.[374]

Several studies have shown correlations with other measures of guest size, including molecular volume,[312,375,376] surface area,[313,364] molecular weight,[73] the parachor,[73,377] and molar refraction.[73] The stabilities of both the 1:1 and 1:2 complexes of α-CyD with cinnamic acid, benzalacetone, and methyl cinnamate (Table 5) are inversely correlated with substrate dipole moment.[130]

b. Free Energy Relationships. Since the hydrophobic interaction is thought by many to play an important role in controlling CyD complex stability, and since log *P* (where *P* is a partition coefficient, often between 1-octanol and water) is widely considered to be a measure of hydrophobicity, many workers have examined their data for evidence of correlation of complex stability with log *P*.[104,237,268,365,372,378,379] The correlations are seldom very good and are sometimes very poor, although the hypothesis is not thereby usually rejected. Often log *P* is incorporated as a variable in a multiple linear regression, as described in section VI.A.2. Some linear correlations with the logarithm of substrate aqueous solubility have been seen.[104,105]

Figures 10 and 11 show Hammett plots of complex stability.[304,307] Obvious trends are seen, but the scatter is greater than that usually observed in

reactions of covalent bond changes. Interaction constants a_{XX} for 1:2 complex formation (eq 11), which are themselves equilibrium constants, have been correlated with σ.[104,105] Other examples are noted in section VII.

Some specialized linear free energy relationships have been proposed to make specific points; these consist of log K_{11} for one series of substrates against the comparable quantity for a related series.[326,368] Kuroda et al.[359b] make a correlation with a reorientation (correlation time) free energy of activation.

Takuma and co-workers[313,380] have argued that the Henry's law constant of a solute is a better measure of hydrophobicity than is the conventional partition coefficient. According to this criterion, benzene is more hydrophobic than is naphthalene, which is more hydrophobic than anthracene, and so on. They then find that log K_{11} decreases as hydrophobicity, by their measure, increases, so they conclude that hydrophobicity is not of major importance in this series of complexes.

Correlations with Hammett's σ show the expected slope if the postulate (section V.G) that complex stability is enhanced by increase in binding site electron density is valid; likewise the dependence on dipole moment is as expected. The log P relationships present a more complicated problem, first because the correlations are often not very successful, but more especially because the "meaning" of log P as the independent variable is not clear cut. There is no doubt that values of log P accord, in their trends with molecular structure, fairly well with intuitive notions of hydrophobicity or nonpolarity. On the other hand, log P seems also to be dependent upon a solute's nonpolar surface area,[381] so it seems that the partition coefficient per unit nonpolar surface area, rather than P itself, is a measure of intrinsic hydrophobicity. That is, correlations with log P may be reflecting dependencies on molecular size rather than on degree of hydrophobicity. A similar problem arises in interpreting correlations with molar refraction, which is considered by many to be a measure of molecular volume, but which is also a measure of polarizability; and the polarizability appears in the potential energy functions for the induction forces and the London dispersion force.

2. Multivariate Correlations

In this approach a wide net is spread, and the catch is examined to identify the significant factors contributing to complex stability. These are the variables that have been incorporated into multivariate correlations (most of these being multiple linear regressions): molar refraction R_D and the Taft steric constant E_S;[382] log P and E_S;[365] R_D, μ (dipole moment), and σ;[306] log S_o (solubility) and μ;[104] heat of fusion and log P;[104] π (Hansch hydrophobic constant), σ, E_S, and a H-bonding "indicator variable";[383] molar refraction and an indicator variable;[384] log P, E_S, and an indicator variable[385] (these were the significant factors identified in a principal component analysis); σ, R_D, and an indicator variable (one term contains a product of Hammett substituent constants);[386] molar volume, Taft−Kamlet π^*, β, and α.[387] The standard deviations of the regressions are typically in the range 0.15−0.4 (in units of log K_{11}, the dependent variable). Indicator variables commonly take the value 1 or 0 depending upon whether a defined structural feature is present or absent.

The signs and relative magnitudes of the coefficients in the regression equation constitute the information to be obtained by this technique. For example, Park and Nah[387] obtain this regression equation for 20 simple organic compounds complexing with β-CyD:

$$\log K_{11} = 7.61(\pm 0.50)V_I/100 - 0.91(\pm 0.28)\pi^* - 1.27(\pm 0.32)\beta - 0.08(\pm 0.42)\alpha - 1.37(\pm 0.31)$$
$$(n = 20,\ r = 0.972,\ s = 0.27)$$

The coefficient of the α term is insignificant (α is a measure of H-bond acidity).[388] π^* is a dipolarity/polarizability measure and β describes H-bond basicity. Complex stability in this series appears to decrease as π^* and β increase, but it is dominated by the volume term, which was interpreted to mean that increasing guest size has a stabilizing influence by increasing dispersion interactions. The negative coefficients of π^* and β were assigned to the possibility of competitive interactions with the solvent.

Any chemical interpretations based on this approach are sensitive to possible correlations between variables of the type mentioned in section VI.A.1 in which log P may be correlated with surface area. The variables should be mutually independent. Matsui et al.[383] have commented on this in the context of CyD chemistry. Silipo and Hansch[382] consider molar refraction to be essentially a "corrected molar volume"; they point out a linear relationship between molar refraction and steric constant E_S. Because of such relationships, some of them subtle, caution is necessary in making inferences about forces of interaction in the complex formation process on the basis of multiple regression analysis.

B. Enthalpy–Entropy Compensation

The demonstration of linear correlations between the enthalpy and entropy changes within a related series of reactions or processes has a long history, which continues to be somewhat excitedly extended by workers in the cyclodextrin field. The presentation of such a correlation raises several questions: (1) Has the correlation been established as a fact rather than an artifact? (2) How "related" must the members of the series be to generate such a correlation? (3) What are the mechanistic or energetic implications of such a correlation?

Suppose a series of reactants varying in some substituent and undergoing a common reaction all yield the same equilibrium constant, so that $\Delta G°$ is the same for all members. This can be written $\delta\Delta G° = 0$, where $\delta\Delta G°$ is the difference between any member of the set and a reference member. Then since $\delta\Delta G° = \delta\Delta H° - T\delta\Delta S°$, it follows that

$$\delta\Delta H° = T\delta\Delta S°$$

and a plot of $\Delta H°$ against $\Delta S°$ for the series will be linear with a slope equal to the experimental temperature. Since the $\delta\Delta H°$ and $T\delta\Delta S°$ terms exactly

offset each other, this is called enthalpy−entropy compensation. (The corresponding behavior in reaction rate studies is known as an isokinetic relationship.) The demonstration and interpretation of such correlations began decades ago[389−396] and continues today; the topic has become a large one that can only briefly be treated here.

Most enthalpy and entropy changes are calculated from the slopes and intercepts of van't Hoff plots (or, for rates, of Arrhenius plots). It is well known[395] that the errors in $\Delta H°$ and $\Delta S°$ values obtained in this way are correlated, and that, even if no real correlation exists, a correlation will be observed as a consequence of the mutual dependence of the errors in the two quantities. Exner[397−399] and Krug et al.[400] have provided data analysis methods that overcome this possible source of an artifactual correlation. Most cyclodextrin workers ignore this problem, or conclude that if the ranges in $\Delta H°$ and $\Delta S°$ are larger than their estimated uncertainties, the error correlation problem is unimportant. This may be unwise.

Calorimetry yields $\Delta H°$ and K_{11} in the same experiment, and $\Delta S°$ can be calculated from these. It is possible that the errors in calorimetrically determined $\Delta H°$ and $\Delta S°$ values are independent, but this situation does not seem to have been analyzed (at least in the context of the compensation effect).

The preceding two paragraphs deal with the first question raised above. The second question, within the CyD field, concerns the scope of the compensation effect, namely, whether a single correlation equation applies to all complexes of a given CyD or only to subsets of them; and whether the several CyDs themselves constitute a single host system, or require separate correlations. First we cite many of the reports of compensation behavior.[11,34,237,244,264,301,312,314,316,369,372a,373,375,378b,401−417] The effect seems to be nearly ubiquitous. This is a key observation. Compensation behavior is so widespread that its absence is more striking, and therefore more interesting, than is its presence.[301] The slope of the $\Delta H°$ vs $\Delta S°$ plot, which is called the compensation temperature, usually has a value in the approximate range 300−400 K. Three studies have amassed a wider variety of structural types to examine in some degree the universality of the compensation effect. Linert et al.[413] used van't Hoff plotting to group enthalpy and entropy values into six classes, on the basis of statistical factors only; the classes accord with chemical intuition. Inoue et al.,[415] collecting data from many sources, combined enthalpy and entropy results for 105 α-CyD complexes, 63 β-CyD complexes, and seven γ-CyD complexes on one compensation plot. A single linear regression line with correlation coefficient 0.88 was drawn. Gelb and Alper,[417] working only with data from the laboratory of Gelb and co-workers, found that 67 α-CyD complexes showed compensation behavior, with the compensation temperature 421 K; a few ionic species deviated from this line. β-CyD complexes behaved differently, with 11 ions or small molecules giving isoentropic behavior and 14 larger substrates giving compensation behavior with compensation temperature 634 K. This is an unusually high value for the slope of such a plot. Bertrand et al.[312] and Rekharsky et al.[416] calculate thermodynamic parameters for the exchange reaction (S represents substrate)

$$\text{S:}\alpha\text{-CyD} + \beta\text{-CyD} \rightleftharpoons \text{S:}\beta\text{-CyD} + \alpha\text{-CyD}$$

and then make compensation plots with these quantities. In the exchange reaction series any solvation effects on the free substrates are eliminated, and the difference in solvation energies between α-CyD and β-CyD is a constant. The slope values are unremarkable.

Molecular-level interpretations of linear enthalpy−entropy compensation have been built on the inference that such behavior constitutes evidence for a dominant mechanism throughout the correlated series. Applications to CyD complexes lead to two types of arguments. In one of these the role of the solvent, water, is controlling, particularly as it participates in "structure making", "structure breaking", and solvation phenomena associated with hydrophobic interactions. This argument has been presented most forcefully (though not in the CyD context) by Lumry and Rajender.[418] A two-state model of water can indeed result in compensation behavior.[419] The other point of view, particularly in the CyD field, is based upon the very common finding that $\Delta H°$ values for CyD complex formation are usually negative and $\Delta S°$ values are also negative; thus complex formation is said to be "enthalpy-driven", and since the "classical" hydrophobic interaction is widely accepted to be "entropy-driven", the conclusion is reached that hydrophobic interaction is not an important factor in the binding. The compensation behavior is taken as evidence that a single mechanism is responsible throughout the series, and which, since by the preceding argument is not the hydrophobic interaction, is often identified with the dipole−dipole or the dipole−induced dipole interaction. As will be shown in section VI.E, however, the occurrence of negative $\Delta H°$ and $\Delta S°$ values does not decisively rule out the hydrophobic interaction, so this reasoning is suspect.

The difficulty in reaching firm conclusions on the basis of the slender evidence available from enthalpy−entropy compensations lies in the lack of a good theory connecting this kind of experimental observation with events at a molecular level. Theoretical workers have recently made some interesting contributions in this field. Weber[420] and Searle et al.[421] emphasize that enthalpy−entropy compensation is to be expected in weak interactions (Weber puts the limit at 5 to 7 RT), and its occurrence cannot be taken as evidence for the controlling importance of solvation or water−structure effects. Grunwald and Steel[422] divide any solution-phase reaction into the conventional chemical equation (called the nominal equation) and an equation (called the environmental equation) describing the involvement of the solvent. They then show that $\Delta G°$ is controlled by the nominal equation, but that $\Delta H°$ and $\Delta S°$ also receive contributions from the environmental equation, which can lead to enthalpy−entropy compensation. Ben-Naim[423] has given a treatment with some of the same features.

There is a related matter, emphasized by Weber;[424] namely, that for covalent bond changes in which bond

energies are much larger than RT it can be expected that $\Delta H°$ and $\Delta S°$ may be essentially independent of temperature, but for weak noncovalent bond changes $\Delta H°$ and $\Delta S°$ are temperature dependent. This temperature dependence, expressed as a large heat capacity change ΔC_p°, has been observed for CyD complex formation,[369,373,425] but most authors overlook it.

C. Theoretical Results

Numerous theoretical approaches have been taken to understanding CyD complex stability.[198,332,335,337,340−342,426−435] A weakness of most calculational methods has been their restriction to the gas phase, so that solvation and hydrophobic effects, which might be anticipated to be significant in many or most aqueous phase systems, play no role in the results. Despite this limitation, some trends of calculated energies with experimental complex stabilities have been noted.[335,341,429,430,432] Such trends are more likely to be seen when calculations are made on a series of guests that are closely chemically related, for then the ignored solvent contributions may be roughly constant within the series. Many workers have concluded that van der Waals interactions (which are usually taken to include both induction and dispersion forces) make the major contribution to complex stability, with the electrostatic contribution being minor or negligible.[341,342,426,428,429,431,435] Harata[198] made a calculation of formation energies of α-CyD, the benzenesulfonate anion, and their complex using Sinanoglu's solvophobic theory,[436] which takes the solvent into account. Mark et al.[434] caution against overconfidence in calculated results solely on the basis of agreement with experiment. They give these three necessary (not sufficient) conditions: (1) ΔG for a closed cycle is zero; (2) increased sampling or equilibration time does not change the free energy; (3) addition of more points does not change the free energy.

D. Solvent Effects

It is probably obvious that most studies of CyD complex stability have been carried out in fully aqueous solution, but quite a few workers have investigated CyD complex formation in binary aqueous−organic solvent mixtures or even in pure organic solvents. There is evidence that the nature of the solvent can influence or control the structure of the complex.[283,414,437,438] Several reports have described increases in CyD complex stability, relative to the fully aqueous system, in mixed solvents or pure organic solvents,[439−443] and complex stability in D_2O is slightly greater than that in H_2O.[444] However, the usual solvent effect consists of a decrease in the stability of the complex relative to water.[445] Most studies have made use of aqueous mixtures with the common water-miscible solvents such as alcohols, dimethyl sulfoxide (DMSO), dimethylformamide (DMF), dioxane, and acetonitrile, but complexes have also been detected in pure solvents of this chemical type,[446,447] and they can form (probably by means of a different distribution of contributing interactions) in hydrocarbons and similar nonpolar solvents.[442,448] Some studies have investigated the effects of salts and substances (like urea and guanidinium chloride) that are protein-denaturing agents.[49−451]

Apparently five different hypotheses have been proposed to account for solvent effects on CyD complex stability. Fairly popular is the idea that the hydrophobic interaction is a major contributor to the complex stability in water, and that increasing the organic content of the aqueous mixture decreases the hydrophobic driving force;[283,449,452−454] quantitative treatments incorporating this idea follow shortly. Eftink and Harrison[455] instead propose that the complex-weakening effect of DMSO on the 4-nitrophenolate−CyD complex results from the greater dispersion interaction between the substrate and DMSO (in the bulk solution) relative to the substrate−water dispersion interaction. While this may be so, their argument is built upon their prior conclusion, based on the signs of $\Delta H°$ and $\Delta S°$, that the hydrophobic interaction is not important. This conclusion, however, is not firmly based.

A third hypothesis invokes a stoichiometric equilibrium that includes water in the complex,[407,456]

$$S + CyD + nH_2O \rightleftharpoons S{\cdot}CyD{\cdot}H_2O_n$$

from which may be written

$$K_{11}(\text{apparent}) = K_{11}(\text{true}) \times a_{H_2O}^n$$

Thus the measured binding constant decreases as the water concentration is decreased by the addition of organic cosolvent. A difficulty with this approach is that it does not take into account any concomitant changes in other solvent properties that may contribute to the effect; that is, it assumes that K_{11}(true) is independent of solvent composition.

Yet another idea is that organic cosolvents are functioning as competitive substrates; as their concentrations are increased, they more effectively compete to displace the primary substrate from the guest cavity.[457−460] With this hypothesis it becomes possible to evaluate binding constants for the postulated cosolvent−CyD complex formation, and the results do tend to be chemically reasonable. The fifth hypothesis supposes that the organic cosolvent undergoes inclusion together with the primary substrate to yield a complex of 1:1:1 (or higher) stoichiometric ratio.[439,440,443,461] This hypothesis can readily account for increases in complex stability as organic cosolvent is added to the aqueous system. Some authors note that combinations of these several effects may occur.

We turn now to quantitative descriptions of solvent effects, beginning with Sinanoglu's solvophobic theory,[436] according to which the free energy change of complex formation may be an essentially linear function of solvent surface tension provided interactions other than the solvophobic interaction (hydrophobic in pure water) remain largely unchanged as the solvent composition is altered. Örstan and Ross[462] found that the addition of ethanol or formamide decreased the stability of the indole:β-CyD

complex, whereas addition of calcium chloride increased the complex stability. Both effects are consistent with the solvophobic theory, and these authors concluded that surface tension is the major controlling factor, or, more explicitly, that the change in molecular surface area exposed to solvent is a critical factor in determining complex stability.

Harrison and Eftink[463] observed that addition of methanol destabilized the adamantanecarboxylate: β-CyD complex and applied a linear extrapolation technique[464] to the plot of ΔG°_{11} against surface tension γ to partition the observed free energy change into a hydrophobic contribution and an "internal" contribution. Since the ΔG°_{11} vs γ plot shows definite curvature, the quantitative result of the extrapolation must be considered questionable.

Our laboratory has developed a phenomenological model of solvent effects that has been applied to the CyD complexing problem. Observed solvent effects are considered to arise from solvent−solvent interactions, which give rise to a *general medium effect* (and which is identified as the solvophobic effect); solute−solvent interactions, giving the *solvation effect*; and solute−solute interactions (the *intersolute* or *intrasolute effect*). Placing a solute in solution gives a free energy change that is the sum of contributions from these three effects.[465,466] The solvation effect is modeled as a competitive stoichiometric equilibrium of solute R solvated by water (W) and organic cosolvent (M) as shown in the two-step (three-state) Scheme 1.

Scheme 1

$$RW_2 + M \overset{K_1}{\rightleftharpoons} RWM + W$$

$$RWM + M \overset{K_2}{\rightleftharpoons} RM_2 + W$$

The solvation energy is postulated to be a weighted average of contributions by the various solvated species

$$\Delta G_{solv} = \Delta G_{WW}F_{WW} + \Delta G_{WM}F_{WM} + \Delta G_{MM}F_{MM} \quad (22)$$

where F_{WW}, F_{WM}, and F_{MN} are fractions of solute in the RW_2, RWM, and RM_2 forms. Further development gives eq 23, where K_1 and K_2 are dimensionless exchange solvation constants defined by Scheme 1, and x_1, x_2 are bulk mole fractions of water (solvent component 1) and organic cosolvent (solvent component 2).

$$\Delta G_{solv} = \frac{(-kT \ln K_1)K_1x_1x_2 + (-kT \ln K_1K_2)K_1K_2x_2^2}{x_1^2 + K_1x_1x_2 + K_1K_2x_2^2} + \Delta G_{WW} \quad (23)$$

In the fully aqueous medium eq 23 becomes $\Delta G_{solv}(x_2 = 0) = \Delta G_{WW}$. Defining the solvent effect operator δ_M by $\delta_M\Delta G_{solv} = \Delta G_{solv} - \Delta G_{solv}(x_2 = 0)$ gives, for a single solute

$$\delta_M\Delta G_{solv} = \frac{(-kT \ln K_1)K_1x_1x_2 + (-kT \ln K_1K_2)K_1K_2x_2^2}{x_1^2 + K_1x_1x_2 + K_1K_2x_2^2} \quad (24)$$

The general medium effect is described by a cavity model.[467] For the placement of a solute species into solution (that is, the dissolution process), a cavity must be created in the solvent with expenditure of energy $\Delta G_{gen\ med}$ given by

$$\Delta G_{gen\ med} = gA\gamma \quad (25)$$

where A is the surface area of the cavity, γ is the solvent surface tension, and g is an empirical factor correcting for the effect of surface curvature on the surface tension. (Actually A is the nonpolar surface area of the solute in contact with the cavity wall.[468]) The model postulates[465] that the surface tension in eq 25 is that appropriate to the composition of the solvation shell about the solute; this postulate leads to eq 26, where $\gamma' = (\gamma_2 - \gamma_1)/2$ and γ_1, γ_2 are the surface tensions of pure water and organic cosolvent.

$$\gamma = \gamma_1 + \gamma'\left[\frac{K_1x_1x_2 + 2K_1K_2x_2^2}{x_1^2 + K_1x_1x_2 + K_1K_2x_2^2}\right] \quad (26)$$

Combining eqs 25 and 26 and applying the δ_M operator gives

$$\delta_M\Delta G_{gen\ med} = gA\gamma'\left[\frac{K_1x_1x_2 + 2K_1K_2x_2^2}{x_1^2 + K_1x_1x_2 + K_1K_2x_2^2}\right] \quad (27)$$

Equation 27 shows how the general medium and solvation effects are coupled through the exchange constants.

Presuming that the intersolute effect is composition independent gives eq 28 for the solvent effect upon solubility:[465,466]

$$\delta_M\Delta G^*_{soln} = \delta_M\Delta G_{gen\ med} + \delta_M\Delta G_{solv} \quad (28)$$

An analysis of the complex formation process[46] gives eq 29, which relates the solvent effect on complex stability $\delta_M\Delta G^*_{comp}$ to the solvent effects on the solubilities of the substrate S, the ligand L (which is the CyD), and the complex C. Thus the solvent

$$\delta_M\Delta G^*_{comp} = \delta_M\Delta G^C_{soln} - \delta_M\Delta G^L_{soln} - \delta_M\Delta G^S_{soln} \quad (29)$$

effect on complex formation is described by the expression obtained upon combining eqs 24 and 27−29. In practice, the small range of x_2 that is experimentally explored in CyD studies allows the system to be simplified to a one-step solvation scheme, so that K_1 is the only solvation exchange constant. The result contains six unknown parameters,[92] too many for practical use, so chemically justifiable approximations are applied to yield two useful forms: When it

is possible to assume $K_1^C = K_1^S = K_1^L = K_1$, eq 30 results

$$\delta_M \Delta G^*_{comp} = \frac{(kT \ln K_1 + \Delta gA\gamma')K_1 x_2}{x_1 + K_1 x_2} \qquad (30)$$

where $\Delta gA = gA^C - gA^S - gA^L$. Note that ΔgA is a negative quantity. When the approximation $K_1^C = K_1^S < K_1^L$ is valid, eq 31 is obtained

$$\delta_M \Delta G^*_{comp} = \frac{(kT \ln K_1 - gA\gamma')K_1 x_2}{x_1 + K_1 X_2} \qquad (31)$$

where it is understood that K_1 and gA refer to species L; gA is a positive quantity.

If the organic cosolvent possesses no special affinity for the CyD cavity, then eq 30 is applicable, whereas if the organic cosolvent is significantly bound to the CyD eq 31 applies; that is, these equations separately describe the cases in which the cosolvent competitively binds (eq 31) or does not (eq 30). The cosolvents to the left of the discontinuity in Figure 1 are described by eq 30, and those to the right of the discontinuity by eq 31; the distinction between these cases is made on the basis of the magnitudes of the parameters.[92] A plot of log K_1 against log P has the same shape as Figure 1 (in which the ordinate is $\delta\Delta G^*_{comp}$ at $x_2 = 0$).

For systems described by eq 30, the contribution of the general medium effect (hydrophobic interaction) to the complex stability in the fully aqueous solution is given, in percent, by the expression 100 $\Delta gA\gamma_1/\Delta G^*_{comp}$ ($x_2 = 0$). For the complexes of methyl orange zwitterion and of 4-nitroaniline with α-CyD, this calculation yields 92% and 108%, respectively, with uncertainties of about 20%.[92] The energetic roles of organic cosolvents upon complex stability can also be evaluated by separately calculating (making use of the experimentally determined parameters) $\delta_M \Delta G_{solv}$ and $\delta_M \Delta G_{gen\ med}$. The results for the above complexes show that, if eq 30 applies, complex weakening from addition of cosolvents arises mainly from the general medium effect, because $\Delta gA\gamma'$ is much larger than is $kT \ln K_1$. For eq 31 systems, however, complex weakening comes mainly from the solvation effect because of the anomalously large K_1 value.

E. Hypotheses

The cyclodextrins have stimulated a considerable volume of prose on the subject of the forces involved in inclusion complex formation. Some of this discussion is not strongly supported by experimental evidence. Before reviewing the ideas that have been proposed it will be helpful to clarify the levels on which the discussion has been conducted. There are three such levels: the phenomenological, the physical, and the chemical. At the least fundamental of these, the phenomenological level, pairwise (or higher order) interactions, such as solute−solute, solute−solvent, and solvent−solvent, are identified and assigned quantitative roles; this approach is exemplified by the solvent effect theory described in section VI.D. At the most fundamental, physical, level, the forces of interaction constitute the goal and the language, these being grouped into the electrostatic forces (charge−charge or Coulombic, charge−dipole, dipole−dipole, and others); the induction forces (charge−induced dipole and dipole−induced dipole); and the London dispersion force. The term van der Waals force(s) is used by many authors, probably with variable meaning; some include all the potential energy functions having the r^{-6} distance dependence, which includes the dipole−dipole, dipole−induced dipole, and dispersion forces, whereas others seem to include only the last two of these. The third level, the chemical level, is entirely a consequence of the other two, yet is not superfluous; it embodies phenomena like hydrogen bonding, charge-transfer interaction, ion-pairing, the hydrophobic interaction, and steric effects. It is characteristic of treatments in the CyD field (as in others) to mix the chemical and physical level descriptions, usually a harmless practice, but carrying the potential for confusion as a result of "double counting"; for example, molecular size can play a critical role in permitting or preventing cavity inclusion, but molecular polarizability, which controls the induction and dispersion interactions, is also related to size, so these chemical and physical descriptions are not independent.

The several hypotheses that have been proposed as responsible, solely or in combination, for CyD complex stability will be separately discussed. Bergeron[3] has reviewed this subject.

a. Relief of Conformational Strain. Saenger and co-workers[49,50,215a,216,219,470] originated the notion that the deviation from hexagonal symmetry of α-CyD hexahydrate in the solid state constitutes a store of energy, whose relief upon complex formation is a major source of energy driving the complexation. This was identified as an "induced fit" mechanism.[470] β-CyD and γ-CyD, however, exist in nearly symmetrical conformations,[54] yet their complexes tend to be stronger, on average, than do those of α-CyD (see section IV), rendering the strain relief hypothesis dubious. Bergeron and Meeley[471] discounted the hypothesis on the basis of comparative studies of native with methylated CyDs, although the argument does not seem conclusive. Eftink and Harrison[445] point out that conversion of the α-CyD from its distorted to its symmetrical conformation must cost energy; the process cannot be a source of energy for complex formation. Suppose Scheme 2 describes the process in which the distorted CyD (presuming it to exist also in solution) forms a complex with a conformational change:

Scheme 2

$$L_{distorted} \rightleftharpoons L_{sym} \qquad \Delta G = +a$$

$$L_{sym} + S \rightleftharpoons SL_{sym} \qquad \Delta G = -b$$

$$L_{distorted} + S \rightleftharpoons SL_{sym} \qquad \Delta G = a-b$$

Thus the existence of the distorted form, which is in its lowest energy equilibrium state, destabilizes the complex by making an unfavorable positive contribution $+a$ to the net free energy change.

Gidley and Bociek[68] provided ^{13}C NMR evidence that α-CyD actually exists in solution in the sym-

metrical conformation, and a molecular dynamics result is consistent with this finding.[69] There now seems to be no support for the relief of conformational strain hypothesis.

The term "induced fit" apparently has been used in two ways in CyD complexation chemistry. In one of these, noted above, the term describes the presumed conformational change as the α-CyD passes from its distorted to symmetrical conformation, with the associated assumption of an energetic driving force. The other usage refers to the flexibility of the CyD structure,[332] which may undergo a conformational change upon binding; but it carries little or no connotation of an associated driving force, though it may be a critical feature in determining complex structure and in optimizing opportunities for other modes of interaction. Gelb and Schwartz[412] emphasize this role of CyD conformational changes.

b. Release of Cavity-Bound High-Energy Water. According to this hypothesis, which was largely developed around observations on α-CyD, the two water molecules in the CyD cavity lack the complement of stabilizing hydrogen bonds that would be available to them in the bulk solvent phase. Upon complex formation these waters leave the CyD cavity, taking up residence in the bulk, and making available their pent-up energy as a driving force for the complexation. The idea is usually credited to Bender,[9,73] but it can be found in the 1965 review by Thoma and Stewart.[8] Griffiths and Bender call the cavity-bound water "enthalpy-rich;" Saenger and coworkers[53,470] refer to it as "activated" water. Many authors mention the hypothesis favorably. Takagi et al.[472] have tried to estimate the thermodynamics of inclusion separately from solvation effects.

The problem with the high-energy water hypothesis is that it focuses on the water and neglects the CyD; or more generally, it fails to consider the energetics of the entire system. It well may be that the cavity-bound water is at a higher energy than is bulk water, but this is only part of the matter. Consider 1:1 complex formation between substrate S, ligand L (which is the CyD), and complex C:

$$S + L \rightleftharpoons C$$

The net free energy change due to solvation phenomena (solute−solvent interactions) is

$$\Delta G_{\text{solvation}} = \Delta G^{C}_{\text{solv}} - \Delta G^{S}_{\text{solv}} - \Delta G^{L}_{\text{solv}} \quad (32)$$

(Equation 32 does not include other contributors to the overall free energy change.)

Each of the quantities on the right side of eq 32 is a free energy change for solute−solvent interactions in the spontaneous process in which a solute (S, L, or C) is introduced to water, so each of these is a negative quantity. Very often they will combine to yield a positive value of $\Delta G_{\text{solvation}}$, so that solvation is usually complex destabilizing, although it is possible that $\Delta G^{C}_{\text{solv}}$ is a sufficiently negative quantity (e.g., if solvation modes are created in C that do not exist in S or L) that solvation could be complex stabilizing.

But our present concern is with $\Delta G^{L}_{\text{solv}}$. If it is true that the cavity-bound waters are of unusually high energy, then that circumstance will cause $\Delta G^{L}_{\text{solv}}$ to be a smaller negative number than it might otherwise be, but the net effect is still to make a positive contribution to $\Delta G_{\text{solvation}}$. I have estimated $\Delta G^{L}_{\text{solv}}$ for α-CyD in water to be about −1.0 in units of log K_{11}.[473] This means, if the estimate is reasonable, that every α-CyD complex, in water, is destabilized to the extent of a factor of 10 in K_{11} by hydration of α-CyD. Perhaps this factor would be greater if the included water were not "energy-rich"; but the phenomenon can hardly be regarded as a major "driving force" for complex formation.

c. Hydrophobic interaction. The contribution of the hydrophobic interaction to the stability of CyD complexes is an unsettled subject. This is because we lack a definitive criterion of the involvement of hydrophobic interaction.

In "classical" hydrophobic interaction between two nonpolar molecules the structure of water in the vicinity of the solutes is a key feature of the phenomenon;[474,475] the enthalpy and entropy changes of the process are both positive, and the association is said to be "entropy driven". This has long been taken as the experimental signature of the effect. The relationship of water structure to CyD complex stability has been discussed[66,476−478] (see also section VI.B, where the connection between water structure and enthalpy−entropy compensation is noted), but as a concept leading to understanding or predictive ability the notion of water "structure making" or "structure breaking" is difficult to apply (or even to take seriously, after reading Roseman and Jencks[479] on the subject).

But with the cyclodextrins we are not dealing with nonpolar molecules and classical hydrophobic interaction. Irrespective of the nature of the guest molecule, the CyD is a "semipolar" molecule. Of course, the CyD cavity appears to be nonpolar relative to bulk water, but, as described in section II.D, the cavity is actually semipolar. If hydrophobic interaction does take place, there should be no expectation that the criterion defining the classical interaction—a positive entropy change—should be applicable in a CyD system.

The experimental observation is that in most (not all) CyD complex formation processes, $\Delta H°$ and $\Delta S°$ are both negative and the association appears to be "enthalpy driven." As a consequence, many authors, on the basis of applying the classical criterion, have concluded that hydrophobic interaction is not an important contributor to the association. Jencks[480] has described a model of "nonclassical" hydrophobic interaction between semipolar molecules that seems pertinent to the CyD situation. In this model the "driving force" for association may appear as either a favorable enthalpy or entropy change, and it follows that to rely on the sign or magnitude of $\Delta H°$ or $\Delta S°$ as a criterion of interaction mechanism or type of intermolecular force is risky in these systems. van der Jagt et al.[481] reached a similar conclusion in 1971.

Despite the inadequacy of the thermodynamic quantities $\Delta H°$ and $\Delta S°$ as defining criteria, many authors have concluded that hydrophobic interaction plays a role, either dominant or at least significant, in the CyD complex systems they have studied;

examples are cited: refs 9, 47, 73, 239, 241, 242, 301, 309, 365, 370, 372b, 373, 378a, 379, 383−385, 449 and 482−486. Several kinds of evidence provide the basis for these conclusions: thermodynamics, solvent effects, partition coefficient correlations, and structural features. A common argument is that complex destabilization upon the addition of organic cosolvents implicates hydrophobic interaction; and correlations of complex stability with guest partition coefficient also are widely taken as evidence in favor of this effect. But, as pointed out earlier in this review, such relationships can also be interpreted as evidence for other mechanisms, the dispersion force in particular. Does an increase of complex stability with partition coefficient mean that the hydrophobic interaction depends upon "degree of hydrophobicity", or is it merely a reflection of dependence on molecular size?

The quantitative solvent effect model outlined in section VI.D provides a phenomenological definition of the hydrophobic interaction as that component of the overall free energy change that arises from solvent−solvent interactions, distinct from the contributions that can be ascribed to solute−solute and solute−solvent interactions. There is some ambiguity in this definition, as in all others, but it provides an experimental criterion whose quantitative application is demonstrated in section VI.D. The identification of solvent−solvent interaction effects with the hydrophobic interaction constitutes an adoption of the cavity model of hydrophobicity, in which hydrophobic association is attributed to the "squeezing-out" effect of water. A further implication of this definition is developed in section VII, where the hydrophobic contribution is calculated by taking into account the guest nonpolar surface area that is removed from contact with water by inclusion in the CyD cavity. This view accords well with the chemical intuition that leads us to infer a hydrophobic interaction when a complex structure determination reveals that the nonpolar portion of a guest is buried in a CyD cavity.

d. Dipole−Dipole and Hydrogen-Bonding Interactions. That hydrogen bonding may play a significant role in contributing to the stability of CyD complexes in aqueous solution is discounted by many authors, but some workers have suggested the possibility that hydrogen bonding may be important.[47,286,372a,385,403] A hydrogen bond between the phenolic hydroxy group and an ether oxygen in the chlorophenol:heptakis (2,3,6-tri-*O*-methyl)-*β*-CyD complex in hydrocarbon solvents has been proposed.[442]

One weakness of some of the proposals that hydrogen bonding and dipole−dipole interactions make significant contributions lies in their authors' rejection of hydrophobic interaction on the basis of an observed favorable enthalpy change. As shown in the preceding paragraphs, however, this argument is not a strong one. Nevertheless, there seem to be reasonable grounds for accepting a role for the dipole−dipole force in some complexes, although, as is often the situation, ambiguity exists. Kitagawa et al.[43] discussed the role of dipole−dipole interaction in determining complex structure. Davies and co-workers[326,327,386] have developed linear free-energy relationships that are consistent with a dipole−dipole mechanism, but they probably also could be interpreted in terms of dipole−induced dipole and dispersion forces. Lichtenthaler and Immel[26,332] and Bonora et al.[276] have emphasized the importance of the polar or hydrophilic portions of the CyD cavity in controlling complex structure or energetics. On the other hand, some cinnamoyl substrates (in Table 5) form α-CyD complexes whose stabilities are inversely correlated with substrate dipole moment.[130] Park and Nah,[387] in a multiple linear correlation, found a negative correlation with the dipolarity/polarizability parameter π^*, and Tabushi and Mizutani[428] concluded from a force field calculation that polar interactions were minor in the 4-nitrophenol:α-CyD complex.

e. Induction and Dispersion Forces. The ambiguity attached to the term van der Waals forces has already been noted. This ambiguity existed 60 years ago,[487] and writers still do not all signify the same collection of phenomena by the term,[488] but it can be inferred that workers in the CyD field mostly seem to mean either the induction and dispersion forces combined or the dispersion force alone. The involvement of these forces in CyD complexes is widely claimed, although to some extent on the basis of the weak argument, described in connection with dipolar forces, that certain thermodynamic quantities rule out hydrophobic interaction, leaving by default the van der Waals forces. Other authors implicate some combination of hydrophobic and van der Waals interactions.

The induction and dispersion interactions depend upon polarizability, which in turn is related to molecular size and electron density, and so to the correlation variables molar refraction, Hammett substituent constant, the parachor, molar volume, the dipolarity/polarizability parameter π^*, and even the partition coefficient. As we have seen, it is possible to interpret correlations with such quantities in more than one way. Roseman and Jencks[479] have emphasized the difficulty in resolving multiple mechanisms of this type (the hydrophobic and van der Waals interactions being such a pair). Theoretical investigations (usually the solvent is not included) suggest that the van der Waals contribution to the interaction energy can be overwhelmingly important for a wide variety of molecules.[342,426,428,429,431]

The particular example of the α-CyD complexes of 4-nitrophenol and of 4-nitrophenolate has attracted a great deal of attention, in part because it is easy to study, but mainly because it exemplifies an apparent exception to the generalization that "partitioning" of charged substrates into a CyD cavity is less favorable than inclusion of an uncharged analog; $\log K_{11} = 2.32$ ($n = 16$, $s = 0.10$) for the 4-nitrophenol complex, whereas $\log K_{11} = 3.36$ ($n = 17$, $s = 0.11$) for the 4-nitrophenolate complex.[183] As described in section V, the nitrophenyl end of the substrate is the dominant (or only) binding site. Both complexes should therefore enjoy approximately the same extent of stabilization from the hydrophobic interaction. That the charged form is able to complex with α-CyD more strongly, by a factor of 10, than the neutral form

is due, first, to this circumstance that the site of ionization is not the binding site (compare benzoic acid, log $K_{11} = 2.88$, with benzoate ion, log $K_{11} = 1.05$, for their α-CyD complexes); and second, to the extensive charge delocalization characteristic of 4-substituted phenolates.[306] This increases electron density at the substrate binding site. The tight fit of the nitrophenyl function in the α-CyD cavity favors dispersion interaction, which probably occurs with both 4-nitrophenol and 4-nitrophenolate, but the anion is especially well disposed to strong interaction because of the resonance delocalization.[228,230,489,490]

The series of halogens, as in halo-substituted aromatics, display CyD complex stabilities that are as expected if the dispersion interaction is significant.[104] Both the polarizability and the size of the binding site increase in the order chloro, bromo, iodo, and the fit of iodophenyl in the α-CyD cavity is very nice. Such correspondences, as we have often noted in this review, are suggestive but not conclusive.

F. Conclusions

The relief of conformational strain hypothesis can now be discounted as a contributor to the driving force for CyD complex formation. Release of cavity-bound waters of hydration may make a contribution, but by itself can never constitute the energy source for complex formation.

Despite the views of many commentators, based on their classical interpretations of observed enthalpy and entropy changes, that the hydrophobic interaction is not a significant contributor, it now seems very probable that this mechanism is important in many CyD complexations. This statement constitutes an acceptance of the reality of "nonclassical" hydrophobic interaction, in which semipolar CyD and guest associate with negative values of $\Delta H°$ and $\Delta S°$. Perhaps the most compelling evidence in favor of this view is the repeated observation, in studies of CyD complex structure, that the most nonpolar portions of guest molecules are enclosed in the CyD cavity.

That other contributors to CyD complex stability must exist is shown by measurements of significant complex stability in systems for which no hydrophobic interaction seems possible; namely, with very polar substrates. Consider the halide ions, which form complexes with α-CyD having these binding constants:[491] F^-, $K_{11} = 1.6\ M^{-1}$; Cl^-, $K_{11} = 1.5\ M^{-1}$; Br^-, $K_{11} = 1.7\ M^{-1}$; I^-, $K_{11} = 12.4\ M^{-1}$. These guests lack dipole moments (they possess quadrupole moments owing to nuclear structure), so, aside from possible quadrupolar forces, the dominant forces must be charge−dipole, charge−induced dipole, and the dispersion force. The fit of the smaller ions in the α-CyD cavity is loose. Presumably solvation destabilization exists, yet significant complexing takes place. The formic acid:α-CyD complex is another in which hydrophobic interaction seems unlikely; it shows[258b] $K_{11} = 4.1\ M^{-1}$. Here dipole−dipole, dipole−induced dipole, and dispersion forces seem the only candidates contributing to the stability of this complex. Some authors have rejected the dispersion interaction as an important contributor on the grounds that the substrate is merely exchanging one set of dispersion interactions (with the water as bulk solvent) for another set (with the interior of the CyD cavity); but the polarizability of water is lower than that of the organic components lining the CyD cavity, so it is quite possible for the dispersion force to have an effect. The distance of separation of guest from the cavity wall is a critical factor.

The phenomenological model outlined in section VI.D, applied in the broadest terms to the CyD complex formation process, gives

$$\Delta G^*_{comp} = \Delta G_{intrasolute} + \Delta G_{solvation} + \Delta G_{gen\ med} \quad (33)$$

Here $\Delta G_{intrasolute}$ describes host−guest interactions, a quantity that can only appear as a stabilizing contribution (or can be absent). The $\Delta G_{gen\ med}$ term has been identified with the hydrophobic interaction; this too can only be zero or stabilizing. The solvation term, $\Delta G_{solvation}$, can be either stabililizing or destabilizing, but will usually be destabilizing. The small, although significant, K_{11} values quoted above for complexes of halide ions and formic acid with α-CyD denote (since the hydrophobic interaction term is absent) a slight domination by $\Delta G_{intrasolute}$ over $\Delta G_{solvation}$. But this may mean that the host−guest interaction (by means of the forces identified above) may be quite substantial, since solvation destabilization should be extensive for these substrates.

The only way to achieve high complex stability (and the meaning of "high stability" can be inferred from Table 3) is with a substrate that receives substantial stabilizing contributions from both $\Delta G_{intrasol}$ and $\Delta G_{gen\ med}$. The 4-nitrophenol and 4-nitrophenolate pair discussed in section VI.E provides a good example, for both of these presumably make the most of the hydrophobic contribution (since the nitrophenyl binding site completely fills the α-CyD cavity), and the electron delocalization in the anion provides an induction and dispersion force boost that yields a 10-fold increase in complex stability. Another type of combination of forces can be seen in comparisons of substrates $CH_3(CH_2)_nX$; when X is a polar group, such as COOH, OH, etc., the complex is much stronger than when X is CH_3. Presumably in both types of systems the hydrophobic interaction is maximized, but when X is a polar group additional interactions (dipole−dipole, hydrogen bonding) of X with the CyD rim may add to complex stability. This picture of the energetics is consistent with the structural evidence summarized in section V.G.

VII. Prediction of Cyclodextrin Complex Stability

Perhaps "prediction" is a misleading word here, for there is no pretense at a fundamental calculation of equilibrium constants using the methods of statistical mechanics and quantum mechanics. Instead the approach, which is common with other physical quantities such as pK_a values and partition coefficients, is to seek patterns of behavior, such as linear free-energy relationships and group additivity schemes, that permit useful numbers to be estimated. This approach is therefore empirical, although it is guided by physical chemical concepts.

All of the correlations described or cited in section VI.A constitute predictive tools of this type. These

can be quite useful, but they possess the drawback that each of them is applicable to only a relatively small subset of all possible complexes (with a given CyD). Williams and co-workers[492,493] have described a method based on summing contributions from many sources (entropic cost of bimolecular association, hydrophobic interaction, restriction of internal rotations, dipolar interactions), but it has not been applied to CyD complexes. Guo et al.[494] used an artifical neural network analysis to predict K_{11} values for α-CyD with monosubstituted benzenes. This method uses molar refraction, the Hansch hydrophobic parameter, and the Hammett substituent constant as inputs, but the chemical content is not evident and the method seems unlikely to attract a following. It is notable that the best-studied of monosubstituted benzenes, benzoic acid, was not included in the study.

The phenomenological model has been applied to this problem by writing, for complex formation in aqueous solution, eq 34, which combines eqs 32, 33, and the cavity model treatment of section VI.D:[473]

$$\Delta G^*_{comp} = \Delta G^{C}{}_{intrasol} + (\Delta G^{C}_{w} - \Delta G^{S}_{w} - \Delta G^{L}_{w}) + \Delta g A \gamma_1 \quad (34)$$

In eq 34, ΔG^*_{comp} is given by

$$\Delta G^*_{comp} = kT \ln K_{mf} \quad (35)$$

where K_{mf} is the binding constant on the mole fraction scale, and the free energy change is on a per molecule basis. $\Delta G^{C}_{intrasol}$ describes substrate−ligand interaction within the complex. (In the present context, the guest is the substrate and α-CyD is the ligand.) The ΔG^{C}_{w}, ΔG^{S}_{w}, ΔG^{L}_{w} quantities are solvation energies for the complex C, the substrate S, and the ligand L, respectively. The $\Delta g A \gamma_1$ term describes the general medium effect, γ_1 being the surface tension of water and ΔgA being given by $\Delta gA = gA^{C} - gA^{S} - gA^{L}$. Each quantity A is a molecular surface area (actually the nonpolar molecular surface area), and g is an empirical factor that corrects for the effect of curvature on the surface tension.

The binding constant K_{mf} on the mole fraction scale is related to K_{11} on the molar scale by eq 36, where ρ is the solvent density and M* is the number of moles of solvent per kilogram of solvent:

$$K_{mf} = \rho M^* K_{11} \quad (36)$$

For convenience, we write $Z = \Delta G^{C}_{intrasol} + (\Delta G^{C}_{w} - \Delta G^{S}_{w} - \Delta G^{L}_{w})$. Then combination of eqs 34−36 gives

$$\log K_{11} = -\log \rho M^* - \frac{Z}{2.3kT} - \frac{\Delta g A \gamma_1}{2.3kT} \quad (37)$$

Equation 37 is general for noncovalent association. We next make the specific application to water at 25 °C by inserting the quantities $\rho = 1.00$, M* = 55.55, $k = 1.38 \times 10^{-16}$ erg K^{-1}, $T = 298.15$ K, and $\gamma_1 = 71.8$ erg cm^{-2}. Equation 37 then becomes

$$\log K_{11} = -1.74 - [Z] - 0.0758 g \Delta A \quad (38)$$

where $[Z] = Z/2.3kT$, and g, which is treated as a constant, has been factored out of ΔgA. The quantity g has been independently estimated, from solvent effect studies, to have the value 0.42 ± 0.05; inserting this into eq 38 gives

$$\log K_{11} = -1.74 - [Z] + 0.032(-\Delta A) \quad (39)$$

which is written in this way because ΔA is negative, so $-\Delta A$ is a positive quantity (having the units Å^2 molecule^{-1}). $[Z]$ is on the same scale as log K_{11}. Equation 39 expresses log K_{11} as a function of just two quantities, namely, the change in nonpolar surface area as the substrate and ligand associate to form the complex, and $[Z]$, which incorporates solvation energies and the substrate−ligand interaction energy. It should be noted, from the definitions of $[Z]$ and Z, that this quantity is composed of four terms, two preceded by positive signs and two by negative signs, so that at least some compensation of terms can be expected in $[Z]$. Prediction of log K_{11} consists of making estimates of ΔA and $[Z]$ for use in eq 39.

This approach has been applied to α-CyD complexes.[473] ΔA is estimated for each reasonable binding site in the substrate, only the nonpolar portion of the surface area being counted in ΔA. The treatment in section II.D, in which the polarity of the α-CyD cavity was inferred to be equivalent to log $P = -0.3$, provided a criterion for determining if a binding site, or any portion of a binding site, is polar or nonpolar. For this purpose the fragmental partition coefficients of Nys and Rekker[495] were used. Then eq 40 gives $-\Delta A$:

$$-\Delta A = \text{area of nonpolar portion of binding site} \quad (40)$$

For a binding site that essentially fills the CyD cavity, an alternative calculation is given by

$$-\Delta A = \text{internal area of CyD cavity} - \text{area of polar portion of binding site} \quad (41)$$

Obviously $-\Delta A$ cannot be larger than the internal area of the CyD cavity. For use in eq 39 all areas are expressed in Å^2 molecule^{-1}. The internal area of the α-CyD cavity was taken as 125 Å^2 molecule^{-1}.

The quantity $[Z]$ was estimated from correlation equations developed on the basis of many literature reports of α-CyD complex stability; these equations are collected in Table 6. The independent variables in Table 6 have these meanings:

σ	Hammett substituent constant; use σ_m or σ_p as appropriate; for the benzodiazepine moiety use $\sigma = +1.7$
σ^*	Taft polar substituent constant; the sum $\Sigma\sigma^*$ refers to groups attached to the carbinol carbon, including hydrogen
f_R	Nys−Rekker fragmental partition constant; Σf_R is for the alkyl group R in RC_6H_5
R_D	ionic refraction at the sodium D line[496]
pK_a	pK_a value of conjugate acids of inorganic anions[184,497]
n	number of CH_2 groups
n_C	number of C atoms

The correlation coefficients show that some of these relationships are crude, yet some of them are quite good, and in general they seem to reflect the influence of guest structure on $[Z]$.

Table 6. Binding Site [*Z*] Values[473]

binding site or substrate type	[*Z*]	*r*[a]
Ar−COOH (m,p)	$+0.39\sigma - 0.62$	0.65
Ar−F (m,p)	$+0.9\sigma + 1.18$	
Ar−Cl (m,p)	$+0.52\sigma + 0.08$	0.72
Ar−Br (m,p)	$+0.54\sigma - 0.38$	0.83
Ar−I (m,p)	$+0.40\sigma - 0.95$	0.78
Ar−OCH_3 (m,p)	$+2.1\,\sigma + 1.36$	
Ar−CH_3 (m,p)	$+0.46\sigma + 0.90$	0.50
Ar−NH_2; Ar−OH (m,p)	$+1.01\sigma + 0.34$	0.72
Ar−H	$+0.69\sigma + 0.33$	0.78
Ar−CN (m,p)	$+1.17\sigma + 0.35$	0.96
Ar−NO_2 (m,p)	$+1.19\sigma + 0.18$	0.95
Ar−$COOCH_3$ (m,p)	$+0.99\sigma + 0.01$	0.68
Ar−$C(CH_3)_3$	$+0.65\sigma + 0.68$	0.95
Ar−X (o)	$+0.43[Z]_p + 0.43$	0.71
Ar−CH=CH−COOH (m,p)	$+0.70\sigma - 1.28$	0.62
Ar−CH=CH−COOH (o)	$+0.68\sigma - 0.37$	0.68
Ar−CH=CH− (p)	$-0.29\sigma - 0.05$	0.45
Ar−CH=CH− (o,m)	$+0.03$ ($\pm$0.25)	
$CH_3(CH_2)_nCH_3$	$+1.03$ ($\pm$0.20)	
$CH_3(CH_2)_nX$ [X=COO^-, SO_3^-, SO_4^-, NH_3^+, $NHCONH_2$]	$-0.10n + 0.03$	0.93
$CH_3(CH_2)_nOH$ ($n \leq 3$)	-0.34 ($\pm$0.07)	
$CH_3(CH_2)_nOH$ ($n \geq 4$)	$-0.47n + 1.75$	1.00
alkylbenzenes	$-0.85\sum f_r + 1.35$	0.77
$CH_3(CH_2)_nCOOH$	-1.07 ($\pm$0.24)	
$CF_3(CF_2)_nCOOH$	-0.95 ($\pm$ 0.05)	
small, highly polar R−COOH	-2.37 ($\pm$0.35)	
branched alcohols	$-0.72\sum\sigma^* + 1.14$	0.64
halide ions	$-0.18\,R_D - 0.18pK_a - 1.39$	0.99
other inorganic anions	$-0.18\,R_D + 0.13pK_a + 0.27$	0.94
phenylazobenzenes	-1.26 ($\pm$0.49)	
naphthylazobenzenes	-0.19 ($\pm$0.15)	
CH_nCl_{4-n}	$+0.70$ ($\pm$0.10)	
cycloalkanes	$-0.24n_c + 2.47$	0.90
acetamides	-1.05 ($\pm$0.21)	
acetates	-1.23 ($\pm$0.09)	
$C_6H_5CH_2-$	$+0.92$ ($\pm$0.08)	
sugars	-1.96 ($\pm$0.23)	
cyclohexenenones, cyclohexadienones (including steroid A ring)	-0.95 ($\pm$0.28)	
$HO(CH_2)_nOH$ ($n \leq 5$)	$+0.42$ ($\pm$0.08)	
$HO(CH_2)_nOH$ ($n \geq 6$)	$-0.52n + 3.78$	0.99
$HO(CH_2)_{n+2}OH$	$+1.17 \times [Z]_{CH_3(CH_2)nOH} + 0.83$	0.99
barbituric acids	-0.89 ($\pm$0.19)	
barbituric acid anions	-0.56 ($\pm$0.11)	
barbituric acid anions	$+0.77[Z]_{acids} + 0.13$	0.91
cycloalkanols	$+0.03$ ($\pm$0.43)	
naphthyl (and other fused aromatic rings)	$+0.73$ ($\pm$0.32)	

[a] Correlation coefficient.

Equation 39 is applied to each binding site in the substrate molecule, and the overall K_{11} is calculated as the sum of binding site constants, according to eq 8; thus no decision has to be made as to preferred or dominant binding site. Figure 12 shows the result of this method applied to 569 α-CyD complexes. Of these estimates, 332 (58%) agreed within 0.30 unit of the experimental log K_{11} values, and 542 (95%) agreed within 1.00 unit.

Extension of this approach to the complexes of β-CyD may contribute to a resolution of the question as to whether α-CyD and β-CyD differ merely quantitatively or are qualitatively different in their behavior. At a deeper level it will be interesting to tease apart [Z] into its constituent parts; this probably will require the acquisition of information from

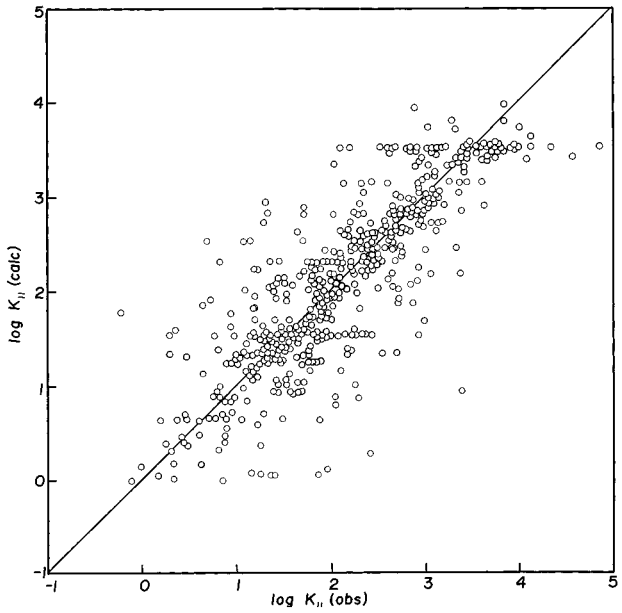


Figure 12. Plot of log K_{11} values calculated with eq 39 (vertical axis) against experimental log K_{11} values, for 569 α-CyD complexes. In the congested parts of this plot some points are suppressed. The line has unit slope. (Reprinted from ref 473. Copyright 1996 American Pharmaceutical Association and American Chemical Society.)

independent sources (such as free energies of hydration). Such results also will aid in establishing the still more interesting matter of whether this approach is fundamentally correct in its partitioning of the overall complex stability into components contributed separately by solute−solute, solute−solvent, and solvent−solvent interactions.

VIII. References

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