Applications of Computational Chemistry to the Study of Cyclodextrins

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I. Introduction

Computational chemistry is a multidisciplinary area of science transcending traditional barriers separating biology, chemistry, physics, and mathematics. Because theory can help rationalize experimental observation, provide information not amenable to experimentation, and even make predictions concerning the outcome of future experiments, it is becoming more widely accepted by experimental scientists as a valuable adjunct to their existing studies.[1] One aspect of applied theory involves molecular simulations at the atomic level. This is sometimes called “molecular modeling”, and it has been warmly embraced by the chemical community and with good reason; much can be derived from it.

Uses of computational chemistry in the area of cyclodextrins have, until recently, been somewhat limited however. The reason for this is not a lack of interest from those studying this material but rather due to the fact that cyclodextrins are relatively large, flexible molecules that are often studied experimentally in aqueous environments. This makes computations on them prohibitive or, as often is the case, forces one to introduce so many assumptions and impose so many restrictions so as to become unrealistic. The size of cyclodextrins and their derivatives makes applications of quantum mechanics difficult even when symmetry conditions are imposed. Because these macrocycles have many rotatable bonds, there exist an enormous number of conformational states. So, even when computationally expedient methods such as molecular mechanics are used, difficulties arise because one needs a complete conformer search to locate all populated states at ambient temperatures. Moreover, cyclodextrins are usually studied experimentally in aqueous media, an environment that until recently has been the bane of computational chemistry, creating a major hurdle that most computational chemists were not willing to surmount. Finally, we need to be cognizant of the fact that only recently has the average chemist had the tools available to carry out these calculations in a reasonable time period. It made little sense for a scientist to do a calculation, even 5 years ago, that would require months or years of computing time. Consequently, other more tractable projects were pursued by computational chemists or the experimentalist simply spent his or her time performing other experiments rather than investing time and resources into computing machinery and software that was inadequate for the task.

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Nonetheless there exist a significant number of computational studies over the past decade that have lead to a more profound understanding of the structure, dynamics and chemical behavior of cyclodextrins. A splendid review article covering theoretical aspects of cyclodextrins and their inclusion complexes has been written by Sherrod.[2] Since then, however, a significant number of computational studies have appeared further delineating the detailed, atomic level behavior of these molecules. In this review we examine all computational studies to date highlighting the more significant ones that, in this author's opinion, are most meaningful from both a computational perspective (veracity) and from the viewpoint of the bench chemist who uses or intends to use cyclodextrins in their work.

This review is written for the experimentalist and not the theoretician. Accordingly, we present below a brief introduction to the area of molecular modeling and computational chemistry. We delineate what computational tools are available, explain how they work, and briefly indicate what those computational methodologies are capable of providing for the experimentalist. By necessity this section must be brief; the computational methods presented below are selected only because they have been used by the authors whose papers are described in this review. With this rudimentary background, though, the average experimentalist will be better able to understand the limitations of the computational tools used and to then to decide how significant a particular paper has been to the understanding of cyclodextrins.

II. Molecular Modeling

A model is a representation of reality. It is a likeness or a semblance, and the term "model" means different things to different people. One may consider two broad categories of chemical models: macroscopic models and microscopic models. Macroscopic models describe coarse-grain features of a system or process. They consider, for example, relative rates of uptake of material, kinetics of transport, rates of depletion of entities involved in a process, and so on, but they do so without consideration of structural features of the individual molecules. In contrast, microscopic models, sometimes called atomistic models, usually take full account of all the atoms in the system.

Microscopic, atomistic modeling, sometimes called "molecular modeling", is done two ways: using fitting procedures or by applying theory from first principles. The fitting procedures are an attempt to rationalize connections between molecular structure and physicochemical properties (quantitative structure property relationships, QSPR) or with biological response (quantitative structure activity relationships, QSAR). Usually the response is regressed on to a set of molecular descriptors, e.g., $\log(1/C) = b_0 + \sum b_i D_i$. Here C is the concentration of a compound needed to elicit a response, b_0 is a constant, b_i are the least-squares multiple regression coefficients, and the D_i are molecular descriptors. One can very accurately predict an unknown molecule's property or anticipated response by computing its molecular descriptors and substituting those values into the model. There are no rules about what kind of descriptors are to be used, but descriptors often include information about molecular size and shape, electronic effects, and lipophilicity. This type of modeling requires use of existing data to create the model and then allows one to interpolate or extrapolate new properties/activities of as yet unknown molecules within that same class of compounds. QSARs and QSPRs have been a major influence on the design of drugs and materials, and one would expect them to have relevance in the industrial application of cyclodextrins.

The second kind of atomistic modeling applies theory, usually from first principles. The major tools implemented are the following:

A. Quantum Mechanics (QM)

The objective of quantum mechanics is to describe the spatial positions of all electrons and nuclei. Most commonly implemented is the molecular orbital theory (MOT), where electrons are allowed to flow around fixed nuclei (Born–Oppenheimer approximation) until they reach a self-consistent field (SCF). This is where the attractive and repulsive forces of all electrons with themselves and the stationary nuclei are in a steady state. The nuclei are then moved iteratively (followed after each movement by more SCF calculations, SCF-MOT) until the energy of the entire system can go no lower. This is called energy minimization or geometry optimization and allows one to predict structural and electronic features of molecules.

The QM methods available for evaluating this include the ab initio methods and the semiempirical methods. The central processor unit (CPU) time scales as approximately n^4 for the ab initio techniques, where n is the number of mathematical functions needed to describe each atomic orbital (that in turn are used to construct the molecular orbitals), while the time scales as n^3 for most semiempirical methods. This, together with the fact that far less functions are used to describe each atomic orbital, makes the semiempirical methods faster than the ab initio methods, and this speed-up becomes even more prevalent as the size of the molecules studied become larger. So, in general, computational chemists rely on the (ideally) more accurate ab initio methods for small molecules while larger ones, like cyclodextrins, are relegated to treatment by semiempirical theories.

B. Molecular Mechanics (MM)

Molecular mechanics is a nonquantum mechanical method of computing structures, energies, and some properties of molecules. Molecular mechanics uses an empirical force field (EFF), which is a mathematical recipe for reproducing a molecule's potential energy surface (the location and motion of nuclei on such surfaces dictate a molecule's structure and dynamical properties). The underlying philosophy of molecular mechanics is to view a molecule as a collection of particles (nuclei) held together by some type of elastic forces (electrons). These forces are

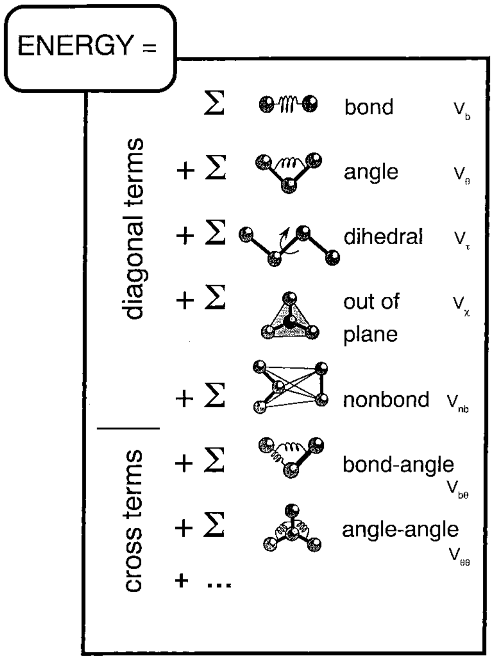


Figure 1. Schematic of a typical empirical force field expression. Diagonal terms refer to interactions that can be expressed as a function of a single internal coordinate, whereas cross terms include coupled interactions involving two or more coordinates. Mathematical expressions (potential energy functions) for each term exist, allowing one to compute the component energies that are summed up to give the total energy of the system. Reproduced by permission from: *Reviews in Computational Chemistry*; VCH Publishers: New York, 1991; Vol. 2, p 104.

defined in terms of potential energy functions of internal coordinates such as bond lengths, bond angles, and torsion angles. Once all the potential functions and associated force constants have been determined, the internal energy is minimized by moving the particles toward their equilibrium positions (geometry optimization). In contrast to QM where electrons are explicitly treated, in MM the electrons are implicitly treated and, thus, one cannot assess bond-making or bond-breaking events as one can with QM methods unless special functions are used. Since EFF's treat electrons implicitly rather than explicitly, the CPU times scale as N^2, where N is the number of atoms (not functions) in the molecule. Hence molecular mechanics is much faster than quantum mechanics and can be used to reliably predict structures of small- to medium-sized molecules quickly or to evaluate very large molecular assemblies, e.g., cyclodextrins in a water bath. Because empirical force fields are so prevalent, not only in molecular mechanics but also in molecular dynamics and Monte Carlo simulations described below, we present a pictorial view in Figure 1 of some of the types of interactions accounted for by a typical valence force field.

C. Molecular Dynamics (MD)

In molecular dynamics the motion of atoms is described by Newtonian laws: $F_i(t) = m_i a_i = m_i \partial^2 r_i(t)/\partial^2 t^2$, where $F_i(t)$, $a_i(t)$, and $r_i(t)$ are the force, acceleration, and position of atom i at time t. The force on atom i is the negative gradient of the potential which is obtained from the same EFF used in molecular mechanics. To integrate the equations of motion, position vectors are determined using these forces along with the previous positions of atoms. From this, atom velocities and a temperature are evaluated. With these ingredients a "trajectory", which is simply a history of the motion of the system over the time period of interest, can be generated. Hence MD has both kinetic and potential energies, in contrast to the QM and MM methods described above. The advantage of this is that by applying enough kinetic energy (temperature) one can move around on a molecule's potential energy surface, sampling many conformational states along the way. Unfortunately these calculations are very CPU intensive and simulation time periods are typically in the picosecond range (10^{-12} s) so that only very fast processes such as low-energy bond rotations can be studied. Nonetheless, even short simulation times provide information concerning the twisting and flexing of rotatable bonds so that dynamical information can be obtained. Many scientists misuse the word "simulation" in their work. In contrast to the MM and QM calculations, MD methods simulate the movement of atoms for a given time period and from that one can determine ensemble averages that (with statistical thermodynamics) allow one to make the connection between the micro- and macroscopic worlds.

D. Monte Carlo Simulations (MC)

This method uses the same EFF's as in MM and MD. One starts with a collection of particles and computes the system's energy, E_1, for that initial configuration. One or more of the particles is then randomly selected and moved to create a second configuration. The energy of this configuration, E_2, is computed, and that new configuration is deemed "acceptable" if $E_2 < E_1$ or if $E_2 > E_1$ with some probability, $p = \exp[(E_2 - E_1)/kT]$. A large number (millions) of random moves are made, and a large number of energetically acceptable states are thus obtained, providing (again using statistical mechanics) averaged energies or averaged properties of the system being studied. This too is considered a simulation.

E. Molecular Surfaces

Several types of molecular surfaces exist, the two most important for this review being the molecular electrostatic potential (MEP) surface and the lipophilic surface. The electrostatic potential around a molecule dominates the interaction of that molecule with incoming reagents or guests because the forces responsible are the long-range Coulomb forces. To evaluate the MEP one needs first to determine the density of electrons in and around the molecule from a suitable QM calculation. The electric potential at each point in the vicinity of the molecule is the electric force acting on a unit positive charge at that point caused by both the nuclei and the electrons. One can make plots of how that potential changes as one slices through the molecule, or one can make other types of plots including projecting the potential onto the molecule's van der Waals surface or making an isopotential surface encapsulating the molecule at some selected electrostatic potential value. Regions of excess negative charge on the molecule are stabilizing toward reagents or guests bearing positive charge and vice versa for negative regions. A molecule's "surface" is typically obtained by simply considering the atomic radii of its constituent, spherical atoms (a CPK surface) or by rolling a suitable probe atom or molecule over the system of interest maintaining the atomic van der Waal radii between the probe and the system being interrogated. These latter "contact" surfaces are simply the points where the probe and molecule touch. Often a solvent probe (a sphere having the dimension of the solvent which is usually water) is used, and the distance from the sphere's center to the molecule is used to define the "solvent accessible surface area", which is a less well defined, extended contact surface. For many of the studies in this review, especially the lipophilic surfaces, various properties are computed and mapped onto each contact point.

F. Molecular Graphics

QM, MM, MD, and MC calculations all generate enormous quantities of data; graphics or visualization methods renders the data manageable and assimilable. The pictures may be graphs or simple chemical structures or they may be highlighted, three-dimensional images emphasizing structural, electronic, or reactivity features of interest. With cleverness four or five attributes of the system can be shown in a single image. Motion pictures can be created to illustrate dynamical processes. Molecular graphics temporarily uncouples the scientist from the underlying theories and equations being implemented so as to focus on the science at hand. It is an aid that helps the chemist to perceive relationships more easily and is now a standard feature of most computational chemistry programs.

These are the major computational tools that will be of use to the reader of this review. But to put much of this into perspective we now must consider a simple potential energy surface (PES) as in Figure 2. This PES is very simple; it involves the rotation around two bonds designated as Φ and Ψ and there exist several minima on that potential energy surface. The problem is that we do not know what the PES looks like ahead of time. But, we want to locate minima on that unknown surface corresponding to stable structures and we use computational chemistry tools to do this. For both the quantum mechanics and molecular mechanics techniques one begins with a starting structure that with some a priori knowledge (e.g. from a structural database or a good guess) is presumed to be close to a minimum on that potential energy surface. The system is allowed to go downhill toward the nearest minimum on that surface. This is called energy minimization which is synonomous with the term geometry optimization. Using QM this is a slow process, but with MM it is fast. With both methods, though, one ends up with a structure whose shape and energy corresponds to the minimum that is nearest to the initial starting geometry (most energy minimizers are not able to seek more distant minima but some can). Obviously multiple starting points must be selected to map out the entire surface and this can be very time-consuming for molecules with many rotatable bonds such as the cyclodextrins.

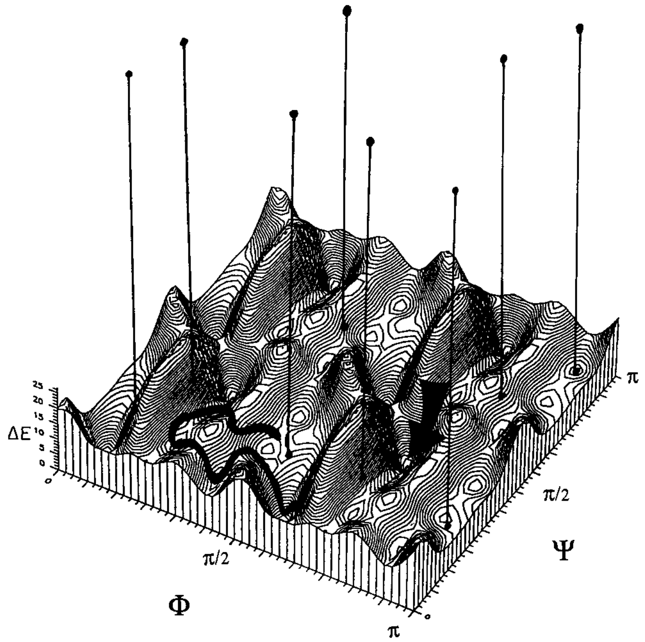


Figure 2. Part of a complex potential energy surface (PES) illustrating the differences between the computational methods used to explore such surfaces. Quantum and molecular mechanics use energy minimization schemes (geometry optimization). Beginning with a structure near a minimum on the PES the atoms are moved so that the computed energy can go no lower (large arrow). Most minimizers seek the nearest minimum on the surface. Molecular dynamics provides kinetic energy allowing the system to meander over part of the terrain (winding line). Monte Carlo methods randomly select internal coordinates, and energies are computed at those points which are accepted or rejected on the basis of an energy criterion (dropped lines onto the surface).

In contrast, MC sampling methods randomly select molecular geometries from a range of suitable Φ and Ψ angles. At each randomly selected point on the surface, whether it be a maximum, a minimum, or somewhere between, the energy is computed and each structure is accepted or rejected using energetic criteria described earlier. The Boltzmann weighted, low-energy structures corresponding to minima can be located this way, and ensemble averaged values can be derived for comparison with experiment. Finally, the MD methods begin at some point on the PES, and a MM calculation is first done to find a nearby local minimum. Kinetic energy is added such that the system can meander over the PES sampling configurations for statistical averaging. The most important feature of MD sampling for this review is that one typically examines a very small region of conformational (and configurational) space, and with such limited samplings the results are biased to reflect the starting region on the PES. This inadequate sampling of "phase space" is an inherent problem with MD that often provides inconclusive results at best or misleading ones at worse. And, for large systems such as cyclodextrins, the results must be viewed with some skepticism.

With a description of the theoretical tools along with the computational methodologies now in use, the reader is in a better position to be able to understand what has been accomplished in the area of computational studies of cyclodextrins, as well as to appreciate the limitations of each study described below. Throughout this review reminders will be given concerning the limitations of the computational methods employed by the various authors whose work is described.

III. Structural Features of Cyclodextrins

Structural features of cyclodextrins have been addressed using data derived mostly from X-ray crystallographic analysis of solid-state structures and from NMR studies of cyclodextrins and their complexes in solution. NMR studies of cyclodextrins are described in detail in this special issue of *Chemical Reviews* by Schneider.[3] A chapter on solid-state structure and dynamics of cyclodextrins is also presented by Saenger[4] as is one by Harata, who focuses on solid-state stereodifferentiation.[5] All three reviews are replete with leading references so no mention of structural features derived from these techniques is presented here. Although this chapter is intended mostly for researchers working in the area of cyclodextrin chemistry, we shall not presume all readers are knowledgeable about common atom-labeling schemes or of existing definitions of structural degrees of freedom commonly used in the literature. Accordingly, in Figure 3, we present a typical cyclodextrin showing its topology and atom labels and, in Figure 4, we depict several important geometry descriptors that will be mentioned throughout this review.

Some of the earliest computational studies directed toward understanding structures of cyclodextrins were published by scientists who were already deeply entrenched in structural studies of carbohydrates. In one study, French and Murphy[6] correlated "virtual" bond lengths with geometric changes of residues in amyloses. In the virtual bond method a residue is a rigid body, that in this case is an α-D-glucopyranose, attached to a virtual bond that is defined as a vector extending from O_4 to O_1 of an adjacent residue. The authors analyzed existing structural data to define a suitable residue geometry, and then a screw operator was used to create the entire polymer chain. For a chain containing n residues with p turns per repeat distance, f, the angle, q, through which a residue must be rotated to generate the next residue is $q = 2p\pi/n$ and the translation along the fiber axis is $h = f/n$ (h is simply the rise per residue). Knowing the length of the virtual bond and helical parameters n, p, and f, one can fully generate the polymer. This way a variety of amylose polymorphs were constructed and studied.[6] These studies laid the groundwork for computing helixes having zero pitch, i.e., completely circular amyloses. French and Murphy derived a set of structural parameters for α-, β-, and γ-cyclodextrins using this approach and then made cogent arguments concerning the interrelationships of the monomer structures and their orientations relative to the macrocycle.[7] While such studies used computers for analysis, we mention them only in passing because they are not in the spirit of modern computational methodology as described in the Molecular Modeling section above. Nonetheless, these and related analyses provided some understanding of the important relationships within this class of molecules and answered a variety of then pertinent questions concerning the feasibility of making larger and smaller ring systems.

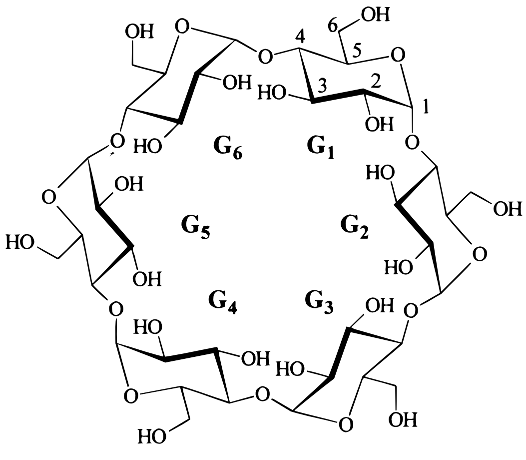


Figure 3. Topology and atom labeling of a typical cyclodextrin. The cyclic oligosaccharide presented here is *cyclo*-α(1→4)-glucohexaoside (*cyclo*[Glc*p* α(1→4)-]$_6$), commonly called α-cyclodextrin. The individual sugar monomers are α-D-glucoses, labeled G_1, G_2, ..., G_n, where n = number of monomers in the macrocycle.

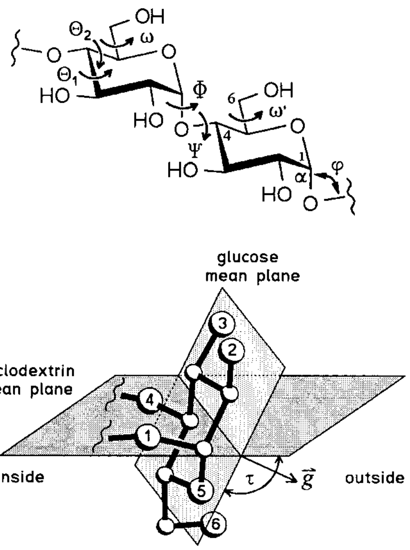


Figure 4. Cyclodextrin geometry descriptors. The intersaccharidic bond angle ϕ is defined by the atoms $C_1-O_1-C_{4'}$, the torsion angles describing the conformations about the glycosidic linkages are denoted as Φ ($O_5-C_1-O_1-C_{4'}$) and Ψ ($C_1-O_1-C_{4'}$-$C_{3'}$). The endocyclic ring torsions around C_4 are designated as Θ_1 ($C_1-C_2-C_3-C_4$) and Θ_2 ($C_3-C_4-C_5-O_5$), and the exocyclic torsion angle ω ($O_5-C_5-C_6-O_6$) describes the orientation of the primary C_6 hydroxyl groups relative to the pyran ring. The tilt angle τ denotes the inclination of the mean plane of the pyranose rings toward the mean plane of the macrocycle described by the intersaccharidic (i.e., anomeric) oxygens. Taken with permission from ref 24.

The first "modern" computational study of cyclodextrins was published in 1970 by Sundararajan and Rao.[8] At that time the X-ray structure of α-cyclodextrin alone was known and those researchers were interested in using computational chemistry to understand the conformations of other ring systems and to determine whether the inability of *Bacillus macerans* to form smaller ring systems was due to enzyme specificity or an inherent instability of smaller cyclodextrins. The computational method employed is what we now call molecular mechanics but with severe restrictions concerning geometry optimization (none were used) and types of potential functions implemented in the force field (see below). Using an algorithm like that described above, a zero pitch helix of amylose monomers resulted in suitable macrocycles but only if the residue geometry was adjusted and if the interresidue bridging oxygen bond angle (C−O−C) was adjusted to allow closure (a small range of Φ and Ψ, the dihedral angles of rotation about the glycosidic bonds, was also considered).

The potential energy function consisted of a nonbonded energy term, i.e., the van der Waals attractive and repulsive interaction of atoms, and a term that treated the C−O−C bond angle as a harmonic springlike assembly. A hydrogen bond energy was also included. For α-cyclodextrin they found that the C−O−C bond angle was at a minimum at 119° when the hydrogen bonding term was included, a number agreeing exactly with that of the crystal structure. Germane to their inquiry was the finding that an increase in steric energy takes place for the *β*- and *γ*-cyclodextrins but was especially severe for macrocycles having fewer than six monomers. This increase in energy for the cyclopentamer was attributed to steric repulsion of the $-CH_2OH$ groups within the cavity. Later in this review we will cover the work of Lichtenthaler and Immel, who evaluated the energetics and structures of these and even smaller cyclodextrins. For the moment, however, we point out that many of the results derived by Sundararajan and Rao were by necessity somewhat speculative, albeit correct in some predictions, because so many degrees of freedom within these flexible macrocyclic systems were held rigid in their calculations. The reader is to bear in mind that at the time of these calculations, PCs and benchtop computers that now adorn most laboratories were 12 years in the future, the existing mainframe computers were slow and limited in memory, and there did not exist the nice pull-down graphical interfaces for visualization we now take for granted thus making much of their work exceedingly arduous by modern standards.

In the intervening years great strides were made in both hardware and software development for molecular modeling.[9,10] Eventually researchers had at their disposal conformer search algorithms that were reasonably robust, being capable of finding most minima on a given potential energy surface,[11,12] and they had enough computing horsepower to energy minimize those conformers without any artificial constraints. Accordingly, several researchers found it a propitious time to begin their studies of cyclodextrin structure.

One such group was that of Venanzi et al.,[13] whose interests focused on the biomimetic properties of cyclodextrins (see later) but whose early work focused on exploring the structural and electrostatic features of *β*-cyclodextrin and *N*-methylformamide "capped" *β*-cyclodextrin that serve as models of α-chymotrypsin. It had been speculated that the enhanced catalytic ability of the derivatized cyclodextrin was due to the formamide groups creating a shallow cavity for substrate binding that positions the acyl group of the substrate nearer to the secondary hydroxyl rim of the cyclodextrin cavity; Venanzi's goals, thus, were to assess the nature of this intrusive floor, evaluate the flexibility of the glycosidic linkages, determine the orientation of the secondary hydroxyl groups, and assess the electrostatic recognition pattern presented by the macrocycle for the incoming substrate.

Initial structures (derived from an X-ray structure of *β*-CD with a barrel-shaped guest included) were constructed. Missing force field parameters were developed, the validity of which were verified by the fact that AMBER could then reproduce the X-ray structures of the systems under study, albeit marginally in the case of the derivatized macrocycle. It was found that the caps induced severe structural changes of the macrocycle with some of the caps moving outward due to pyran ring twisting while one moved into the interior of the macrocycle to form a floor within that cavity. The ensuing discussions focused on this nonsymmetric structure, but the reader should note that no other symmetric structures were considered and, for a molecule like cyclodextrin, having so many minima on its potential energy surface, using a single conformer to rationalize dynamical properties may be misleading. Indeed, later we point out that Venanzi addressed this problem head-on by carrying out exhaustive conformer searches.

The derived structures were then used to generate electrostatic potential maps to assess the molecular recognition by electrostatic complementarity. At each point in and around the cyclodextrin an electrostatic interaction was computed as described in the Molecular Modeling section of this review. Slices through these electrostatic fields were presented as contour maps. For the *β*-cyclodextrin the electrostatic potential in the interior parallel to the plane formed by the acetal linker oxygens is both symmetric and positive, providing a "bull's-eye" pattern for directing the trajectory of incoming nucleophiles. The detailed features of the electrostatic contour maps are very much the same as those computed by Sakurai (see later), who derived his potentials using the semiempirical quantum mechanical CNDO method. The electrostatic potential maps for the nonsymmetric capped derivative were surprisingly similar to the native cyclodextrin that also contained fairly symmetric, positive electrostatic regions within the cavity. So, the long-range electrostatic forces are similar for the two macrocycles but the derivatized system has a shallow floor capable of pushing substrates toward the secondary rim, and by virtue of losing its symmetry, several of the secondary alcohols are canted inward providing a complementary geometry required for the acyl transfer transition state.

The concept of having macrocyclic structures with complementary, or near-complementary, structures to enhance guest binding efficiency was well established at that time. One group interested in predicting the conformational complementarity of β-cyclodextrin complexes as found in the solid state along with binding energies of such complexes was Janssen's. To predict binding energies Kostense et al.[14] first had to evaluate, in general terms, the conformation of β-cyclodextrin. This was done by retrieving 18 cyclodextrins from the Cambridge Structural Database[15] and evaluating characteristic structural features that would allow them to eventually create a suitable cavity geometry for binding of different classes of hosts. Their analysis revealed that the O_4 (acetal linker oxygens) were not always located in a circular arrangement but in some instances formed an ellipse. When the long axis of the ellipse was plotted versus the computed van der Waals volume of the included guest, two categories of guests could be discerned: one group being small or spherical and the other being substituted benzenes. Equations correlating the guest volume with ovality of the O_4 atom positions were then derived. It became clear that when guests enter the empty cavity of the host the host, adopts a conformation which fits best around the guest (see next section). One observation is that as the volume of the guest decreases the elipticity increases. A second (expected) observation is that benzene derivatives of volume comparable to that of spherical guests give a more pronounced ellipse.

The upshot of these studies is that if one knows how the distortion of the β-cyclodextrin is related to the van der Waals volume of the guest, one might be able construct a cyclodextrin in a suitable geometry that would complement the guest as found in the crystal. A set of rules for selecting glucose moieties required to generate such cavities were developed. These rules include the following: (1) The O_4 atoms are to be located on an ellipse, the dimensions of which can be calculated from the van der Waals volume of the guest to be bound. (2) Use the existing relationship relating the $O_4-O_{4'}$ distances with the $C_4-O_4-O_{4'}$ angles. (3) Use glycosidic bond angles of 117.8°. (4) Tilt each glucose 10.3°. The structures generated with these rules were then used to compute guest binding energies (discussed in a later section of this review).

Developments in data analysis of X-ray scattering intensities along with an accelerated interest in cyclodextrins for host−guest chemistry led to a proliferation of solid-state structural studies. From the data being deposited into the CSD it was clear that most cyclodextrins are toroidal, cone-shaped molecules. Moreover, the literature was replete with diagrammatic schemes from various researchers in many subdisciplines of chemistry depicting these molecules, in caricature, as symmetrical, round structures. It was not clear to Lipkowitz[16] at the time if the authors of those papers intended to convey to the reader that these molecules are inherently symmetric or whether the symmetric structures were simply a time-averaged view.

Lipkowitz argued that results from NMR spectroscopy, a "slow" spectral technique, by necessity give symmetrical structures and that X-ray and neutron diffraction results may obfuscate the inherent structure of the macrocycles because of crystal packing effects in addition to waters of hydration. To address this issue he posed a simple question: "Do cyclodextrins have C_n symmetry where n is the number of glucose monomers in the macrocycle?" To answer that question he carried out molecular mechanics calculations on a large number of cyclodextrin conformations, void of waters of hydration, guests, and lattice environments, and he intentionally used two very different force fields (MM2 and AMBER) to cross-validate his results. Typical geometries (structures akin to those within the CSD) and atypical geometries were considered. The summary from that investigation is the following: (1) C_n symmetric structures are not the most stable; symmetry breaking lowers the energies of those structures. (2) Both gauche (−) and gauche (+) orientations of the primary hydroxyl groups are energetically allowed with the former being more stable. (3) The notion that the belt of acetal linker oxygens (O_4) linking the monomer together must be planar is incorrect; substantial buckling can be induced. (4) Low-energy structures can exist where the secondary hydroxyl groups are directed in toward the macrocycle's cavity, splaying the primary hydroxyls outward. While the interconversion from one conformer to another was not explicitly addressed, it was concluded that the cyclodextrins, as a class of compounds, are remarkably flexible and that the symmetric structures portrayed in the literature are to be considered as time-averaged structures only. These conclusions were echoed by Dodziuk and Nowinski,[17] who likewise used the MM2 force field to study α-cyclodextrin. These assertions, however, have been challenged by Lichtenthaler and Immel, who used the PIMM force field which implicates native cyclodextrins as being inherently symmetrical (see below).

The computational discovery that cyclodextrins need not be symmetric prompted Lipkowitz, Green, and Yang[18] to evaluate the known solid-state structures of cyclodextrins. Using the 1990 Cambridge Structural Database the authors found 121 structures (43 α-, 70 β-, and 8 γ-cyclodextrins) and carried out a very detailed analysis of the monomeric glucose structures, especially the primary hydroxyl torsion angle and the ring pucker of the pyran, but they focused mainly on the structural features of the macrocycle. In particular they addressed (1) the deviation of the O_4 atoms from the mean plane, (2) the pseudo-dihedral angle formed by adjacent O_4 atoms (the dihedral formed by the pseudobonds described earlier), (3) the orthogonality of the glucose mean plane with respect to the mean plane formed by the O_4 oxygens, i.e., the tilt angle of the pyrans into or out of the macrocycle's cavity, (4) angular deviations from C_n symmetry, and (5) the distance from the macrocycles centroid to the centroid of each pyran ring. This analysis was done for the entire collection of cyclodextrins. The authors also examined cyclodextrins containing guests vs those without guests and also native vs derivatized cyclodextrins. Rather than simply present the mean values and the corresponding standard deviations (second moments of a distribution), the authors presented histogram plots for the reader to see the asymmetry of the distributions (third moments) as well as the peakedness of the distributions (the kurtosis or fourth moment of a distribution) making this analysis somewhat unique to other reviews of crystallographic structures.

At the outset of that study Lipkowitz made it clear that his real interest was to evaluate the energies of the cyclodextrin conformations for comparison with those derived earlier. It was presumed that the geometries of the cyclodextrins extracted from the CSD would be near local minima on the cyclodextrin's potential energy surface and that by energy minimizing those structures one could carry out, in a very limited way, a conformational analysis. Of particular interest was the distribution of conformational energies of cyclodextrins trapped in a lattice. Using MM2, CHARMM, and AMBER force fields the authors found a wide range of conformational energies, all of which were less stable than structures found from their earlier force field investigation, leading to the conclusion that most cyclodextrins, as found in the CSD, are trapped in high-energy conformational states. The lattice, ions, guests, and waters of hydration tend to distort these relatively flexible macrocycles from their most stable low-energy conformations, and consequently one may conclude that a crystal environment is an especially bad place to investigate the inherent features of cyclodextrins.

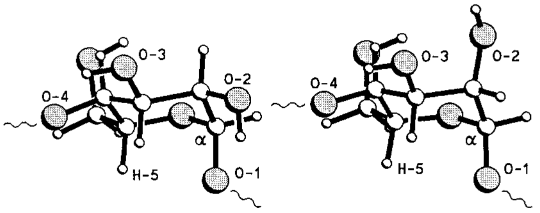
Other analyses of CSD structures have been carried out, albeit on a far more restrictive basis. For example, Lawrence's group[19] wanted to be able to predict the structures and energies of drug inclusion complexes of β-cyclodextrins so they evaluated the ring radii, glycosidic bond angles, and $\Phi\Psi$ dihedrals of 14 β-cyclodextrin complexes. Many of their findings were consonant with those of Lipkowitz. However they found that the overall shape and conformation of native β-cyclodextrin is not significantly affected by the inclusion of guest molecules, in complete disagreement with the conclusions of Kostense et al.,[14] whose work was mentioned above. Moreover, for purposes of binding calculations (described later in this chapter) they felt the macrocyclic ring could, to a good approximation, be treated as a rigid body, an assumption that the author of this review will rebuke later in this review.

Until now, relatively little has been said about conformational analysis of these complex macrocycles. One person cognizant of the pitfalls of relying on a limited set of structures to derive physically meaningful properties was Venanzi, who with Wertz[20] carried out a conformational analysis of β-cyclodextrin using two completely different conformer search strategies. One was the "distance−geometry" (DG) method,[21] a well established conformer generating technique that is applicable to ring systems like cyclodextrins. Unfortunately the authors generated new conformations by altering only the glycosidic torsion angles, and accordingly they derived a small number of conformers (99). The second method was to carry out molecular dynamics simulations beginning from some of the low-energy structures found in the DG search. To do this the authors performed 40−60 ps MD simulations saving a structure every picosecond. Each of those "snapshots" taken along the MD trajectory was then energy minimized by molecular mechanics with the AMBER force field. Again only a limited number of conformers were obtained this way, but an important finding was that standard conformer search strategies, even being limited in scope, can find conformers of lower energy than those obtained through energy minimization of crystal structures, thus echoing one of Lipkowitz' concerns about relying on crystallographically derived geometries to define the preferred shapes of these molecules when they are found in nonlattice environments. Finally we mention a molecular mechanics-based conformational study of $3^A,6^A$-anhydrocyclomaltohexaose, a modified α-cyclodextrin, carried out to confirm solution phase NMR results. The computed coupling constants compared to experimental values agreed only for a distorted structure in that study.[22]

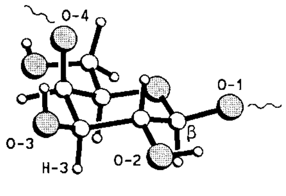
The most comprehensive assessment of cyclodextrin structures and properties comes from a series of papers on the topic of *Molecular Modeling of Saccharides* by Frieder Lichtenthaler and his then Ph.D. student, Stefan Immel. Beginning in 1994 efforts were directed toward assessment of geometries and lipophilic characteristics of cyclodextrins as well as other cyclic sugars. These scientists pointed out that within each sugar residue there exists $2^5 = 32$ stereoisomeric possibilities, that, when extended to six, seven, or eight sugar units comprising a cyclic oligosaccharide, give rise to an enormous number of possible stereoisomers. It is nearly impossible to synthesize all of them in a quest to understand the complexation properties of macrocyclic carbohydrates, and accordingly, one must restrict synthetic activities to targets of greatest interest. The most feasible targets, in turn, were to be evaluated by computational protocols, and a concerted effort commenced to study cyclic oligosaccharides in an attempt to understand how known species behave as well as to uncover unique properties of as yet unknown species.

In their first paper, cyclodextrins, cyclomannins, and cyclogalactins with five and six (1→4)-linked sugar units were evaluated[23] using the PIMM empirical force field. The computed mean structures of the monosaccharide monomers comprising the macrocycle are depicted in Figure 5 to illustrate the stereochemical differences of each residue.

Of particular concern in that study were monomer geometries, especially their conformations and ring pucker and the relative orientation of the primary C_6 hydroxyl group, along with macrocyclic features such as Φ and Ψ dihedral angles, $O_4-O_{4'}$ distances, and the tilt angle, τ, describing the mean plane of each pyran relative to that formed by the acetal linker oxygens, as depicted in Figure 4. This (τ) is



cyclodextrin cyclomannin



cyclogalactin

Figure 5. Minimum energy structures of cyclodextrin, cyclomannin, and cyclogalactins computed by the PIMM force field. Each structure is the mean geometry for all residues comprising the macrocycle. View for each is seen perpendicular to the cyclooligosaccharide mean plane. Due to the inclination of the pyranoid rings the α-D-glucosyl and α-D-mannosyl units are seen from their "bottom" sides whereas the *β*-D-galactosyl residue corresponds to a conventional depiction of $^4C_1$ pyranose conformation. Taken with permission from ref 23.

an especially important descriptor of the cyclodextrins because it defines how cylindrical or conical they tend to be, which in turn influences their binding properties as host molecules. The authors searched for all tilt angles between 60 and 140° in 5° increments to assess this. Other key macrocyclic features were also evaluated.

One important finding was that the structures of these systems are predicted to be symmetrical, in contradistinction to the results of Lipkowitz.[16] In this regard one should not be surprised because Lipkowitz used one set of force fields while Lichtenthaler and Immel used another. The beauty of science is to discover the truth and neither group claims their method to be "right". At this point both acknowledge that additional studies using other force fields to validate the results of each group's findings compared to the other's is warranted.

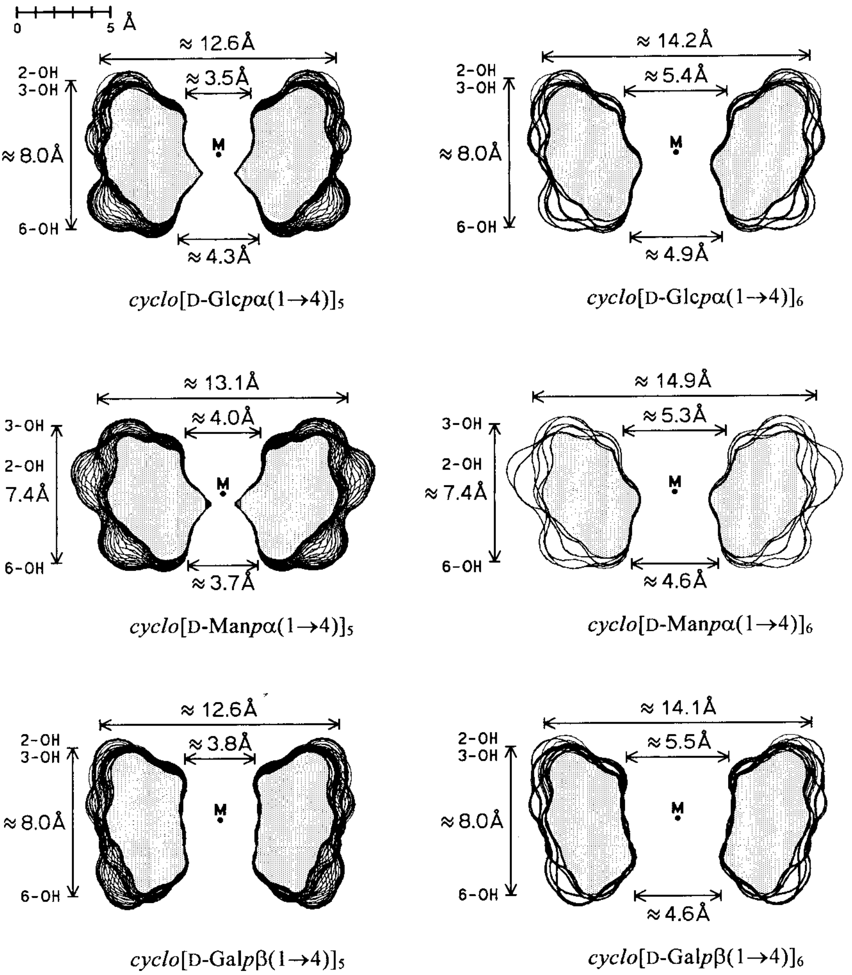
A comparison of the cyclomannins with the cyclodextrins showed them to have very similar backbone structures implicating the stereochemical inversion of the C_2 hydroxyl group on the pyran to be relatively unimportant. Likewise the tilt angles for these ring systems were very similar. In stark contrast, though, are the cyclogalactins where the major structural differences arise from the epimerization at C_4 and the *β* linkage at C_1. The authors called these structures "*inverso*-cyclodextrins" and promptly pointed out that they have an inverse orientation of the pyran ring in the macrocyclic assembly. While the cyclodextrins have their H_2 and H_4 atoms pointing outside of the macrocycle's cavity, the cyclogalactins have their H_2 atoms pointed inward. Going from the cyclodextrins to the cyclogalactins it is the change from C_3-H_3/C_5-H_5 pointing inward to C_2-H_2 and O_5 (with only lone pair electrons) directed inward giving rise to a more uniform shape and wider cavity. The dimensions of these unique cyclodextrins are depicted in Figure 6, where slices through the macrocycles' contact surfaces are presented. The heights, widths and other computed dimensions of these cavities are to be found in the original reference.[23]

Because the hydrophobic effect plays such a dominant role in host−guest complexation of cyclodextrins, Lichtenthaler and Immel were especially interested in mapping out domains of hydrophobic and hydrophilic patches that exist in and around these molecules. To do this they mapped the molecules' lipophilic surfaces in an easy to interpret and stunningly beautiful set of molecular graphics pictures, depicting which regions are more or less hydrophilic than other regions. For the cyclodextrins the wide rim of the torus is distinctly hydrophilic while the narrow rim bearing the primary hydroxyl groups is intensely hydrophobic. The cyclomannins have lipophilic surfaces, but their exteriors are more hydrophilic than that of the cyclodextrins. The authors conclude that cyclomannins would have a smaller cavity than cyclodextrins and that their cavities would be more hydrophobic. Not unexpectedly the "*inverso*-cyclodextrins" have extensive hydrophobic surfaces extending from the cavity well out to the exterior of the macrocycle because of the inside-out topography of these unusual molecules, and this cavity is less hydrophobic than their normal counterparts.

In the following year Immel, Brickmann, and Lichtenthaler[24] extended their studies not to oligosaccharides composed of diastereomeric pyranosides of glucose but to cyclodextrins containing fewer than six units made of α(1→4)-linked D-glucopyranose itself. These small-ring cyclodextrins were investigated in part because it was felt that earlier predictions concerning the limitations of the size of the macrocycles one could make were perhaps premature,[8] but also because these were logical extensions to pursue and they are inherently interesting strained ring molecules. Investigated were *cyclo*-α-(1→4)-glucopentaoside (*cyclo*[Glc*p* α(1→4)-]$_5$), *cyclo*-α(1→4)-glucotetraoside (*cyclo*[Glc*p* α(1→4)-]$_4$), and *cyclo*-α(1→4)-glucotrioside (*cyclo*[Glc*p* α(1→4)-]$_3$) along with α-cyclodextrin itself, *cyclo*-α(1→4)-glucohexaoside (*cyclo*[Glc*p* α(1→4)-]$_6$).

Upon ring contraction from the hexameric α-cyclodextrin to the smaller cyclodextrins the authors found a subtle yet complex interplay between glycoside bond angle expansions and changes in glycosidic torsion angles, Φ and Ψ, tilt angle, τ, and pyran ring puckering. This particular study provides the best published assessment of pyranose ring puckers in cyclodextrins as illustrated in Figure 7.

The most significant finding in this regard is that there exists a progressive shift from chair $^4C_1$ conformers in strain-free cyclodextrins to full envelope E_1 conformers in the trimer. As before, the authors evaluated the molecular dimensions and cavity characteristics of these small-ring cyclodextrins (the trimer and tetramer have no cavity!) and again mapped out their lipophilic and hydrophilic domains for comparisons with larger ring cyclodextrins. Some of these findings and those from previous studies



cyclo[D-Glc*p*α(1→4)]$_5$ *cyclo*[D-Glc*p*α(1→4)]$_6$

cyclo[D-Man*p*α(1→4)]$_5$ *cyclo*[D-Man*p*α(1→4)]$_6$

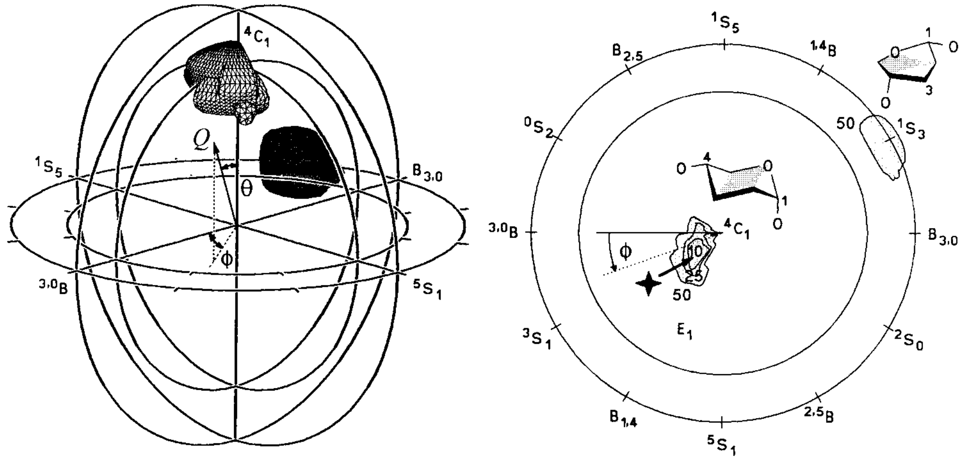
cyclo[D-Gal*p*β(1→4)]$_5$ *cyclo*[D-Gal*p*β(1→4)]$_6$

Figure 6. Slices through the contact surfaces for the (1→4)-linked cyclodextrins (top), cyclomannins (middle), and cyclogalactins (bottom). The contour lines were generated by successive 10° rotations around the geometrical center M for each energy-minimized structure. In each case the wider secondary rims are pointed upward while the narrower primary rims are pointed down. Approximate molecular dimensions are included. See Figure 2 for atom labeling. Taken with permission from ref 23.

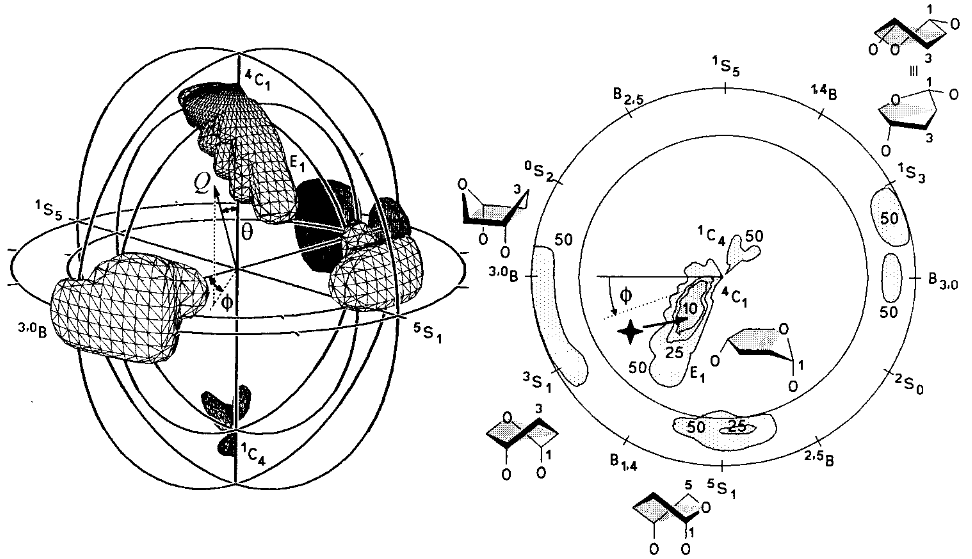
were put into perspective in a review article comparing the computed chemical and biological properties of sucrose, the cyclodextrins, and amylose.[25] Parenthetically we cite here a paper by Shimada et al.[26] concerning the conformations of very large cycloamyloses having a degree of polymerization up to 48 in contrast to the very small-ring cyclodextrins described above. Unfortunately the atomistic simulations of such large ring systems are somewhat beyond the scope of this review, but we highly recommend studying this paper nonetheless.[26]

Another study by Immel and Lichtenthaler evaluated these same kinds of issues but focused on α-cyclofructin (*cyclo*-*β*(1→2)-linked fructohexaoside), an intriguing 18-crown-6 substructure with spiro-annelated furanoid rings in a propeller-like fashion.[27] The unusual shapes and bizarre lipophilic character of this molecule when compared to more normal cyclodextrins is intriguing. A follow-up study comparing and contrasting cyclodextrins, cyclomannins, cyclorhamins, cyclofructins, cycloaltrins, and cyclogalactins has also appeared.[28] More recently, a collaboration between Fujita and Lichtenthaler[29] has appeared in which the synthesis, structure, and conformational features of α-cycloaltrin are described. This particular cyclooligosaccharide has alternating $^4C_1$ and $^1C_4$ pyran chairs. A molecular mechanics and molecular dynamics investigation was undertaken to understand the stability of this unusual geometry and to assess the dynamics of its conformational interconversion.

Earlier, Lipkowitz had published a detailed assessment of solid-state cyclodextrin structures.[18] This work was apparently unknown to Lichtenthaler and Immel, who had likewise decided to examine the structures of solid-state cyclodextrins contained within the CSD (they also included a *δ*-cyclodextrin in addition to the lower α-, *β*-, and *γ*-homologs).[30] These authors used 98 native cyclodextrins, both with and without included guests, but omitted 24 *per*-2,3,6-*O*- and *per*-2,6-*O*-substituted derivatives from their assessment because those substituents can substantially effect the macrocycle's backbone geometry. Interestingly, these authors similarly provided mean values and the corresponding standard deviations (the square root of the second moment of a distribution) for various molecular descriptors, but they also presented histograms of the distributions to show what the asymmetry and kurtoses of those distributions look like. Most of the results were comparable to those of Lipkowitz with one major exception: Immel found a normal (Gaussian) distribution rather



cyclo[D-Glc*p*α(1→4)]$_6$
(α-CD)



cyclo[D-Glc*p*α(1→4)]$_5$

Figure 7. Isoenergy contour surfaces of total molecular energy as a function of Cremer–Pople puckering parameters Q, θ, and ϕ for α-cyclodextrin (top) and its next lower homologue (bottom). The polar coordinates at left signify a contour value of +50 kJ/mol above the global minimum; the circles in the 3-D plots mark constant puckering amplitudes of Q = 0.60 and 0.80 Å. On the right, projections of the 3-D energy contours onto the equator plane (θ = 90°) are shown at relative +10, +25, and +50 kJ/mol levels. The global energy minimum is marked by an asterisk. Relevant glucopyranose conformations are inserted as pictograms. Taken with permission from ref 24.

than a bimodal distribution of pyran tilt angles. The origin of this discrepancy lies in the fact that Lipkowitz used the original numbering scheme of the CSD entries where some rings were apparently numbered in reverse order from others while Immel totally renumbered the pyrans to have a consistent numbering scheme deriving, thus, the unimodal rather than bimodal distributions. This was an error on Lipkowitz' part that is now rectified. Immel was then able to define contact surfaces, cavity dimensions, and molecular lipophilicity patterns as before.

Finally we bring to light the not too unexpected, yet unique finding by Immel and Lichtenthaler concerning the hydrophobic/hydrophilic nature of peralkylated cyclodextrins.[31] It had been recognized for some time that by replacing the "polyalcohol" linings of cyclodextrins with alkyl (and other) groups one would create "polyether" like behavior, wherein the system resembles more of a crown-ether than a cyclodextrin. This in turn gives rise to several concomitant changes in both the shape and behavior of the cyclodextrin. Upon examination of crystal structures of per-O-methylated α- and β-cyclodextrins containing included guests, the following was found: (1) The torus dimensions of these derivatives are slightly larger than their parent, unmodified analogues, but having wider secondary rims and narrower primary rims. (2) These cyclodextrins have cavity volumes approximately 10–20% larger than their parents due to the increase in torus height. (3) The increased root-mean-square deviation in geometry of these molecules compared to their parents indicate they are conformationally more flexible (distortable); moreover they have different pyran tilt angles and orientations of 2-OR and 3-OR groups and are elliptical in shape. (4) The steric bulk of the OR groups along with the elimination of the intra-/inter-ring hydrogen bonding network leads to a flattening of the macroring geometry.

More important, though, is the result from their computations of lipophilicity patterns. In the native cyclodextrins the wider, secondary hydroxyl rim is clearly hydrophilic while the primary rim is hydrophobic (vide supra). In the permethylated cyclodextrins, though, the bipartite separation into hydrophilic and hydrophobic hemispheres is almost completely eliminated because both torus rims are covered by equally dense layers of alkyl groups having equivalent lipophilicities. What this gives rise to, then, is a hydrophobic band wrapping around the exterior of the cyclodextrin tori but now with hydrophilic surface regions inside the cyclodextrin. The result, then, is that per-O-alkylated cyclodextrins have "inverse" lipophilicity profiles compared to their native, underivatized analogues and that one should anticipate some far reaching and unusual behavior of these molecules in their capacity to bind guest molecules in comparison to their underivatized analogues. Indeed the authors[31] use this argument to explain why the same guest molecules have reversed orientations in the crystal structures of native vs peralkylated cyclodextrins.

With this exception, until now we have discussed primarily native, underivatized cyclodextrins. Derivatization of these cyclooligosaccharides is discussed in detail by D'Souza[32] in this special journal issue, but of those derivatized systems, very few have been examined computationally. As part of a research program in artificial redox enzymes, D'Souza's group covalently linked a flavin molecule to the secondary rim of a β-cyclodextrin and modeled the orientation of benzyl mercaptan in the cavity of that host.[33] Of particular concern was the geometry of this artificial enzyme; more specifically, a key issue was whether the flavin self-includes in the cavity. Using the MM2 force field it was discovered that the flavin tends to reside over the top of the secondary rim, stabilized by intramolecular hydrogen bonds (consistent with experiment). Of special note in this study was the use of a solvation model (see later) that was found to be important in predicting both the energetics and structures of this artificial enzyme. Another study like this involved the synthesis and evaluation of dicyanoanthracene as a water-soluble cap for β-cyclodextrin.[34] Using the MMX force field the authors found that both "lid" and inserted type structures are energetically feasible for the A,D-capped isomer but for the A,C-linked system only a lid-type conformation is possible. Another computational study of derivatized cyclodextrins was published by Reinhardt, Richter, and Mager,[35] who focused on permethylated α-, β-, and γ-cyclodextrins. These authors used both molecular mechanics and semiempirical quantum mechanics to evaluate the structural changes that take place when native cyclodextrins are fully alkylated with methyl groups. They found the following: (1) Alkylation always leads to an increase in both the cavity opening and the internal diameter. (2) The diameter of the cavity on the secondary side changes more than that of the primary side (except for α-cyclodextrin). (3) The cavity opening on the primary rim is larger than the internal diameter of the O_4 glycosidic oxygens (the "out" structures predicted by Lipkowitz[16]). Alkylated cyclodextrins are very common. Less common is a unique class of macrocycles referred to as glycophanes, a cyclodextrin–cyclophane hybrid, and Co-terón[36] used the CVFF force field to predict the shapes of these unusual macrocycles. Finally, we mention the calculations of Kahn, Tong, and D'Souza,[37] who had synthesized an amino-substituted β-cyclodextrin (secondary rim) and found from spectral data that this system self-assembles. Their calculations using the Discover force field showed the dimer to be ~30 kcal/mol more stable than the two monomers, and the intermolecular hydrogen bonds between hydroxyl and amino groups were depicted with molecular graphics.

Most structural studies of cyclodextrins, until recently, did not treat the environment of the cyclodextrin unless it was in a solid lattice (see next section). One paper beginning to address the topic of cyclodextrin solvation was published by Linert, Margl, and Lukovits,[38] but the focus of that work was on algorithms to efficiently locate binding sites for substrates around a rigid cyclodextrin. However, another paper by Linert, Margl, and Renz[39] was published where Monte Carlo strategies were used to understand the solute–solvent interaction between cyclodextrins and water. Many conclusions were derived. Of special interest are the following: (1) The water density around the α-cyclodextrin is noticeably lower than around the β-cyclodextrin. (2) The innermost hydration sphere for β-cyclodextrin is substantial but not very populated for α-cyclodextrin. (3) α-Cyclodextrin causes a smaller disturbance of bulk water than β-cyclodextrin. (4) β-Cyclodextrin is better stablized in water than α-cyclodextrin due to its ability to bind more water molecules. A complete analysis of the intramolecular ring of hydrogen bonds in these systems was also given along with dynamical aspects of hydrogen bonding and the Lewis acidity/basicity of those groups. There have been other computational studies of cyclodextrins in water, most of which are described in following sections on molecular dynamics and host–guest complexation.

At this point one might ask: "Why are not there any quantum mechanical calculations done to predict structures and properties of cyclodextrins?" There are, and they will be discussed below, but here we need to highlight several aspects of quantum mechanics to put this into perspective. Earlier it was pointed out that QM methods are much more CPU-intensive, i.e., slower, than MM methods. Moreover, because empirical force fields tend to give reliable results, their speed and reliability make most users adopt this technique to study the large molecules described in this review. Interestingly, many scientists seem to presume that quantum mechanics, based on "first principles", is infallible and those scientists would be inclined to use the method if faster machines existed. Faster machines do exist! But this author cautions against the use of these theories for structural predictions of cyclodextrins. The semiempirical molecular orbital theories do a horrendous job in predicting hydrogen bond energies and structures. The question posed to J. J. P.

Stewart, author of MOPAC, was “Would you advise against using AM1 or PM3 for structure predictions of cyclodextrins?”, and the answer was a definite “Yes, avoid it at all costs”.[40] This statement does not deride semiempirical theories nor should it discourage one from using these methods for other purposes for which they are known to work well.[41,42] It simply points out that one must be very careful about the pitfalls of existing computational tools and is highlighted here as a cautionary note because nowadays the computing horsepower exists and the easy to use pull-down menus of most molecular modeling packages might tempt the user to do something he or she ought not to do.

One thing these semiempirical theories are good at predicting are molecular dipole moments. Throughout the cyclodextrin literature a list of driving forces attributable to guest binding are usually presented. One of the more significant ones are the electrostatic forces because these forces fall off as the square of the interatomic distance and, thus, are “long range” forces compared to others. To investigate the role of electrostatics in determining the orientation of guests in inclusion complexes, scientists at the Tokyo Institute of Technology began a series of semiempirical quantum mechanical calculations. In their first paper Inoue[43] and his group used the CNDO/2 Hamiltonian to evaluate the molecular dipole moment of α-cyclodextrin (it was unknown at that time) and of *p*-nitrophenol. The geometry of the cyclodextrin used for the calculation, i.e., the atomic coordinates, was that of the phenol−cyclodextrin complex with the guest removed. The computed dipole moment was 13.5 D in agreement with a value from MM2 (12.4 D), and that of the phenol was 5.0 D. The positive end of the dipole is at the secondary rim of the macrocycle, and the negative end at the primary rim and this vector deviates from a 6-fold axis because the cyclodextrin is distorted. The guest’s dipole is antiparallel to the host, and the authors’ conclusion is that dipole−dipole stablization plays an essential role in stabilizing the complex as well as determining its orientation.

This work was followed by a far more detailed analysis of the electrostatic fields around α-cyclodextrin. Sakurai[44] computed electrostatic contour maps using atomic charges derived from CNDO/2, using the same atomic coordinates as above. The wider secondary rim generally has regions of negative potential, while the more narrow primary rim has regions of large positive potentials giving rise to a large electronic polarization along the cavity axis. A plot of the electrostatic potential through a plane showing this positive potential at the narrow rim is presented in Figure 8, and that of the negative potential sliced through the secondary rim is presented in Figure 9. These findings are consistent with the MM-derived maps of Venanzi[13] discussed earlier.

One would expect, however, that both the magnitude as well as the shape of these electrostatic maps would change as the cyclodextrin structure is changed, and indeed, this is what is found. Significantly, for this review, we point out that when Sakurai used another cyclodextrin structure corresponding to a distorted ring geometry the potential gradients not only changed but they actually reversed direction! The conclusion, then, is that the potential profile inside the cavity is highly dependent upon the macromolecular ring geometry. The Tokyo group then published a paper where several other α-cyclodextrin structures were used for their CNDO calculations.[45] The point of that paper was to better understand the orientations of guests in the host environments, and their results will be described later in this review.

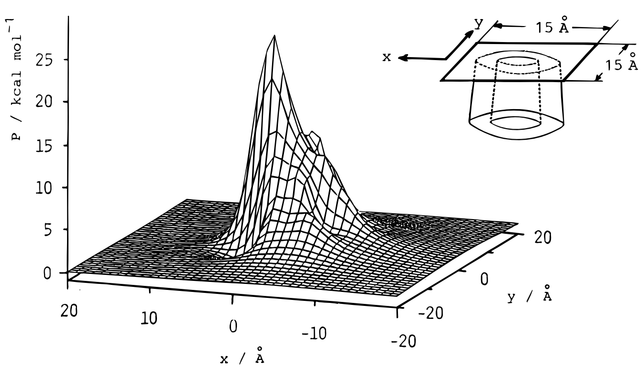


Figure 8. Electrostatic potential map for the primary hydroxyl rim of α-cyclodextrin. The atomic charges were determined using the CNDO/2 Hamiltonian for a rigid cyclodextrin. The region being mapped corresponds to the *xy* plane of the insert showing the conical cyclodextrin in caricature. Taken with permission from ref 44.

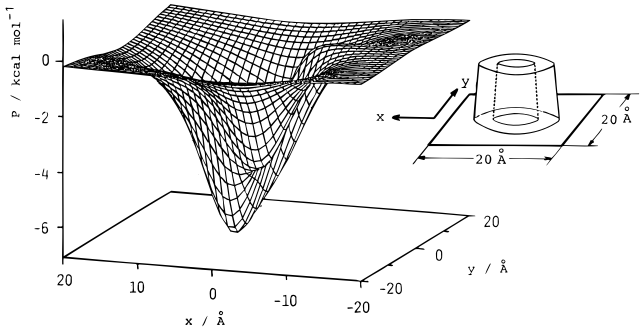


Figure 9. Electrostatic potential map for the wider secondary hydroxyl rim of α-cyclodextrin. The atomic charges were determined using the CNDO/2 Hamiltonian for a rigid cyclodextrin. The region being mapped corresponds to the *xy* plane of the insert showing the conical cyclodextrin in caricature. Note that the electrostatic potential is inverted compared to that in Figure 8. Taken with permission from ref 44.

The results of other semiempirical quantum chemical calculations have been published. Bakó and Jicsinszky[46] used the AM1 Hamiltonian to energy minimize α-, *β*-, and *γ*-cyclodextrin beginning from their crystal coordinates. Many structural features of the monomer and the macrocycle were elaborated upon, but the authors indicated their main goal was to obtain reliable charge distributions that, parenthetically, were similar to those of free glucose. More recent AM1 calculations exist.[47] A comparison of ab initio (STO-3G basis set), semiempirical (AM1 and PM3 Hamiltonians), and empirical force fields (AMBER, CHARMM, and MM2) geometries of α-, *β*-, and *γ*-cyclodextrins can be found in a symposium proceedings.[48] In another recent paper Margheritis and

Table 1. Published Studies Using Quantum-Based Computations

Hamiltonian	host	guests	ref
CNDO/2	α-CD	*p*-nitrophenol, benzoic acid, *p*-hydroxybenzoic acid	43, 45
CNDO/2	α-CD	*m*-nitrophenol	93, 94
CNDO/2	α-CD	none	44
CNDO/2	α-CD (model)	benzoic acid, *p*-hydroxybenzoic acid	112
AM1	α-,β-CD	none	182
MNDO	α-CD model	phenylcyanoacetate	111
AM1	2-HP-β-CD[a]	2,2,6- and 2,4,6-substituted phenols	183
AM1	α-, β-, γ-CD	none	46
AM1	β-CD	phenylacetate	113, 114
AM1	α-, β-, γ-CD; 2,3,6-HP-β-CD; 2,6-dimethyl-β-CD; others	none	184
AM1	β-CD	1,7-dioxaspiro[5.5]undecane, nonanal	95
AM1 PM3	α-, β-, γ-CD; others	none	48, 185
AM1	α-, β-, γ-CD	phenol, methylated benzoic acids, buckminsterfullerene	186
PM3	β-CD	hexafluorophosphate	140
AM1 PM3	β-CD	none, water	49
CNDO/2, AM1	PM-α-, β-, γ-CD;[b] α-, β-, γ-CD	none	35
AM1	α-, β-, γ-CD	crocetin, water	75

[a] HP = Hydroxypropyl. [b] PM = permethyl.

Sinistri[49] used AM1 and PM3 to compute β-cyclodextrin−water interaction energies. They found that formation of β-cyclodextrin·11H_2O is enthalpically unstable and must arise from other effects to compensate for this. In the context of the current discussion, these authors also find conformationally dependent dipole moments. Changing the orientation of only a single hydroxyl group allowed the molecular dipole to be raised or lowered by 1.5−2.0 D. Conformations with large dipoles (>10 D) could be generated but at the energetic cost of 40−50 kcal/mol. So, it would appear that the large dipole-containing crystal structures are, as Lipkowitz pointed out,[18] in high-energy conformational states.

A summary of quantum mechanical calculations on cyclodextrins (listed in chronological order) is presented in Table 1. All of the calculations have been carried out at the semiempirical level of theory and generally without an explicit or implicit treatment of solvation. The early calculations relied mostly on the CNDO/2 Hamiltonian, but more recently the Dewar's AM1 Hamiltonian has been used regularly. No ab initio calculations using Hartee−Fock theory or density functional theory have been reported yet, but given the developments in both hardware and software, we anticipate seeing such calculations soon.

IV. Dynamical Aspects of Cyclodextrin Structure

The geometry optimized molecular mechanics and quantum mechanics structures reside at the bottom of potential energy wells on a potential energy surface. They are vibrationless and have no kinetic energy. In molecular dynamics calculations both kinetic and potential energies are included. Because the system is a conservative one, i.e., the total energy remains constant, kinetic energy increases as the potential energy decreases and vice versa. As explained earlier, Newton's equations of motion are computed and the history of the system over a time period (the trajectory) is followed. If enough kinetic energy (the "temperature") is supplied, the system can move from minimum to minimum over the potential energy surface, but transits over constricted passes from one valley floor to another on such potential energy surfaces are rare. Likewise, transits over high-energy barriers are rare. For cyclodextrins many conformational changes take place over unconstricted and low-energy barriers, making transits from one conformational state to another nearby conformational state fairly easy. Calculations such as this have already been described in our earlier discussion of the conformer search strategies of Wertz, Shi, and Venanzi.[20a] In their study they ran the simulation at 298 K. At uniform time periods along the trajectory they saved "snapshots" of the cyclodextrin that were then energy minimized, hoping those structures would fall to the bottom of a new energy well (a new conformer) on an otherwise unknown PES. This process is referred to as "quenched dynamics". In quenched dynamics, simulations using high temperatures have enough kinetic energy to surmount even large barriers (usually these simulations are run at temperatures around 1000−1500 K or higher) allowing the system to move over vast regions of the PES sampling a larger volume of conformational space than at lower, more normal room temperatures. Structures pulled from the trajectory are then energy minimized to 0 K; i.e., they are thermally quenched. The short time periods and low temperatures used in the Venanzi study gave a representative, but small, set of cyclodextrin geometries.

One of the first publications using MD to study cyclodextrins actually came from a nucleic acids chemistry group. Prabhakaran and Harvey[50] carried out 30 ps simulations using the GROMOS program on α-cyclodextrin in a free state and with two pseudo-guest molecules trapped in the interior (one guest was simply a van der Waals sphere of 6 Å diameter, with a heavy mass of 1000 amu). Their general conclusions are the following: (1) The molecule is highly flexible, traversing wide regions of conformational space even with cyclic constraints imposed by the guests. (2) The cyclodextrin undergoes asymmetric oscillations. (3) The glucose retains its chair conformation throughout these motions. This work was extended by Prabhakaran,[51] who carried out 100 ps MD simulations with GROMOS on β-cyclodextrin in the gas and in aqueous phases. The objective of that study was to examine the glycosidic Φ and Ψ angle distributions under those conditions (note that a slightly different definition of these dihedral angles is used in that paper). The author saved 2000 structures for analysis. Because there are seven Φ and seven Ψ dihedral angles, the author had 14 000 values to plot. Scatter plots of Φ and Ψ derived from the simulations reveal the following: (1) The high-density regions of Φ and Ψ are shifted from the known crystallographic values. (2) New conformational species (i.e., new regions of Φ and Ψ compared to crystal structures) are very heavily populated. (3) Water limits the accessible conformational space of β-cyclodextrin somewhat compared to the gas-phase simulation.

The most comprehensive assessment of cyclodextrin's dynamical structural features can be found in a series of papers by Koehler, Saenger, and van Gunsteren beginning in the late 1980s. In their first paper the authors derived a set of molecular mechanics parameters for the GROMOS force field and then evaluated the dynamics of crystalline α-cyclodextrin hexahydrate.[52] Their goal was 2-fold, first to test the GROMOS force field on cyclodextrins and second to derive dynamical properties inaccessible to experimentation. These authors simulated the motion of four unit cells, each consisting of 4 α-cyclodextrin molecules and 24 water molecules (1632 total atoms) at 293 K. Even for an empirical force field this is a large system so the authors were able to carry out the simulations for a very short time period only. The computationally derived structure of the α-cyclodextrin$\cdot 6H_2O$ was obtained by averaging over the 16 molecules for 10 ps. The root-mean-square (rms) deviation of the MD averaged structure compared to the experimental structure was 1.8 Å (the smaller the value, the better the fit). This value could be decreased if rotational/translational positioning was included in the least-squares fitting procedure. Crystallographic ellipses of thermal motion were well reproduced as were a variety of structural features of the cyclodextrin. The authors had thus verified the quality of both the force field and their parameter set. Four of the six water molecules were reproduced within experimental accuracy, and the other two were shifted from their experimental positions because they were associated with dynamically disordered hydrogen bonds of the flip-flop type that is discussed in detail in the review by Saenger.[4]

That first paper by Saenger was followed by a similar one focusing on β-cyclodextrin dodecahydrate at ambient and low temperatures.[53] The difference between the 293 and 120 K crystal structures involves the hydroxyl and hydroxymethylene groups and the water molecules which, at room temperature, exist with partially occupied atomic sites but at low temperatures are fully occupied. The simulations were done on 8 β-cyclodextrins each with 12 water molecules (1072 atoms). Structural averaging was done over a 15 ps time period. Comparison of the MD-averaged 293 K structure to that of the 293 K crystal structure gave an rms deviation of 4.8 Å while that for the low-temperature simulation was 5.1 Å. Information gleaned from these simulations included details of the following: (1) anisotropic thermal motions of atoms; (2) bond and dihedral angle distributions; (3) occupancy factors of glucose atom sites; (4) position and mobility of water molecules.

Another important aspect of this study was the assessment of the network of hydrogen bonds in these molecules and with their waters of hydration and lattice environment. This analysis appeared in a follow-up paper.[54] A greater variety of hydrogen-bonded states are found in the simulation compared to experiment, but that result is to be expected because the lifetimes and statistical populations of these states are not discernible to the experiment. This is an elaborate and seminal paper concerning the structure and dynamics of hydrogen bonding of cyclodextrins in the solid state.

Earlier in this review we pointed out that one can observe differences in the conformations of cyclodextrins in the solid versus the gas phase. The next logical question Koehler, Saenger, and van Gunsteren posed was the following: "What are the similarities and the differences between cyclodextrin conformations in the crystalline state versus in water?" An α-cyclodextrin was placed into a truncated octahedral environment containing 611 water molecules, and a simulation was carried out for 90 ps at 293 K.[55] Comparisons were made to the results obtained in the aforementioned 16 α-cyclodextrin−96-water solid-state simulation. The authors found the following: (1) The rms fit of crystal simulation compared to the neutron diffraction structure is 0.23 Å, while the aqueous structure fits less well by 0.98 Å. (2) The mobility of the cyclodextrin is about twice as large in solution as it is in the solid. (3) The O_6 atoms and the hydroxyl hydrogens attain substantially different positions in solution than in the solid. (4) The macrocycle becomes more symmetric than in the solid, but the macrocycle is inherently asymmetric due to internal strain and the system adopts a 2-fold symmetry in solution. (5) The 6-fold symmetric structure, defined as when the cyclodextrin has near-equivalent O_2-O_3 interresidue hydrogen bond distances, can exist but these symmetric structures appear only as transients as one collapsed cyclodextrin interconverts to another collapsed form. (6) Hydrogen bonds that are present in the solid are observed in solution, but a number of hydrogen bonds in solution are not found in the crystal. This latter finding indicates that the crystal structure is only one member of a wide family of structures that are accessible to α-cyclodextrin in solution. Recall, too, that it was found by Lipkowitz that even in the solid state a range of high-energy conformers of cyclodextrins exists.[18] Van Helden, van Eijck, and Janssen[56] also studied the conformational behavior of α-cyclodextrin in aqueous solution, likewise using the GROMOS force field but with aromatic guests moving around the interior of the macrocycle. These authors measured the asymmetry of the macrocycle by determining the distances between O_4 (linker acetal) oxygens on opposite sides of the cyclodextrin cavity. In their simulations they find that correlated changes in orientation of guest with changes of the longest diagonal of the cyclodextrin cavity occur simultaneously. On one hand, we would expect the macrocycle to be asymmetric in these simulations because the guests these authors studied contained planar aromatic rings, yet in light of the findings of Saenger and of Lipkowitz, the 2-fold symmetry of this system is perhaps a fundamental, inherent feature of this particular macrocycle and perhaps such correlated motions are driven by the cyclodextrin host rather than by the guest. A conclusion of van Helden et al. is that the cyclodextrin is much more flexible than has been previously suggested from crystal structure and molecular mechanics studies.

The nature of hydrogen bonding in cyclodextrins has been a thematic issue in many papers by Saenger. In this regard Koehler, Saenger, and van Gunsteren[57] analyzed the occurrence of bifurcated (3-center) hydrogen bonds compared to normal 2-center hydrogen bonds using the data generated in their previous MD simulations. Comparisons between solid state and solution phase hydrogen bonding exist with more 3-center hydrogen bonds being found in the latter state. The simulations recast the static picture emerging from their crystallographic studies with a more dynamic character. Finally, all the abovementioned simulations and analyses have been reiterated in a book chapter by Koehler.[58]

A more recent set of MD simulations have been carried out by Pozuelo, Madrid, Mendicuti, and Mattice.[59] They used the Tripos 5.2 force field at very high "temperatures" of 400 K studying cyclodextrins containing 5−9 monomeric glucoses linked $\alpha(1\rightarrow 4)$ to assess the energetics and structural features of these molecules. From the 2500 structures generated along each simulation trajectory the authors determined that the potential energy per monomer, i.e., the relative strain per glucose, is a maximum at *cyclo*-$\alpha(1\rightarrow 4)$-glucopentaoside (*cyclo*[Glc*p* $\alpha(1\rightarrow 4)]_5$), where high-energy contributions originate mainly from torsional and angle bending deformations, and a minimum exists at β-cyclodextrin. The authors evaluated distributions of bond angles of bridging acetal oxygens, key torsion angles, and other structural features in this homologous series. The authors find generally that the cavities become cone-shaped with the primary rim typically 12−24% smaller than the secondary rim and that the depth of the cavities change in a regular progression along the series. The computed radius of gyration (a measure of flexibility) show that the flexibility of the macro-ring increases as the number of residues increases and that cavity entrances are more rigid for the β- and γ-cyclodextrins than for the α- and δ-cyclodextrins. Again, nonsymmetric structures are observed.

Kozár and Venanzi recently compared and contrasted conformers derived from Kozár's random molecular mechanics sampling procedure with those derived from molecular dynamics simulations in a detailed paper that focused on the conformational flexibility of β-cyclodextrin.[20b] The complementary sampling methods agree with each other, and several conclusions regarding the molecule's flexibility were formulated. Most of the paper focused on the molecular dynamics simulations aimed at assessing (1) the flexibility of the macrocycle, i.e., the distribution of $\Phi\Psi$ dihedrals for a comparison to a subset of experimental values from the Cambridge Structural Database, and (2) the nature of the intramolecular hydrogen bonding where at low temperatures and dielectrics homodromic hydrogen bonding patterns are preserved but at higher temperatures or dielectric a "flip-flop" hydrogen-bonding pattern emerges. Many of the conclusions contradict earlier conclusions, with the authors attributing these differences to possible inadequacies of the AMBER force field used in the early study. Other MD simulations of cyclodextrins have been carried out, but those calculations focus on host−guest binding; these papers will be described later in this review. A compilation of all known molecular dynamics simulations is provided in Table 2. The entries are in chronological order.

V. Computational Studies of Host–Guest Complexation

Most computational studies of cyclodextrins involve host−guest complexes. Their shapes, energies, preferred binding orientations, selectivities, and so on are typically computed. In this section we consider these papers. For convenience we artificially classify the published work into sections based on the following categories: energetics of binding; structural analyses of inclusion complexes; uses of computational chemistry to aid in spectroscopic studies of binding; applications in molecular recognition. This is a completely intellectual ersatz of reality because many experimental studies of cyclodextrins involve multifaceted analyses that provide data and interpretations concerning more than just one of the above categories. Likewise, in terms of computational studies where, for example, geometry optimizations have been carried out, structure and energy are inextricably linked. Nonetheless these are some of the major issues scientists focus their attention on and such delineation of topics provides a convenient "structure" for the remainder of this review.

A. Energetics of Binding

By energetics of binding we mean how the energy of the system changes from state to state where the states involved are the free state and the guest-included state. Of special interest are the signs and magnitudes of enthalpic and entropic components of the free energy changes taking place upon association or dissociation of cyclodextrin complexes in various environments. The reader is referred to a more in-depth analysis of published thermochemical studies on this topic in the chapter by Inoue and Rekharsky[60] in this special issue of *Chemical Reviews*.

Throughout the cyclodextrin the literature the binding forces purportedly contributing to the formation of cyclodextrin inclusion complexes are listed as the following: (1) Nonbonded attractive forces. Usually researchers refer to this as "van der Waals

Table 2. Published Studies Using Molecular Dynamics Simulations

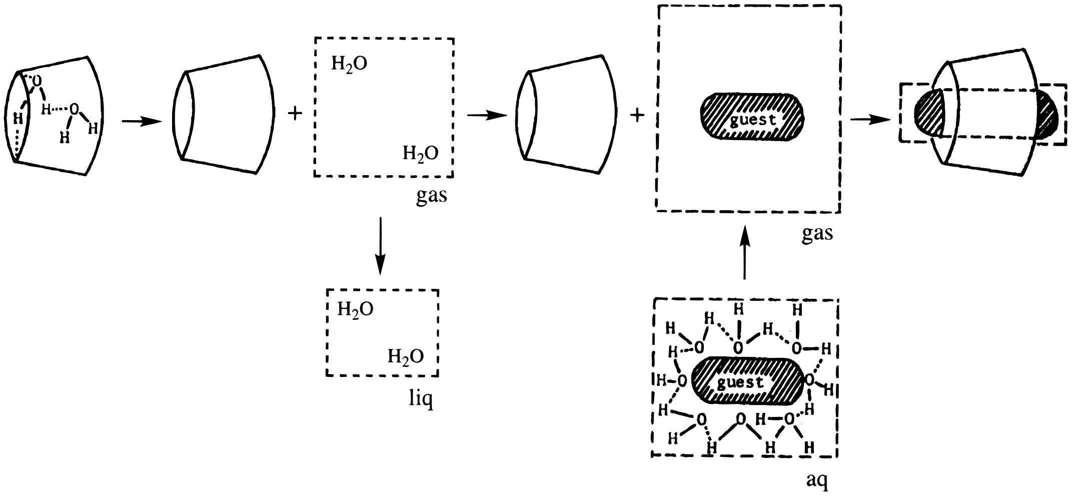
force field[a]	hosts	guests	ref
GROMOS	α-CD	none, 3 Å vdw sphere with mass = 1000	50
GROMOS	α-CD	water (α-CD·6H_2O lattice)	52, 54, 57
GROMOS	β-CD	water (β-CD·6H_2O lattice)	53, 54, 57
GROMOS	α-CD	water solution	55, 57
GROMOS	β-CD	none, water solution	51
MM2	α-CD	tryptophan	82
CVFF	TFADM-γ-CD[b]	styrene oxide	169
CVFF	ADP-γ-CD[c]	methyl-2-chloroproprionate	167, 168
GROMOS	α-CD	*p*-hydroxybenzoic acid, *p*-chlorophenol	56, 187
AMBER	β-CD	none	20
GROMOS	β-CD	amiloride	114
GROMOS	α-CD with laterally linked 1,6-glucose	none, water solution, lattice	188
GROMOS	α-CD	various *p*-substituted phenols	66
MM3*	glycophane	4-nitro, 2,4-dinitrophenyl glycosides	189
DREIDING	β-CD-perphenylcarbamate	atenolol	163
CHARMM	β-CD	CI-933 (cognition activator)	122
CHARMM	β-CD	anti-Alzheimer drugs	123
CHARMM, PIMM	3-, 4-, 5-membered CDs	none	24
CHARMM	β-CD	methylmandelate	161
AMBER	β-CD, permethyl-β-CD	binaphthyl derivatives	131
	α-CD	phosphatidyl inositol	190, 191
CVFF	β-CD	indomethacin (anti-inflammatory)	98
AMBER*	α-, β-, γ-CD	1-bromoadamantane	86b, 103
	2-HP-β-CD[d]	phenobarbital	192
	α-CD	1-hexanol in water	193
TRIPOS	β-CD	chlorogenic acid and water	70
TRIPOS	5−9-membered CDs	none	59a
MM+, TRIPOS	α-, β-, γ-CD	none	35
MM2, GROMOS	18-, 24-, 48-membered CDs	none, water solution	26
AMBER	non-cylic β-CD analog	naproxen	135
CVFF, MM2	β-CD	none	206
	β-CD	thymol, carvacrol	194
TRIPOS	γ-CD	fluvastatin	195
	β-CD	synthetic pyrethroids	196
TRIPOS	α-CD rotaxanes	poly(ethylene glycol)	59b
TRIPOS	α-, β-CD	nothing, 2-methylnaphthoate in water	78
AMBER*	permethyl-β-CD	small organics with various functional groups	176
CHARMM	α-cycloaltrin	water solution	29
CVFF	DMTBDMSi-β-CD[e]	dihydrofuranones	172
CHARMM	α-CD	glycerol	100
AMBER*	permethyl-β-CD	limonene, pinene, fluorophenylethane	178

[a] A blank indicates the potential functions used had no name associated with them or that the authors did not specify the force field used. [b] TFADM = octakis(3-*O*-trifluoroacetyl-2,6-di-*O*-methyl). [c] ADP = heptakis(3-*O*-acetyl-2,6-di-*O*-pentyl). [d] HP = hydroxypropyl. [e] DMTBDMSi = heptakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl).

forces” when the interactions are attractive or “steric effects” when the van der Waals forces are collectively repulsive.[61] But also included are electrostatic attractions/repulsions. These latter interactions are typically viewed as multipolar expansion series, e.g. monopoles, dipoles, quadrupoles, octupoles, and the like on one molecule, interacting with comparable electrical moments on another molecule. Most scientists consider only the first few terms in their assessment of host−guest binding, e.g., monopole−monopole, dipole−dipole, dipole-induced dipoles, etc., because these are the leading and most prominent terms in such expansion series though other terms contribute. (2) Hydrogen bonding (a primarily electrostatic phenomenon) that is especially significant to cyclodextrins because there are so many oxygen atoms that serve as Lewis base sites and hydroxyl groups acting as Lewis acid contributors. (3) Relief of conformational strain energy (of the cyclodextrin host) implying that the empty cavity results in a cyclodextrin conformation that is energetically less stable that of an included structure, perhaps due to unfavorable hydrogen bonding of the glucose monomers with water or due to a collapsed macrocycle. (4) Hydrophobic forces, still ill-defined yet powerful driving forces for nonpolar solutes to become excluded from bulk water. (5) Relief of high-energy water. This refers to water molecules existing in a cyclodextrin cavity that are incapable of forming a full complement of bonding with other waters (as in bulk water) and are, accordingly, enthalpy-rich. These forces and other energetic concepts will be described below.

One approach used for addressing the contribution each of these forces makes toward complexation is to rely on quantitative-structure−activity relationships (QSAR).[62] Conceptually QSAR allows one to separate one type of interaction from another and to do so quantitatively. In this regard a mathematical model is constructed. This model should be both informative, meaning it should describe the merits of each force involved in the binding process, and predictive, meaning it should be able to predict the behavior (in this case association) of a yet unknown molecule. Many such studies have been carried out, primarily by Matsui, Nishioka, and Fujita, the latter of whom is a major contributor to the field of QSAR, and this type of computational chemistry directed

Scheme 1



toward the mechanism of cyclodextrin binding has been reviewed in a book chapter by those scientists.[63] Nonetheless it is instructive to present an example here of how this type of modeling is done and to describe the information one can derive from such a powerful method, especially when compared to the other molecular modeling methods described throughout this review.

A good example in this regard involves the work by Matsui and Mochida,[64] who tabulated the thermodynamic stabilities of alcohols, presented as log $1/K_d$, for α- and β-cyclodextrin. A regression analysis comparing the binding data for branched and cyclic alcohols was made using the following molecular descriptors: P_e, the partition coefficient of alcohols in an ethyl ether/water system, and E_s, the Taft steric substituent constant. Equations 1 and 2 were derived for alcohol binding to α- and β-cyclodextrin, respectively.

$$\log 1/K_d = 0.92 \log P_e + 0.42E_s + 1.24 \qquad (1)$$

$$n = 17 \quad r = 0.953 \quad s = 0.271$$

$$\log 1/K_d = 0.97 \log P_e - 0.65E_s + 0.60 \qquad (2)$$

$$n = 18 \quad r = 0.938 \quad s = 0.383$$

A key point embedded in these mathematical models concerns the sign of the regression coefficients for the steric descriptor, E_s. For α-cyclodextrin the sign is positive meaning that a bulky alcohol (relative to the cavity size) will experience van der Waals repulsions upon binding. But for β-cyclodextrin, whose sign is negative, these same alcohols experience van der Waals attractions. Such insights may seem trivial in retrospect, but they are revealing and valuable and, most importantly, they are predictive. As you would imagine, other kinds of molecular descriptors can be used to reveal even more information about the forces responsible for inclusion complexation, but many scientists want more detailed information than that provided by such QSAR analyses. They want a more detailed, atom-by-atom accounting of what is happening upon complexation rather that the fuzzy and ill-defined “effects” ascribed to each descriptor. And so, many scientists have turned their attentions to atomistic modeling using quantum mechanics or empirical force fields embodied in molecular mechanics and molecular dynamics.

Moving in this direction was Tabushi.[65] In a seminal paper addressing the driving force of inclusion he considered van der Waals interaction energies, molecular mechanics energies, solvation energies, hydrogen bond energies, and other kinds of energies to account for observed free energy changes of aromatic guests binding to α-cyclodextrin. The model he developed for doing this is represented in Scheme 1, where the overall free energy change is the sum of four processes. First the water molecules contained in the cyclodextrin cavity are released. This involves a loss of van der Waals stabilization and hydrogen bonding, but one gains motional freedom of the waters (translation and rotation) that did not exist when bound to the cavity. The second hypothetical step is the transferal of the gas-phase waters to the liquid. The third hypothetical step is the removal of a nonpolar guest from water to the gas phase, leaving behind a water cavity that collapses with restructuring of water. The last step involves the change in conformational energy of the cyclodextrin and the van der Waals stablization as the guest is inserted into the host.

Tabushi found that the enthalpy of inclusion is mainly dependent on the van der Waals stabilization of the complex and the dissolution of the water cluster solvating the nonpolar guest. The larger the van der Waals stabilization becomes the more extensive is the water collapse during the inclusion process, and the relative contribution of these two compensating terms dictates the relative stability of guest−host complex for a series of related guests. Evidence for “high-energy water” molecules was found, and confirmation of disrupting water clusters around guests in the bulk aqueous phase (hydrophobic force) as being an important driving force was presented. The increase in entropy accompanying the disruption of the water shell surrounding the nonpolar guest is substantial in magnitude and contributes significantly to the stability of the inclusion complex. Tabushi also found, contradicting extant theories, that the conformational energy change from the hydrated structure to the included guest structure of cyclodextrin was large and of positive energy; i.e., there is no relief of conformational strain stabilizing the event. The work by Tabushi relied on a significant amount of atomistic calculations to derive his conclusions, but there were introduced many ad hoc assumptions and approximations, especially concerning the solvation energies and the introduction of macroscopic information. In other words, the computational study by Tabushi was not a fully atomistic simulation.

In contrast, a simulation predicting the differential free energies of binding, $\Delta\Delta G$, of substituted phenols inside α-cyclodextrin has been carried out by Mark et al.[66] These predictions relied exclusively on atomistic simulations, not using any macroscopic information at all. The technique used is called free energy perturbation (FEP) theory,[67] allowing one to compute free energy differences between two molecules in a given environment as exemplified by, for example, two drug candidates in a protein receptor. The methodology makes use of thermodynamic cycles, but the technique itself is computational alchemy because the interconversion from one molecule to another is physically unrealistic (the free energy change of state functions involves only the initial and final states, which are real molecules, but the pathway between those states is irrelevant). In the FEP method one carries out MD simulations while mutating one molecule into another and evaluating how the free energy of the system changes during the course of that mutation. It has become a major computational tool in the pharmaceutical industry where it is used in drug design, but it could just as well be used for predicting the free energy differences between guests included in a cyclodextrin cavity as done by Mark.

The goal of Mark et al. was to evaluate the convergence properties of two FEP techniques: slow growth, where one molecule is continuously mutated into another during the course of a simulation, and thermodynamic integration, where one molecule is mutated stepwise throughout the simulation. In their study the results of both methods were compared to the experimentally derived free energy differences of inclusion complexation of *p*-chlorophenol, *p*-methylphenol, *p*-cyanophenol, and *p*-methoxyphenol. Two major computational issues are at play here. One involves the effects of performing the perturbation at a rate faster than which the system can keep pace. If the perturbation is not done slower than the relaxation time of the system, it lags behind the mutational changes and does not reflect the lowest free energy of the system. The second issue concerns adequate sampling of the equilibrium ensemble. The equilibrium ensemble is not a single state but a collection of related states that are populated by their Boltzmann weights. This collection, in turn, depends on how adequately one samples configurational space. One way to determine how well the changes in free energies are being predicted, for a given force field, is to mutate, say, *p*-chlorophenol to *p*-methylphenol and calculate ΔG for that transformation. Then one mutates *p*-methylphenol back to *p*-chlorophenol again calculating ΔG. If the system is reversible and does not lag behind the mutations being made (i.e., no hysteresis), the overall change, $\Delta\Delta G$, will be close to zero if one samples enough configurations because we end up where we began. Inadequacies in the methodology show up as larger differences.

The authors noted that the hysteresis did not decrease as the simulation times were extended from 25 ps, a time interval they found to give good results, to 100 ps. Instead, the errors increased indicating a poor mutation. When the simulation time was extended to 300 ps, however, the hysteresis decreased to that of their 25 ps simulation. The genesis of this seemingly erratic behavior comes from differences in motional time scales. There exist three major motions of the guest in the cyclodextrin cavity: (1) rotation of the aryl ring along the 6-fold cyclodextrin axis; (2) movement of the guest in and out of the cyclodextrin along the 6-fold axis; (3) tilting of the plane of the guest relative to the cyclodextrin. Trajectories of these motions were plotted, and it was clear that the first motion is fast but the latter two are slow. The increase in hysteresis, i.e., the poorer result when going from 25 to 100 ps, and then the decrease in hysteresis when extending the simulation to 300 ps relate to these motions and those time scales. Within 25 ps little or no rotational motion of the guest in the cavity takes place and the system is essentially frozen, and so little hysteresis (error) is observed but for the wrong reason. When the mutation takes place over a 300 ps time period, the rotational motion is fully sampled and again one has a small hysteresis but for the right reason. The authors suggest that if the mutations were done over a longer time period of 600 ps or 1 ns, the other two motions would come into play and those slow motions would not be adequately sampled, again giving a large hysteresis and poor predicted free energies of binding. Clearly great care must be taken when doing FEP calculations.

The reason for describing this work in detail was 2-fold. First we note that when going from the studies of Matsui to Tabushi to Mark, there is a change from fuzzy, ill-defined QSAR descriptors to more and more atomistic content that is defined precisely. This is a trend that is taking place in most areas of computational chemistry and is not just found in host–guest studies of cyclodextrin research. Second, just because one uses a full atomistic simulation does not mean that better results will be obtained; the QSAR methods are especially robust and powerful methods for making predictions, and those in the cyclodextrin community wishing to make such predictions ought not think that a QM or MD approach is better than QSAR just because it appears mathematically more complex.

Computing free energies is a computationally demanding task. Several attempts to simplify this have been made, however. Lukovits,[68] for example, investigated the energetics of alcohols binding to *β*-cyclodextrin. The simplification in that study was to hold fixed the geometries of both host and guest while minimizing the geometry of the binary complex. Using an empirical force field Lukovits located the minimum energy structure on the rigid body intermolecular PES. First derivatives of the computed intermolecular forces were used to determine if the binary complexes were truly minima (vs saddle points), and analytical second derivatives were used to perform normal coordinate analyses from which entropies could be determined. For the simplest alcohol, methanol, 50% of the total interaction energy was attributed to van der Waals' forces, and this percentage increased for heavier alcohols. This result, parenthetically, is fully consonant with the QSAR regression analysis described earlier. The computed values for $T\Delta S$ were always lower than the corresponding ΔH value, but the two thermodynamic quantities are of comparable magnitudes. Importantly, a good correlation between computed enthalpy changes and computed entropy changes was found, indicating that compensating enthalpy and entropy effects are at play for the binding of the alcohols considered.

Plots of ΔH vs ΔS providing straight lines, however, can be misleading, having only an artificial statistical relationship but containing no information. The use of isokinetic relationships (IKR) with molecular mechanics calculations by Linert, Han, and Lukovits[69] illustrates this point. The isokinetic point is the common intersection point in van't Hoff and Arrhenius planes. The authors measured the temperature dependence of 48 guests binding to α- and β-cyclodextrin in water, and six groups of compounds, based on their isokinetic relationships alone, were resolved from one another. Group 1, for example, consisted mostly of common organic solvents, and from the nearly parallel van't Hoff lines it is concluded that the inclusion complexation is mainly an entropy-driven process. Group 2 contained mainly carboxyl groups connected to aromatic rings with the well-defined isokinetic temperature being higher than the temperature range of the experiments and accordingly with enthalpy playing a major role in the complexation process. The other groups were similarly defined and interpreted. Molecular mechanics calculations were carried out, again using the rigid body approximation as before, to compute ΔH and $T\Delta S$. Good correlations between computed vs observed enthalpies were found while modest correlations between experimental and theoretical entropies were found. However, the MM calculations were done in a vacuum giving isoentropic behavior in stark contrast to the authors' IKR data, implicating the significance of solvation effects contributing to the entropy changes in real systems. Another paper addressing solvent effects on thermochemistry and enthalpy–entropy compensation exists, but the computational studies there focused more on the number of solvent molecules involved in the inclusion complexes than on the enthalpic–entropic relationship.[70]

Computing entropies can be done several ways,[71] but evaluating this component of free energies of binding is difficult. Thus most computational studies, in contrast to the above-mentioned work, do not compute entropy. Molecular mechanics calculations provide a potential energy. The change in energies between free and complexed states corresponds to an enthalpy difference of binding, and most computational papers focusing on cyclodextrin energetics report only these energy changes. An example of this is the work by Pang and Whitehead,[72] who compute E_p, a "complexing energy". E_p is the difference in potential energies at infinite separation (zero energy) compared to that of a bound complex. Using α-, β-, and γ-cyclodextrins that had been previously energy minimized by the MMX force field the authors docked benzene and *p*-dihalobenzenes into those cavities. The energetics of such docking were described, and plots of experimental association constants (log K) vs minimum energy potentials gave very poor correlations. These results could be improved substantially, however, by plotting log K vs the complexing potential summed over all bound states that are appropriately Boltzmann averaged. Another example where only binding enthapies are computed is provided by Copper and Sepaniak,[73] who correlated computationally derived host–guest complexation energies (using the Tripos force field) with cyclodextrin-modified micellar electrokinetic capillary chromatography separations of benzopyrene isomers. Here, as in Whitehead's study, a large number of orientations were searched for in a systematic manner, resulting in a wide range of docking orientations and energies. In contrast to Whitehead, though, Copper and Sepaniak energy minimized the lowest energy rigid-body docking structures. Their computed elution orders agreed with experiment. Other similar papers focusing on energetics of binding exist. These include the following: the use of binding energies to help interpret calorimetrically determined binding energies of antigenic determinants (haptens) in water;[74] the computation of interaction energies of crocetin, a natural light sensitive colorant binding with cyclodextrins;[75] the use of MM-derived complexes to assist in the interpretation of the thermodynamics of α-cyclodextrin complexes of *p*-nitrophenyl glycosides;[76] a molecular mechanics investigation of the stability of the triflumizole·β-cyclodextrin complex in solvent.[77] This latter study, like the others, did not have an entropy term, but it did attempt to include a hydrophobic driving force by minimizing the hydrophobic contributions to the solvent accessible surface area of the complex. In this approach the authors used the Metropolis Monte Carlo method. Here, each randomly generated configuration is either rejected or accepted based on an energy criterion. The authors cleverly realized that when computing these configurations they could also determine the solvent accessible surface areas of those configurations and, hence, the hydrophobic solvation energy. The hydrophobic character of each complex was used as a criterion for acceptance or rejection together with the energetics of the complex. This way an optimal hiding of the nonpolar groups within the cyclodextrin cavity was induced while retaining energetically feasible structures. This treatment of the solvation effect is an implicit one because the water molecules are not treated explicitly.

A molecular mechanics treatment using the Tripos force field of the energetics of 2-methylnaphthoate binding to α- and β-cyclodextrin in the presence of explicit waters has been published.[78] Periodic boundary conditions were used to fully immerse the host and the guest, both in the free and in their complexed states, in a water environment. The naphthyl ring was inserted incrementally into the cyclodextrins, scanning for low-energy configurations at each step. This reaction coordinate for inclusion complexation was evaluated for host and guest in vacuo and in solution, and the minimum energy structures derived from this search were compared. For both cases the authors found the van der Waals forces to be dominating the stabilization.

Finally, we point out that a significant number of researchers have focused their attention on the energy changes associated with transits through the cyclodextrin torus. Representative examples can be found in the articles published by the groups of Dong,[79] Sato,[80] Janssen,[14,81] Lipkowitz,[82] D'Souza,[33] Berg,[83] Köhler,[84] and Jursic.[85] However the most comprehensive assessment of such transits have been done by Jaime et al. in a series of papers[86−90] most of which will be discussed in the following section. To obtain these energies most authors incrementally move the guest molecule through the cyclodextrin's interior in small steps and at each point compute the system's energy, typically with an empirical force field. This is accomplished by first defining a mean plane composed of the glycosidic linker oxygens connecting the monomers (O_4 in Figure 4). The origin of a Cartesian coordinate system is then placed at the centroid of those oxygens, with the z axis perpendicular to that mean plane. A centroid is arbitrarily selected on the guest molecule which is then placed along the z axis and moved through the cyclodextrin's orifice, stepwise, in small increments. In some studies the cyclodextrin and guest are held rigid and the guest is not allowed to deviate from the z axis, but in other studies the guest is allowed to meander about at a fixed z coordinate (i.e., at some height above or below the cavity openings). In other calculations the entire assembly is allowed to fully relax. Plots of energy as a function of distance reveal which rim of the cyclodextrin is preferred by the guest for entry and the minima on such curves define how deeply sequestered the guests are within the cyclodextrin cavity. Depending of the size of the cyclodextrin and the size of the guest there can exist bottlenecks preventing complete transit through the macrocycle's cavity.

A compilation of papers using molecular mechanics is presented in Table 3. This particular computational method has been used more frequently than any other method because of its speed and accuracy. While one would ideally use Monte Carlo or molecular dynamics based simulations for statistical averaging, i.e., to better make the connection between the macroscopic experimental results from the laboratory with the microscopic atomistic view from the computer, such calculations are very time-consuming and they are also more difficult to perform. The MD calculations in Table 2 were generally carried out by expert computational chemists or by researchers in collaboration with such groups who had the computing horsepower and the expertise to successfully carry out those calculations. Many of the molecular mechanics calculations, in contrast, have been carried out by bench chemists without the assistance of a computational chemist, and accordingly, many errors and misinterpretations of data exist (see the conclusion section).

The data in Table 3 are presented in chronological order. Note that some of the force fields have various modifying symbols, viz, MM2, MM2′, MM2*, and the like. The reason for this is that many of the authors of molecular mechanics force fields used a force field from another author but then adulterated that force field by adding or deleting from the potential functions or by changing the parameter sets. So, although the force field is derived from, and even very similar to, the original, it is nonetheless different and is marked accordingly.

B. Structures of Included Complexes

Preceding the computer revolution and especially the advent of molecular modeling, most chemists used hand-held mechanical models to visualize complex systems and to assist their understanding of molecular structure and chemical reactivity. This was true for researchers attempting to predict the geometries of CD inclusion complexes as well.[91] In the early days of cyclodextrin host−guest complexation studies, scientists were especially interested in the regioselectivity of binding, i.e., head-first vs tail-first inclusion, of seemingly simple mono- and disubstituted aromatic rings that were known to form tight inclusion complexes and which could be obtained as high-quality crystals for X-ray diffraction studies. Most of the early computational studies likewise focused on these dipolar guests, partly because their structures were in the literature but also because they were rigid so relatively simple conformational analyses were needed (if any) and because they were small enough for computation using the computers of that generation.

Matsui, whose QSAR work was described earlier, was fully aware of the tremendous potential computational chemistry had for making such predictions, and he was well aware of the inherent limitations of mechanical models. In an early computational study[92] he considered the structural analysis of several α-cyclodextrin inclusion complexes on the basis of van der Waals interaction energies alone. This was done with the intention of relating structures, stabilities, and reactivities of those complexes with energies derived from molecular mechanics calculations. In his study Matsui used the same type of nonbonded (van der Waals) function Allinger used in his force fields. Rather than compute the total molecular mechanics energy Matsui computed only the van der Waals energies between guest and host, basing his choice to do so on the assumption that the two dominant forces holding the complexes together are the van der Waals forces and hydrophobic forces. In that study he also wanted to make clear the scope or limitations of such a simplified approach to structure determination.

Matsui began by constructing a cyclodextrin. He assumed each glucopyranose to be the same as the

Table 3. Published Studies Using Molecular Mechanics Calculations

force field[a]	hosts	guests	ref
	CDs having 5−8 monomers	none	8
	α-CD (hexahydrate)	benzene, methyl orange, *p*-iodoaniline	65
	α-CD	Kr, methanol, 1-propanol, *p*-nitrophenol	92
	β-CD	various organic alcohols	68
	α-, β-CD	organic solvents, aromatic/aliphatic carboxylic acids, dyes	69
MM2*	α-, β-, γ-CD	ferrocene derivatives	108−110
MM2	β-CD	nitrophenols, nitroanilines, dihydroxybenzenes	79
MM2*	β-CD	various xylenes, cresols, phenols, anilines, benzoic acid	155
	α-CD	*p*-nitrophenol, *p*-iodoaniline	120
AMBER	β-CD, *N*-methylformamide-β-CD	none	13
GROMOS	α-CD	*p*-substituted phenols	197
TRIPOS	α-, β-CD	pharmaceuticals, vitamins, agrochemicals	198
MM2	β-CD	none, 1-bromoadamantane	86a,b
MMP2	β-, γ-CD	none, cyanine dyes	80a
COSMIC	α-CD	diazo compounds	74
MMX	β-CD-anthraquinone derivatives	none (self-inclusion)	117
CHEM-X,MM2*	β-CD	various guests from CSD	14
MM2*, AMBER*	α-, β-, γ-CD	none	16
MM2, MM2′	β-CD	adamantane	87
MM2*	α-CD	none, *p*-hydroxybenzoic acid	81
MM2*, AMBER*, CHARMM	α-, β-, γ-CD	none	18
MM2*	α-, β-, 2-flavo-β-CD	none, phenol, benzyl mercaptans	33
MM2	γ-CD, acetylated γ-CD	diastereomeric dipeptides	156
MM2	β-CD	7-amino-4-methylcoumarins	199
MM2*	β-CD	nootropic drugs	124, 125
CVFF	TFADM-γ-CD,[b] permethyl-γ-CD, others	styrene oxide	169
AMBER	β-CD	none	209
MMX	α-, β-, γ-CD	none, benzene, *p*-dihalobenzene	72
CHARMM	3,6-anhydro-α-CD	none	22
CVFF	glycophane	none	36
MM2	β-CD	*cis*-decalin	101
MM2*, AMBER*	α-, β-CD; permethyl-α-, β-CD	various guests in crystalline lattice	18
TRIPOS	DMTBDMSi-β-CD;[c] permethyl-β-CD	limonene, 1-phenylethanol	170
MM2*	α-, β-CD	HP-128 (cognition activator)	126
CHEM-X	hydroxyethyl-6-thio-γ-CD	anthraquinone-1-sulfonate	129
	highly derivatized prophyrin CD dimers	adamantylquinone	80a
TRIPOS	β-CD	adamantane diazirine	115
MMX	γ-CD	1,2,3-tri-*tert*-butylnaphthalene	200
MM2	α-CD	none	17
AMBER	β-CD, permethyl-β-CD	none, indomethacin, iodophenol, salicylic acid, others	
PIMM	cyclodextrins, cyclomannins, cyclogalactins each having 5−6 monomers	none	23
MMX	dicyanoanthracene-capped-β-CD	none	34
BIOGRAPH	γ-CD	buckmisterfullerenes (C_{60}, C_{70})	132, 133
CHARMM	6-(dimethylamino)-β-CD; 6-permethyl-β-CD	various nucleosides, nucleotides	127
CHEMMOD	β-CD	none, water, methylphenobarbitone	164a
TRIPOS	γ-CD	DNS-derivatized amino acids	166
CVFF	2,6-di-*O*-methyl-β-CD	heavily substituted porphine	130
MM2	γ-CD	none, substituted aromatics	88
TRIPOS	β-CD-phenylalanyl ester	none (self-inclusion)	128
MM3	β-CD	triflumizole	77
TRIPOS	γ-CD	benzopyrene isomers	73
CVFF	β-CD	substituted acetophenones	118
MM3*	glycophane	none, *p*-nitrophenol gluco- and mannopyranosides	189
MM2	α-CD	dimethylbicyclo[2.2.2]octane	83
MM2	α-, β-CD, 2,3,6-HP-β-CD,[d] 2,6-dimethyl-β-CD, others	none	184
PIMM	CDs having 5−6 monomers	none	24
CVFF	heptakis-3-amino-β-CD	none (dimer)	37
CVFF	β-CD	flurbiprofen	159
CVFF	β-CD	hisoldipine (calcium antagonist)	165
MM2, MM3	β-CD	phenol, dimethylphenols, trimethylphenols	137
DREIDING	phenylcarbamoyl-β-CD	atenolol	163
MM2*	β-CD	CI-933 (cognition acivator)	122
MM2	β-CD	substituted ketones and nitroxides	89
MM2	α-, β-CD	glucose	201
MM2	β-CD	none, water	49
MM2, AMBER, CHARMM	α-, β-, γ-CD; others	none	48, 185

Table 3. (Continued)

force field[a]	hosts	guests	ref
TRIPOS, CVFF	TFADM-β-, γ-CD	amino acid derivatives, lactones, alcohols	171
AMBER	γ-CD; 6-(trimethylammonium)-γ-CD	buckminsterfullerene (C_{60})	139
CHARMM	α-, β-CD	*p*-substituted phenols, admantane carboxylate	96
CHEMMOD	β-CD	ibuprofen, mandelic acid, pseudoephedrine, hexobarbitone, others	164b
TRIPOS	α-, β-, γ-CD; permethyl-β-CD	tricyclene, pinene	173
CVFF	α-, β-CD; permethyl-β-CD	pinene, cyclohexanetriol derivatives	174, 175
MM3	α-, β-CD	dimethoxybenzenes	138
AMBER*	α-, β-, γ-CD	bromoadamantane	103
AMBER	β-CD, permethyl-β-CD	binaphthyl derivatives	86b, 131
MM+, TRIPOS	α-, β-, γ-CD; permethyl-α-, β-, γ-CD	none	35
MM2, GROMOS	CDs with 18, 24, and 48 monomers	none	26
CVFF	β-CD	indomethacin	98
MM2	β-CD	benzoic acid	90
MM+	α-, β-, γ-CD	water, crocetin	75
MM3	β-CD	*tert*-butylbenzene	85
MM3*	α-CD, glycophane	*p*-nitrophenylglycosides	76
CHARMM	β-CD	glucose	134
MM3, MM3*	β-CD	substituted adamantanones	116
MM+	γ-CD	6-doxylpalmitic acid	180
	β-CD	decyltrimethylammonium ion	181
CVFF, MM2	β-CD	none	206
TRIPOS	α-, β-CD	2-methylnaphthoate	78
MM3	β-CD	cyclohexylnaphthalenes, cyclohexylanthracenes, phenyldecalins	105
MM3	α-, β-, γ-CD	aliphatic and alicyclic hydrocarbons	106
	β-CD	cyclopentadiene, acrylonitrile, methyl vinyl ketone, others	202

[a] A blank indicates the potential functions used had no name associated with them or that the authors did not specify the force field used. [b] TFADM = octakis(3-*O*-trifluoroacetyl-2,6-di-*O*-methyl). [c] DMTBDMSi = heptakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl). [d] HP = hydroxypropyl.

"G1" residue of the α-CD·potassium acetate complex and that the structure of the macrocycle would contain 6-fold symmetry. The tilt angle of the pyran rings were computed with a force field treating only van der Waals and angle bending terms. This structure was held fixed as guests were docked into its interior and the interaction energy, E_{vdw}, was computed. The guests considered were Kr, MeOH, 1-propanol, and *p*-nitrophenol. The agreement between computed structures and crystallographic structures was poor for the first two guests but good for the latter two (note that a root-mean-square deviation between the structures was not provided but only the coordinates for guest atoms along the z axis; however, graphical superpositions showing computed vs experimental geometries suggest these values to be small). Moreover, Matsui was able to predict the relative orientation of *p*-nitrophenol inside the cavity, an elusive problem in the early days of CD structure prediction. Explanations for the inability of the method to predict the smaller guest geometries correctly were presented; the author appears to conclude that other interactions need to be accounted for to more successfully compute the structures of inclusion complexes.

In contrast to the assumption made by Matsui that van der Waals forces were dominating the regioselectivity of inclusion is the assumption made by a group of scientists from Tokyo Institute of Technology who felt that "From the standpoint of intermolecular interaction theory, long range types of interaction, especially electrostatic interaction, should be primarily important for stabilizing such non-covalent types of molecular complexes".[45] In the first of a series of papers, Kitagawa et al.[45] use the CNDO/2 semiempirical molecular orbital method to compute the dipole moments of α-cyclodextrin and several guest molecules in their complexed states (known from crystallographic studies) and to describe the role of dipole−dipole interactions in stabilizing those complexes. Again, the guests considered were simple, disubstituted benzenes: benzoic acid (BA), *p*-hydroxybenzoic acid (PHBA) and *p*-nitrophenol (PNP). Figure 10 depicts the dipolar relationships between the guests and the host molecules. Note that the dipole of the cyclodextrin runs from the secondary side to the primary side as discussed earlier in this review (see section on structural features of cyclodextrins) and that it can be tilted by some angle, θ, relative to the near 6-fold symmetry of the macrocycle. Likewise the dipole of the guest molecule can be twisted by some angle, ϕ, relative to the long axis of the aromatic ring. The molecular axis of the guest is tilted by an angle, ψ, relative to the pseudo 6-fold axis of the cyclodextrin. Using these descriptions one can define ω, the angle between the dipole moment vectors of the cyclodextrin and the guest by knowing θ, ϕ, and ψ. In the complexed state the dipoles are nearly antiparallel suggesting that dipole−dipole interactions (the leading term of an electronic expansion series) are the main contributors stabilizing the complexes orientation.

Two key issues were addressed in this paper. First, the relative orientations of PNP and PHBA were computed and the lowest energy orientations were consistent with experimental orientations (the energy difference for PNP orientations was much different than that determined by Matsui, however).

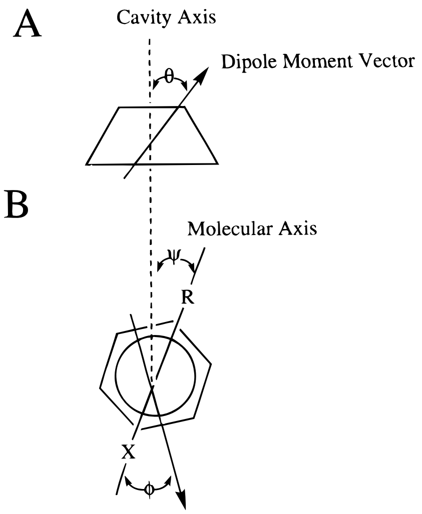


Figure 10. Definitions of the dipole moment vectors of α-cyclodextrin and *p*-substituted guest molecules (top). The dipole moment vector runs from the wide, secondary hydroxyl rim toward the narrower primary hydroxyl rim. Its direction is defined by the tilting angle θ relative to the near 6-fold symmetry axis of the host. The dipole moment of the guest is defined by the tilting angle ϕ compared to its 2-fold molecular symmetry axis (bottom). The molecular axis is usually tilted from the host's major axis by an angle ψ, and the dipole moments are usually aligned head-to-tail as depicted. See ref 45 for details.

Moreover, they found that as the magnitude of the guest dipole increases, so does the value of the cyclodextrin's dipole but in the opposite direction. The origin of this comes from the fact that the cyclodextrin can change its shape (induced fit binding) and it does so to maximize the dipole−dipole stabilization. So, dipole−dipole stabilization is of premier importance. The second issue concerned the mechanism of inclusion, i.e., the dynamical behavior of host and guest leading to the formation of the complex. For the guest's dipole to slide into the cavity of the cyclodextrin, its positive end must pass the positive end of the cyclodextrin's dipole moment. This results in a destabilizing interaction producing an energy barrier keeping the guest from entering the host cavity (see Figure 10). The authors proposed that this problem can be avoided if the cyclodextrin changes its shape both before and after complexation. The 6-fold cyclodextrin has the highest dipole moment but can substantially reduce that dipole by adopting a shape similar to the highly distorted α-cyclodextrin−water complex found in the solid state by Saenger. This distorted structure has a very low dipole moment allowing the permanent dipole of the guest to slide past, surmounting now only a small energy barrier. Once the guest is included, the cyclodextrin changes its shape back to a more symmetric structure to maximize the dipole−dipole attractions. Other concerns were raised in this paper, but the concepts that an induced-fit binding mechanism is operative in these systems and that dipole−dipole interactions are dominating the regioselection of inclusion are the two key points the authors highlight. A preliminary account of this work was published as a communication, and that work was cited above in the section on cyclodextrin structures.[43]

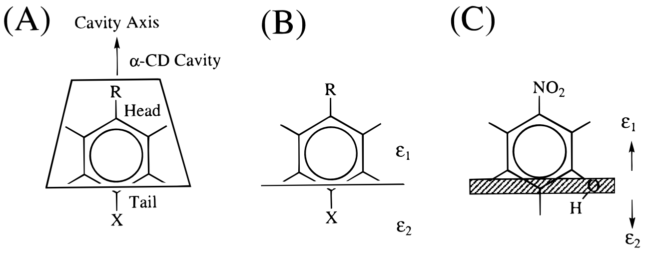


Figure 11. (A) Geometry of an α-cyclodextrin inclusion complex with a typical host molecule embedded. The inverted bucket represents the cyclodextrin to illustrate the depth of penetration and relative orientation of the cyclodextrin relative to the guest. (B) "Double layer model" depicting two regions of differing dielectric. ϵ_1 corresponds to a low dielectric inside the host, and ϵ_2 corresponds to a high dielectric region exterior to the cavity. (C) Final positioning of the borderline separating the interior and outer regions for inclusion of *m*-nitrophenol. The atoms in the region ϵ_1 are inside the cyclodextrin. This borderline provides the best reproduction of ^{13}C-induced chemical shifts. See ref 93 for details.

This same group then began an alternative approach to describe the orientation of included guests within the cyclodextrin cavity.[93] The technique they used is not predictive because it does not explicitly involve a cyclodextrin molecule but rather is interpretive in nature because it helps understand experimental NMR data. Previous ^{13}C NMR studies of α-cyclodextrin binding with molecules such as benzoic acid, *p*-nitrophenol, and other substituted benzenes revealed that the included part of the guest gave rise to high-field chemical shifts while parts protruding from the cyclodextrin interior demonstrated low-field shifts; these characteristic displacements could be used to infer the orientation of the guest in the cavity (see the companion chapter by Schneider[3]). A simple model was developed by Inoue on the basis of the idea that the interior of the cyclodextrin is nonpolar compared to the exterior and that this difference in electrical environment is mostly responsible for the induced chemical shifts. The model was called the "double layer model" because the authors created an artificial boundary between atoms in the guest molecule creating two sets of atoms as depicted in Figure 11.

CNDO/2 molecular wave functions were used to compute chemical shifts. An implicit solvation scheme was incorporated into the quantum chemical calculations. Atoms belonging to one set had a dielectric constant of 2 (inside the cavity), while atoms of the other set had a value of 80 (outside the cavity in water). The molecule under investigation in this study was *m*-nitrophenol, which could have either the NO_2 or the OH group embedded in the cavity but not both. A series of calculations were performed, moving the boundary (for both orientations of guest). The position of the borderline dividing the two sets of atoms was progressively moved until experimental and computed chemical shift displacements agreed. Their best dividing line is also presented in Figure 11, where the NO_2 group rather than the OH group is directed toward the (low dielectric) interior of the cavity. This is the same orientation as found in the solid state. Hence by dividing the included species into two layers, one being on the interior of the host and the other protruding from the host, this “double layer model” is able to assist spectroscopists in their interpretation of data concerning preferred orientations of guest species. A more detailed analysis of the *m*-nitrophenol-induced chemical shifts computed this way was eventually published.[94]

Since then relatively few predictions of inclusion regioselectivity using quantum theory have been published. One example, however, is the work of Botsi et al.,[95] who used the AM1 Hamiltonian to compute the structure of an empty β-cyclodextrin and the energetics and structures of the corresponding inclusion complexes of nonanal and 1,7-dioxaspiro-[5.5]undecane, the latter of which was found to be only partly included from the secondary rim of the macrocycle while the aldehyde was found to be completely ensconced within the cavity. The relationship between computed binding energies and ΔH and ΔS values derived from van’t Hoff plots of NMR chemical shifts was also discussed. By far, though, most of the computational studies directed toward prediction of the structure of these kinds of host–guest complexes have been performed with empirical force fields implemented in molecular mechanics or molecular dynamics simulations rather than by quantum mechanics. The reason for this is basically that these potential functions better treat the dispersion forces between molecules, and for large systems, they can be 2–3 orders of magnitude faster than most quantum mechanical methods.

Lü, Zhang, and Dong[79] took advantage of this to compute the energetics associated with movement of disubstituted aromatics (*o*-, *m*-, and *p*-dihydroxybenzenes, nitrophenols, and nitroanilines) through a β-cyclodextrin cavity using the MM2 force field. Though not clearly stated it appears that the cyclodextrin was constrained to retain 7-fold symmetry. The authors deduced the preferred orientations of the included guests by examining minima along those slices through the systems’ potential energy hypersurfaces. They ended their paper by correlating the computed binding energies with dissociation constants derived from electrochemical measurements. Like Lü et al., Jursic, Zdravkovski, and French[85] pushed *tert*-butylbenzene, another simple aromatic ring, into and eventually through a β-cyclodextrin, plotting the potential energy as a function of distance for both regioisomeric orientations of guest. Once inside the cavity these authors translated and rotated the guest to find the most stable structure computed with the MM3 force field. Structural characteristics of the most stable complex computed with different dielectric constants were given.

Another study that also used an empirical force field to predict the preferred orientations of simple dipolar guests in cyclodextrin cavities is that of Rüdiger et al.[96] These authors were particularly keen on assessing the energetics of binding as well as determining the structure of the resulting complexes, and accordingly, they used both calorimetric as well as NMR data for comparison with their molecular mechanics calculations. The systems they focused their attention on were *p*-nitrophenol, *p*-iodophenol, and adamantane-1-carboxylic acid along with their conjugate bases. The modes of binding and the extent of inclusion were assessed for these systems. Using the CHARMM force field the authors found the iodo-substituted rings to be fully immersed within the host cavity while the nitro compounds were protruding from the α-cyclodextrins, a result in agreement with their NMR data. For the adamantanes binding to a β-cyclodextrin the following conclusions were derived from their molecular mechanics calculations: (1) No room exists for water molecules in the cavity. (2) The larger β-cyclodextrin allows for maximal contact between host and guest in comparison to α-cyclodextrin. (3) The carboxylate forms an additional hydrogen bond to the secondary rim hydroxyl group leading to a tilted orientation (see above description of Jaime’s studies for comparisons).

Earlier we mentioned the work of Pang and Whitehead,[72] who evaluated the energetics of benzene and *p*-dihalobenzenes binding to different cyclodextrins. Inextricably linked with that evaluation of energies are the corresponding structures. Only two orientations were considered by those authors for these highly symmetric guests: one where the cavity axis of the host and the symmetry axis of the guest coincide and the other having the cavity axis of the host perpendicular to the benzene ring plane. Molecular packing and molecular motion of the guest inside the host cavities were computed with potential energy functions. It was found that the interaction energies could be correlated with experimental association constants and that the host and guest molecules have maximum molecular surface contact at the minimum potential.

We now return to the study of van Helden, van Eijck, and Janssen,[56] whose work concerning structural aspects of cyclodextrins was described earlier. They had carried out MD simulations of *p*-chlorophenol and *p*-hydroxybenzoic acid complexed with α-cyclodextrin in a water bath. In contrast to the above-mentioned papers in this section, their study was dynamical and no single “snapshot” of any complex was depicted. Instead, the motion of the guest was monitored over the total time period of the simulation. The authors described, for example, the rotation of the chlorophenol around the cyclodextrin *z*-axis, its movement parallel to that axis, and the tilting of the guest over the simulation time, each plotted as a trajectory. There exists a correlated motion between the macrocycle ring puckering and the guest rotation within the cavity, and there exists a motion of the guest moving in to and out of that cavity (see earlier discussion). While large tiltings of benzenes are not typically found in solid-state inclusion complexes, the guest was found to be tilted between 70 and 110° 66% of the time in the simulation, albeit because the guest spends a significant amount of time outside the cavity. The hydroxybenzoic acid behaves similarly. The authors conclude their paper by elucidating the number and the locations of hydrogen bonds between the guest and the host. In a follow-up paper[81] the authors described the preferred orientation of the latter guest inside the cavity which was not described in their previous paper.

The molecular mechanics and quantum mechanics studies described in this review involve docking a guest molecule into a cyclodextrin and (usually) energy minimizing the entire complex. The results so obtained depend on the initial docking position and orientation because the energy minimizers seek only the nearest minimum on the system's potential energy surface. This poses a problem; one that I call "self-fulfilling prophesy" because many scientists presume they know where and how a guest binds. They place the guest in that position and orientation, do the geometry optimization, and derive a molecular structure similar to the one they presumed exists. In other words they get out of the calculation what they put into it. Ideally one should search all minima on the inclusion complex's potential energy surface, but for molecules such as cyclodextrins containing so many conformational degrees of freedom, exacerbated by the intermolecular degrees of freedom, this is a formidable task that few people attempt to challenge. Usually simplifying assumptions and approximations such as imposing symmetry to the cyclodextrin are made to make the calculations more tenable. Later, in the section on molecular recognition, we will examine how such searches have been done. Here we simply mention that several groups were cognizant of these issues, and they did discuss their docking strategies.

A good example of this is the work of Pang and Whitehead[72] described above and another is by Tran, Delage, and Buléon.[97] These latter authors published a paper describing a systematic docking approach that was applied to the binding of phenylethanol to α-cyclodextrin. Their approach involves the following: (1) systematically scanning of guest positions to exclude improbable structures; (2) clustering the remaining, acceptable structures into families; (3) refining the best structures of each family for further analyses. To accomplish this the authors defined the relative position and orientation of the guest molecule with respect to the host molecule using six parameters. These parameters include a distance, an angle, and four dihedral angles between molecular centroids (e.g., virtual or dummy atoms in the middle of a ring) and virtual bonds. The authors indicate this provides a "crankshaft" searching technique that is preferable to other types of systematic searches where simple translations and rotations of guests are done. The searches scanned the primary side and the secondary side of a rigid cyclodextrin using the Tripos force field. Details of the search and clustering of structures into families for more refined molecular modeling are described in the original paper.[97] The two forms of this inclusion complex found in the crystal were also located with this search strategy. Systematic rigid body grid searches were also carried out by Kostense, van Helden, and Janssen[14] for a series of guest molecules binding to β-cyclodextrin and in a follow-up paper by van Helden[81] for guests binding to α-cyclodextrin. These authors used the search algorithm of Chem-X but eventually energy minimized the structures with the MM2 force field. Isoenergy contour maps for translation and rotation of guests in their respective cavities indicated which initial configurations should be used for the energy minimizations. The energy of the docked structure, derived *de novo* from their modeling, compared to the energies of the complexes found from the crystallographic literature agreed very well ($r^2 = 0.96$ for the six structures determined for binding to β-cyclodextrin).

Many of the inclusion complexes studied computationally (also experimentally) involve fairly simple guests having high symmetry. Above we pointed out that many of those computational studies focused on simple, rigid molecules containing a permanent dipole moment. Not all researchers were interested in the structure of these types of molecules, however. Because cyclodextrins were being studied for their ability to transport and release drugs, several groups focused on the modeling of cyclodextrin−drug complexes. To rationalize the use of β-cyclodextrin for pharmaceutical uses Myles, Barlow, France, and Lawrence[19] thought it useful to know the structural features of drugs qualifying them as candidates for inclusion and to be able to predict the structure and properties of the inclusion complexes. Earlier in this review we described many of these authors' findings concerning the shapes of cyclodextrins (and how their conclusions differ from those of Kostense concerning this). The authors had concluded that guest inclusion causes only minor distortions of the cyclodextrin and that they could use suitable rigid hosts for their modeling but that they had to account for the stoichiometry of the complex, the conformation of the guest, and the degree of penetration and orientation in the host. The focus of Myles' work centered on the antiinflammatory drug indomethacin, containing both an indole ring and a linked chlorophenyl group. Manual docking was done taking advantage of known propensities for *p*-halo-substituted rings to bind regioselectively (see above) to certain cyclodextrins. Both 2:1 and 1:1 cyclodextrin:drug stoichiometries were considered. The pertinent features of the final 2:1 complex were consistent with NMR data and are summarized: (1) The two cyclodextrins are arranged head to head with an aromatic ring of the drug in each. (2) Both indomethacene rings are in van der Waals contact with their respective cyclodextrin rings and tilted with respect to the principal axis of the complex. (3) The drug's methoxy and carboxylate groups protrude from the cavities to facilitate hydration. (4) The drug's ketone group is at the interface of the two cyclodextrins forming hydrogen bonds to the secondary rims. (5) The head to head binding of the cyclodextrins is stabilized by hydrogen bonding (see also the study by D'Souza[37] described earlier). They also found that the conformation of the drug bound to the interior of the cyclodextrin is different, by about 1 kcal/mol in energy, from that in a crystal lattice.

More recently another group studied this same drug binding in solution by evaluating NOE buildup curves of the inclusion complex of an indomethacin methyl ester derivative (rather than the salt of the acid itself).[98] In a forthcoming section of this review focusing on computations used to help interpret spectroscopic data we shall describe the work of

Fronza et al., but for now we foreshadow that section by saying their NOE buildup curves could be interpreted in one of two ways: (1) the existence of two 1:1 diastereomeric adducts, each involving a different part of the drug, or (2) the presence of a single complex having the drug in the thermodynamically less stable configuration. This group was apparently unaware of the full paper published by Myles[19] or of their modeling studies (it was not cited although a preliminary account of Myles' work was). The authors first carried out a full conformational analysis of the guest molecule using the CVFF force field and then evaluated a variety of orientations of the drug inside a β-cyclodextrin host. Their conclusions are that the drug exists in solution as an equilibrating mixture of *E* and *Z* stereoisomers, with the latter being more prevalent, but that complexation with the cyclodextrin leads to a selective stabilization of the thermodynamically less stable *E* diastereomer. The molecular mechanics calculations were limited, however, to a complex having only a 1:1 stoichiometry in contrast to the work of the British group, thus leaving many issues concerning the structure of the β-cyclodextrin–indomethacin complex still unanswered.

Other structures of drugs binding to cyclodextrins have been addressed using computational methods. Armstrong[99] relied on computer graphics to interpret the propensity for β-cyclodextrin to enantioselectively bind D-propranolol rather than its optical isomer and to compare the diastereomeric inclusion complexes formed by that host with (*R*/*S*)-warfarin. Klein et al.[77] used the MM3 force field along with stochastic search methods to predict the energetics and structures of β-cyclodextrin·triflumizole complexes. The initial docking strategy was to push the drug stepwise through the cyclodextrin orifice (see discussion above about transits through the cavity) minimizing the energy of the complex at each step. This was done with triflumizole's aliphatic chain embedded in the cavity and also for its aryl ring embedded in the cavity, but the authors felt uncomfortable with this search strategy so they adopted a Monte Carlo sampling approach to better explore the possible structures that are energetically allowed. Both 1:1 and 2:1 host:guest stoichiometries were computed, but no clear conclusions were elaborated describing a preference for one type of complex or the other.

Computational studies directed toward elaborating the structures of inclusion complexes with other types of guests have been carried out. Examples include the following: the use of molecular dynamics simulations to help determine the preferred binding site of glycerol in an aqueous α-cyclodextrin (only microcalorimetric data was used to determine binding affinity);[100] the binding of an adamantyl quinone to a highly derivatized cyclodextrin-sandwiched porphyrin;[80a] the binding of cyanine dye monomers and dimers to cyclodextrins.[80b] This latter study was a complete molecular mechanics investigation of cyanine dye binding requiring force field parametrization, docking, and energy minimizations with the MMP2 force field. The authors found that, with the exception of one example, the dyes prefer a 2:1 rather than 1:1 dye:cyclodextrin complex. The shapes and orientations of those complexes were presented as were the structural and energetic changes along the inclusion pathway. Yet another example of the use of molecular simulations to derive structural information about cyclodextrin inclusion complexes is the work of Pozuelo, Mendicuti, and Mattice,[59] who used molecular dynamics simulations to assess the conformations and molecular mobility of α-cyclodextrins strung along a poly(ethylene glycol) polymer that has been end-capped to prevent the cyclodextrins from falling off (i.e., polyrotaxanes). van der Waals forces stabilize the complexes, and hydrogen bonds between adjacent cyclodextrins slightly favor head-to-head, tail-to-tail sequences instead of head-to-tail alignments of the threaded cyclodextrins. The ethylene glycol polymer is noted to become more extended in the included state than in the free state because it has a larger fraction of trans bonds when included. The size, shape, distortion, and flexibility of both the host and the guest are described in this paper.

The most extensive set of studies presented from a single group focusing on the structure of cyclodextrin-included guest molecules comes from the laboratory of Jaime and his colleagues in Barcelona. Their first paper[86] focused on the relative orientation of 1-bromoadamantane included in β-cyclodextrin. A 1:1 ratio of host:guest was determined from NMR studies. Intermolecular NOE results suggested a preference for one of two possible guest orientations. Using molecular mechanics, the guest was moved incrementally through the cyclodextrin's cavity and the energy of the complex was minimized at each step using the MM2 force field to provide a reaction path for inclusion. This was done for both orientations of guest, one of which was designated “apical” and the other “basal”, and the authors conclude that the latter orientation having the adamantyl ring entering the host cavity from the secondary rim is preferred. That work was followed by a related study[87] of unsubstituted adamantane binding to the same host where again NOE data were providing some information about the location but not about the orientation of the guest. Three possible orientations exist for adamantane: apical, basal, and vertical, each of which was moved through the cavity and whose energy was computed as before. The conclusion of this work is that all but the vertical orientations are allowed. Keeping with the theme of hydrocarbons binding to cyclodextrins, Fotiadu, Fathallah, and Jaime[101] used a grid search to map out the intermolecular potential energy surface for translation and rotation of *cis*-decalin embedded in β-cyclodextrin. This molecule is chiral, and the authors indicate that they find the more stable diastereomeric complex derived computationally to be the same one that is most stable on the basis of NMR results.

These authors then addressed the issues raised by Janzen[102] concerning the mode of binding to γ-cyclodextrin of a nitroxide having an aryl group, a *tert*-butyl group, and varying alkyl side chains. Using MM2 the authors demonstrated that a bimodal inclusion complex forms through the wider rim of the cyclodextrin cavity.[88] Moreover they were able to predict the association constants for nitroxides having different alkyl groups. Janzen eventually studied more complex systems having the potential for one or more of several rings binding to β-cyclodextrin and Pérez, Jaime, and Sánchez-Ruiz[89] followed suit computationally. They translated and rotated each one of those guests, beginning from six initial orientations, through the cyclodextrin cavity to map out potential energy surfaces and to define the relative orientations of the guests in the host. Ivanov, Salvatierra, and Jaime[103] eventually redirected their attention back to 1-bromoadamantane, but this time they assessed the binding to α-, β-, and γ-cyclodextrin using both NMR spectroscopy and molecular modeling tools. Their goals were to define the stoichiometry of the complexes, their association constants, and their geometries. It was found that the α-cyclodextrin forms a 2:1 complex while the others form 1:1 complexes. The computations done in this work involved molecular dynamics simulations rather than simple molecular mechanics energy minimizations, and the lowest energy structures so derived were described. For the α-cyclodextrin host the bromoadamantane guest was found to be located outside of the torus. For the other cyclodextrins, clearly depicted in overlays of their simulation trajectories, it prefers to be inside with an orientation almost perpendicular to the two cyclodextrin planes. Finally, Salvatierra et al.[90] evaluated the relative orientation of benzoic acid in β-cyclodextrin, again using NMR data with molecular mechanics calculations. She found the carboxylic acid group pointed toward the primary hydroxyl rim of the cyclodextrin, a result the authors felt was surprising (see also the work of Lichtenthaler below in this section). A more recent paper has appeared[104] focusing on the orientation of *n*-alkyl-substituted benzene and cyclohexane. In these systems the ring or the chain can enter from the secondary rim on one of two orientations. Using the MM3 force field and molecular mechanics the authors show a clear preference for the phenyl ring to be included at the primary rim when the chain has less than five carbons with a lesser preference for the same orientation for the other *n*-alkyl chains. For the cyclohexyl system, in contrast, no clear orientational preference is observed. This work was further extended to evaluate the bimodal complexes of cyclohexylnaphthalenes, cyclohexylanthracenes, and 24 stereoisomeric phenyldecalins (both cis and trans) with β-cyclodextrin.[105] Similar conclusions concerning both the preferred docking orientations and rationales for these kinds of inclusion complexes were noted. Sánchez-Ruiz, Ramos, and Jaime[106] also examined the influence of α-, β-, and γ-cyclodextrins on the conformational equilibria of simple aliphatic and alicyclic hydrocarbons. While small changes in conformer populations were noted when compared to similar MM3 calculations in vacuo, the changes in those populations were small and relatively insignificant.

Several computational studies have been done to better understand the mechanistic details of chemical reactions mediated by cyclodextrin microenvironments (see Takahashi's companion chapter in this special issue[107]). Knowledge of the shapes and orientations of species inside the cavity are critical for defining mechanisms and for interpreting stereoselectivities in these environments. A good example of this is the debate between Menger[108] and Breslow[109] concerning their rationalizations for β-cyclodextrin-induced rate enhancement of 3-ferrocenylacrylate ester cleavage. Both groups independently developed parameters for the MM2* force field and evaluated the orientations of ferrocene and of several 3-ferrocenylacrylate esters in cyclodextrins. Menger finds the relatively inactive ethyl and very active *p*-nitrophenyl esters to have comparable orientations and distances relative to the cyclodextrin's secondary hydroxyl groups, supporting his claim that structural variations of the initial complexes are unimportant. Breslow's group originally presumed the ferrocene maintains an initial orientation with its principal axis aligned with the cyclodextrin's principal axis, requiring substantial twisting of the enone moiety of the ester for nucleophilic attack, but after performing the computations, he agreed that the ferrocene is not parallel to that axis. Both groups found substantial distortions of the ester moieties from their calculations, and interestingly, both appear to interpret their computational results to reaffirm their own hypotheses concerning the mechanism and rationales for catalysis of ester cleavage. Another paper describing the parametrization and docking orientations of ferrocenes in more detail was published by Sherrod.[110]

Chûjô's group[111] followed up on the theme of computing rate enhancements in cyclodextrin cavities by noting that the molecular mechanics calculations of Menger and Breslow did not account for solvent effects, nor was there a satisfactory description at that time of how the cyclodextrin's microenvironment could lead to such rate accelerations. Chûjô's group had previously developed a reaction field method for treating solvents (a continuum model) and applied that methodology to probe the rate enhancements of the decarboxylation of phenylcyanoacetate anion by native cyclodextrins. Many assumptions were made on the basis of empirical data including the pathway of decarboxylation, the orientation of reactant inside the host cavity, and that the intracavity could be described by a cylindrically shaped dielectric. The environment surrounding the included substrate was approximated by a multidielectric system. Reaction coordinates for bond breaking, using the MNDO Hamiltonian with the reaction field included, were computed for the decarboxylation in the gas phase as well as in homogeneous and heterogeneous condensed phases. The calculations consistently reproduced experimental results. The authors found that the calculated E_{act} become smaller as the reactant is pushed deeper into the cyclodextrin cavity and that the computed activation energy is very sensitive to the environment surrounding the phenyl group. Using computed atomic charge differences the authors also found that the electronic polarization of the substrate decreases with increased penetration of substrate into the host cavity. Moreover, albeit somewhat counterintuitive, the authors found that the carboxylate moiety undergoing dissociation did not need to be surrounded by a low dielectric medium for the reaction to be accelerated. The solventlike function of the cyclodextrin cavity was dubbed a "microsolvent". A preliminary account of this work was also published.[112]

Venanzi, whose work was described earlier in this review[13] where she evaluated the shapes of β-cyclodextrin and *N*-methylformamide "capped" β-cyclodextrin that serve as enzyme models of α-chymotrypsin, also evaluated the influence of solvent in ester hydrolysis reactions. Luzhkov and Venanzi[113] similarly used a semiempirical quantum mechanical method (AM1 Hamiltonian) to compute the reaction path of ester hydrolysis. They considered nucleophilic attack by OH^- as well as by two possible alkoxide ions of β-cyclodextrin in both the gas-phase and polar environments. The two key questions Venanzi posed were the following: (1) What role does the cyclodextrin microenvironment play in phenylacetate hydrolysis? (2) Is there a difference between the C_2 and C_3 hydroxide reactivity on the secondary rim of the cyclodextrin? In this study the solvent was treated as Langevan dipoles. Here the solvent system is partitioned into a spherical interior compartment, where the solvent molecules are polarizable point dipoles, and an exterior compartment, where the solvent is treated as a continuum using reaction fields. Computer modeling to locate the transition state for nucleophilic attack on phenylacetate was carried out, and large differences between reaction coordinates in condensed and vacuum phases were noted as expected. To evaluate the microenvironment of the cyclodextrin the authors first determined the conformations of the cyclodextrin when O_2 or O_3 alkoxide ions are present. They determined the relative stabilities of those ions and then computed the inclusion complexation of the ester. Computation of the various tetrahedral adducts arising from O_2 and O_3 attack was performed, and then the reaction path of ester bond cleavage was computed for each adduct. The authors found, despite the lower pK_a value for the O_2 site and despite the tighter fit of the substrate into the host cavity at that site, that an alternative thermodynamically and kinetically favorable pathway is obtained for reaction at the O_3 site. Attack of the O_3 hydroxyl was shown to lower the activation barrier by about 10 kcal/mol compared to attack by a hydroxide ion in solution. This is by far the most extensive assessment of the site- and regioselectivity of cyclodextrin catalyzed reactions, and it is the most complete paper to date concerning the role of solvent and the role of the cyclodextrin microenvironment in its capacity to act as a catalyst. A follow-up review of this study along with other solvation effects of bioactive molecules has appeared.[114] Another study focusing on the catalytic properties of cyclodextrins was published by D'Souza's group where the emphasis was directed toward artificial redox enzymes as mentioned earlier.[33]

Not all computational studies of cyclodextrin reactions were focused on explaining the catalytic properties of these molecules, however. Molecular modeling was used by Brinker et al.,[115] for example, to gain some insights about the fit and orientation of an adamantane diazirine in β-cyclodextrin that, upon photolysis, generates the adamantylidene (carbene) as a reactive intermediate ultimately giving rise to a set of insertion products. Another paper focusing on photochemical reactions inside cyclodextrins was published by Entrena and Jaime.[116] These authors used molecular mechanics calculations to explain the reversal in facial selectivity of 5-substituted-2-adamantanones undergoing 2 + 2 cycloadditions with fumaronitrile in the presence of native, β-cyclodextrin. In this work Entrena and Jaime used the MM3 and MM3* force fields to predict the populations of two dominant binary host−guest inclusion complexes. In all cases studied the preferred geometry of the complex corresponded to a structure having the anti face of the carbonyl group directed toward the wide, accessible rim of the cyclodextrin and the syn face buried in the interior of the cyclodextrin cavity. Syn attack is preferred in solution, but that route becomes inhibited when the adamantanone is bound to the cyclodextrin. In that case, anti attack dominates (hence the reversal in facial selectivity). The computed syn/anti ratios agree with experimental ratios especially when the MM3* force field is used with the GB/SA continuum solvation model to account for solvent. The photoinduced chemical reactions of several anthraquinone-substituted β-cyclodextrins were studied by Aquino et al.,[117] who likewise used molecular mechanics to interpret their hydrogen abstraction results. The question at hand was whether the abstraction was an intramolecular or intermolecular process, and a limited conformational search showed that essentially strain-free structures could be derived for each of the abstraction sites suggesting the former rather than the latter process was taking place. The authors also computed a "transition state" enthalpy for the reactions and found variable results depending on force field parameter sets and assigned dielectric constants. Finally we mention Deratani and Renard's study[118] of the $NaBH_4$ reductions of substituted acetophenones entrapped in β-cyclodextrin cavities. To help rationalize the observed asymmetric inductions, molecular mechanics calculations were used to discern the relative accessibilities and orientations of the carbonyl groups to the borohydride. In all of the studies just described a significant number of assumptions, approximations, omissions, and preconceived notions jeopardize the conclusions of those computational studies.

We conclude this section by focusing on the work of Lichtenthaler and Immel,[119] who wanted to better comprehend the formation and stability of cyclodextrin inclusion complexes, in general, and, in particular, the relationship between the hydrophobic characteristics of both the guest and the host. To assess this the authors computed the molecular lipophilicity patterns as described in an earlier section of this review. Several crystallographically well-characterized complexes were selected as representative examples. In the α-cyclodextrin−*p*-iodoaniline complex conformities between the most hydrophilic and hydrophobic surface regions of the host−guest interface are found, and the authors point out that this is a general trend in other α-cyclodextrin complexes as well but provide caveats where this may not hold. Three complexes of β-cyclodextrin were similarly evaluated including that of 1,4-butanediol, where the congruence of lipophilicity maps is essentially independent of the guest's precise extended conformation, and for two adamantane derivatives having a 1-methanol substituent and a 1-carboxyl substituent. For these latter two systems the significance of head-to-head dimers is discussed, an issue omitted by most other authors in their computational studies of adamantane binding. Finally, the 12-crown-4 ether complex with γ-cyclodextrin, resulting in an intricate supramolecular lattice containing head-to-head and head-to-tail orientations, was examined. From all these examples the authors conclude that the reciprocal interplay between hydophilic and hydrophobic patches on the host and guest molecules are especially important in determining the relative positions, orientations, and stabilities of guests in cyclodextrin inclusion complexes but that other inextricable forces are also at play.

C. Computational Studies Assisting Interpretation of Spectra

We now pay homage to the use of molecular modeling in the area of spectroscopy. All of the spectroscopic data collected is just that—data. This information, regardless of whether it originates from rotational/vibrational, electronic, or nuclear magnetic resonance spectroscopies, must be put into context; i.e., a structural model must be presented that is consistent with the spectra, and deciphering that data can sometimes be difficult because of the limited information content derived from the spectroscopic probe being used. Moreover, interpretations of these data, whether it be line broadening, intensity changes, lifetimes, or frequency shifts, are subject to misinterpretation. Therefore many scientists examining host—guest complexes of cyclodextrins experimentally have also attempted to use molecular modeling tools to provide a basis for accepting or rejecting a model they are positing. In this section we mention several published studies where molecular modeling has assisted the spectroscopist in his or her interpretation of their data. We curtail any in-depth discussions here because many of the papers to be cited here have already been mentioned earlier in this review or they will be discussed later. The two major spectroscopic techniques described here are NMR and UV—vis spectroscopies, though others like circular dichroism will be mentioned.

Earlier we discussed the work of Inoue[93] and of Sakurai,[94] who had available to them induced ^{13}C NMR chemical shifts resulting from inclusion of simple aromatic guests in α-cyclodextrin. To interpret the orientation of the guests in the host the authors used CNDO/2 calculations to predict how chemical shifts are influenced by chemical environments that are polar (exterior of cavity) or nonpolar (inside the cavity). Although no calculations were done on the cyclodextrin itself, the predicted shifts were used to interpret NMR data that were otherwise ambiguous (see discussion above). In the following section of this review we shall focus on aspects of molecular recognition and describe the work of Tabushi and Mizutani.[120] These authors carried out force field calculations of polar guests binding to a derivatized cyclodextrin and discovered that the dispersion forces were dominating the interaction rather than the Coulombic forces. The lack of electrostatic interactions was discussed from several points of view including a spectroscopic one, where several ^{13}C NMR chemical shift displacement correlations were made, thus dismissing previous proposals that the interactions influencing these shifts are polar in nature.

The binding of indomethacin with β-cyclodextrin was studied by ^{1}H NMR spectroscopy by Myles et al. as described earlier in this review.[19] The changes in chemical shifts and line broadening was attributed to guest complexation with the drug spanning the entire length of the cyclodextrin cavity. The authors proposed a 2:1 host:guest complex rather than invoking two 1:1 complexes. The results of their molecular mechanics calculations were consistent with induced chemical shifts of both the host and the guest. In a different study Fronza et al.[98] carried out NMR studies to better define the conformational properties of indomethacin (ester derivative) and from 2D ROESY spectra found protons of the *p*-chlorobenzoyl ring to have intense cross-peaks with H_3 and H_5 of the cyclodextrin, implicating its binding inside the cavity. Using $^{1}H\{^{1}H\}$ transient NOE experiments carried out at slightly elevated temperatures (to increase correlation times so positive NOEs could be obtained) the authors had semiquantitative information concerning the extent of penetration of this group into the cavity. NOE buildup curves can give detailed information about relative spatial relationships of nuclei, but because of the complexity of the system, i.e., the fact that the guest is partly included and freely oscillating in the cavity, the solution geometry of the complex could not be determined unambiguously. Several different hypotheses were formulated, and to test the reliability of those hypotheses the authors relied on molecular mechanics calculations (vide supra). Another drug binding study was published by Berthault and Perly,[121] who used NMR spectroscopy to explore the stoichiometry, association constants, and structural details of drug inclusion into a derivatized β-cyclodextrin. Unfortunately only a preliminary account of their molecular modeling results were included in that paper. Other drug binding studies have also been published where NMR data required interpretation with the assistance of molecular mechanics and dynamics calculations. Amato et al. studied the binding of racemic 1-(4-methoxybenzoyl)-5-oxo-2-pyrrolidinepropanoic acid, CI-933, with β-cyclodextrin.[122] Her ROESY data clearly showed short contact distances from the drug's aromatic ring to the H_5 protons of the cyclodextrin interior, but the relative orientation of the drug in the cavity had to be interpreted with the assistance of molecular modeling. The enantioselectivity of the ring toward these chiral drugs will be described in a forthcoming section of this review, but here we point out that the authors eventually concluded the mode of binding corresponds to inclusion from the secondary side of the host. Amato et al. then presented another combined NMR/molecular modeling study of drugs binding to cyclodextrins with the focus being on three structurally related anti-Alzheimer drugs.[123] Molecular dynamics simulations with explicit water molecules indicated one of the drugs to bind to the interior of the cyclodextrin cavity but not the other two, a result that is fully in accord with ROESY and chemical shift data. The authors point out that for charged drugs, such as the tetrahydro-9-aminoacridines presented in their paper, one must exercise great care when using continuum models for treating solvation. Earlier work by these authors focused on NMR and molecular mechanics studies of several nootropic drugs binding to β-cyclodextrin[124] and of tenilsetam binding to α- and β-cyclodextrin.[125] In both these cases rigid body docking preceded MM2* energy minimizations, and in each study both *R* and *S* enantiomers were included into the cyclodextrin cavity. Comparisons were made in these papers between the NMR data (NOESY and ROESY) with the molecular mechanics structures. Another study from the Pappalardo group focused on the binding of suronacrine, a drug for the treatment of senile cognitive disorders, to α- and β-cyclodextrins. Molecular modeling of both enantiomers was carried out, and again comparison to ROESY data was made.[126]

Earlier we described the many studies of Jaime and his group, who carried out combined experimental and computational studies of cyclodextrin host−guest complexes. In most of those studies the authors relied heavily on NMR experiments to define complex stoichiometry, association constants, and average orientations of the guests in the cyclodextrin cavity. In cases where the NMR data were unambiguous and interpretations could be made with certainty, the authors showed that molecular modeling was virtuous in reproducing the conclusions derived from NMR measurements. In cases where the experimental data were ambiguous, though, the molecular modeling studies assisted their interpretation of the data. The papers mentioned previously[86,87,88,101,103] represent a full “collaboration” between theory and experiment. Another study previously mentioned is that of Botsi et al.,[95] but those authors used NMR only to measure association constants for comparison with their quantum mechanically derived results.

Eliseev and Schneider[127] explored the molecular recognition of nucleosides, nucleotides, and sugars by aminocyclodextrins using NMR spectroscopy. From the induced chemical shift data the authors could state that inclusion complexes existed but they could not provide conclusions concerning the shape of the complexes. Intermolecular NOE data provided semiquantitative information about the geometry of the complex, and molecular mechanics calculations were used to (a) rationalize why fewer “salt bridges” between host and guest exist experimentally than anticipated from those predicted from idealized electrostatic interactions and (b) to elucidate the nature of the observed sugar−cyclodextrin interactions. Eliseev, then working with Menger,[128] prepared cyclodextrins having both D- and L-phenylalanine esters tethered to the primary rim by succinoyl spacer chains to monitor the enantioselective folding of those systems at the cyclodextrin’s surface. Molecular modeling predicted the system was flexible enough to induce self-inclusion where the phenyl ring would be inserted into the cavity from the primary side, but NMR measurements did not resonate with that conclusion. Instead, spectral measurements suggested that the appended chiral chains are only folded near the cavity entrance, albeit in a way leading to enantioselection.

Other molecular modeling studies carried out to help interpret data from spectroscopy exist. Berg, Gustavsson, and Åström[83] were able to determine the stoichiometry and to monitor the rates of interconversion of the 1:2 complex of 1,4-dimethylbicyclo[2.2.2]octane with α-cyclodextrin using NMR techniques. The MM2 force field was used in that study to show that the structure of a 1:1 complex is not symmetric and that room exists at the secondary rim for a second cyclodextrin to approach and form the 2:1 complex. In another study Ling and Darcy[129] synthesized and used derivatized α-, β-, and γ-cyclodextrins as expandable host molecules. Using sodium anthraquinone-2-sulfonate, an NMR shift reagent for cyclodextrins proposed earlier by one of the authors, the question of complex stoichiometry arose. The authors used molecular mechanics calculations to show that the side chains of the cyclodextrin can be organized so as to provide a hydrophobic pocket with sufficient depth to include a second sulfate molecule. Moreover, side chain rotameric states were described to further explain the magnetic inequivalence of some side chain protons. Yet another application of modeling was by Matile et al.,[130] who regioselectively hydrolyzed peripheral phenyl esters in the presence of native and derivatized β-cyclodextrins. The cyclodextrins were used effectively as blocking or protecting groups that could be deprotected later. The structure of the blocked complex was analyzed by mass spectrometry to determine the number of cyclodextrins involved. The structure of the complex was further elucidated with NOE data revealing an unusual orientation of cyclodextrins having the narrower, primary rim encapsulating the peripheral groups on the porphine. From their molecular mechanics investigation the authors rationalized why only two cyclodextrins can sheathe the diagonal phenyl groups, that vicinal encapsulation is not possible due to steric interference and that, indeed, the observed NOEs are only compatible with the primary opening of the cyclodextrin pointed toward the porphyrin’s center.

Kano, Kato, and Kodera[131] used NMR spectroscopy to study the chiral recognition of binaphthyl derivatives by cyclodextrins. Methylated β-cyclodextrins recognize well the axial chiralities of these systems, and the authors examined the binding of 1,1′-binaphthyl-2,2′-diyl hydrogen phosphate and 1,1′-dinaphthyl-2,2′-dicarboxylic acid. Chemically induced shifts of both the guests and the host, NOESY data, and thermodynamic data derived from van’t Hoff plots were presented and interpreted. Energy-minimized complexes for the two enantiomers binding to a permethylated β-cyclodextrin were presented, but relatively little was said about them. Finally we mention an integrated NMR and molecular modeling study of the binding of tryptophan to α-cyclodextrin that was studied in great detail by Lipkowitz, Raghothama, and Yang.[82] Various NMR results including coupling constants and chemical shifts for bound and free states of the species in solution, intra- and intermolecular NOE data, and relaxation times were presented for comparison with their molecular dynamics simulations. The focus of their work was on chiral recognition, a topic discussed later in the chapter.

NMR spectroscopy has inherent limitations, but as a spectroscopic technique, it has many strengths too. Over the years it has become the tool of choice for organic and physical chemists studying host−guest complexes because it can divulge detailed structural information for the user. The relationship between this structural information derived experimentally and that obtained computationally is such that a direct comparison between theory and experiment can be made. For that reason a significant number of papers have been published using NMR together with theory to better understand the shapes, energetics, and mode of guest inclusion with cyclodextrins. Other spectroscopic tools are commonly used to probe the nature of these inclusion complexes, but far fewer studies have relied on computational chemistry to help interpret those results.

Wennerström's group published several reports concerning the complexation of fullerenes with cyclodextrins. In one study the UV spectrum of the C_{70}−γ-cyclodextrin complex and its ground and excited-state laser-induced bleaching provided insights about the nature of these very weak complexes.[132] Molecular mechanics calculations of possible 1:1 and 2:1 host:guest complexes were evaluated. In a second paper[133] UV−vis and NMR data were used to provide indirect information about the C_{60}−γ-cyclodextrin complex. From the molecular modeling of a 1:1 complex it was revealed that the host cavity is not quite large enough to fully encapsulate the fullerene which, consequently, has a significant amount of its surface area exposed to solvent. In the head-to-head, 2:1 complex the fullerene is fully encapsulated but some water molecules are also enclosed thus filling the cavity and influencing the spectra. A complex equilibrium between 2:1, 1:1, and uncomplexed cyclodextrins exists in solution. Other studies exist where UV,[96] fluorometric competition titrations,[134] and circular dichroism data[128] were collected and where molecular modeling was used to assist in the interpretation of those results. Finally, we point out a study by Bettinetti et al. concerning the binding of naproxen to maltoheptaose.[135] These authors carried out differential scanning calorimetry, X-ray powder diffraction, fluorescence, and solubility studies followed by molecular dynamics and molecular mechanics calculations to explain their results. Note that maltoheptaose is a noncyclic analogue of β-cyclodextrin. Based on their modeling, though, it is believed to take on a cyclic conformation forming a "pseudo" inclusion complex with the drug.

The best collection of papers illustrating the use of molecular modeling for assisting in the interpretation of spectroscopic results (non-NMR) comes from Köhler and his colleagues in Vienna. In one paper the excited-state proton transfer of 2-naphthol included in cyclodextrin was studied.[136] Optical absorption spectra, fluorescence spectra, and fluorescence decays were measured to determine ground- and excited-state acid−base properties. Docking studies using molecular mechanics were carried out to construct reliable models, and much of the interpretation of spectral data was based on the geometries of those complexes. In another study Marconi et al.[137] measured the rotary strengths of phenol, *p*-cresol, and several di- and trisubstituted methylphenols included in β-cyclodextrin. The induced circular dichroism of those complexes were computed and compared to experiment. To compute transition energies, oscillator strengths and rotational strengths, the authors used theoretical methods requiring geometrical information about the complex. To do this the authors moved the guests incrementally through the host cavity and carried out molecular mechanics calculations with Monte Carlo structure samplings. From that, a Boltzmann distribution of accessible structures was provided that were then used for further calculations. Unfortunately several of the predicted signs of the induced circular dichroism spectra for these 1:1 complexes were inconclusive or outright wrong compared to experiment suggesting their computational protocols need improvement. Grabner et al.[138] studied the influence of cyclodextrins on the photophysics and photochemistry of 1,2- and 1,4-dimethoxybenzenes. Absorption, fluorescence, circular dichroism, and transient absorption spectroscopies were used, and the results from those techniques were discussed in light of model structures derived from molecular mechanics calculations. The authors used a simulated annealing methodology they call "dynamic Monte Carlo" to derive suitable low-energy structures. The energetics, structural features, and stoichiometries of these complexes were described in detail in that paper, and the relationships between those structures and interpretations of spectroscopic data was presented. Two additional spectroscopy-related papers have appeared since this review was written. The first by Tanaka[180] used molecular mechanics calculations to help interpret ESR data on the discrimination by γ-cyclodextrin of palmitic acids containing paramagnetic probes, and the second by Tardajos[181] used molecular mechanics with NMR spectroscopy in their studies of the transfer process of a cationic surfactant from water to β-cyclodextrin.

This type of synergistic interplay between theory and experiment illustrates that molecular modeling can be of great use to the scientist to help interpret spectra and to better understand the nature of these inclusion complexes, particularly their structures, energies, and stoichiometries. A preponderance of these studies involve NMR spectroscopy, but other kinds of data from other spectroscopies can likewise be evaluated as best demonstrated by Köhler and his collaborators. Full-scale molecular simulations are usually needed to do this effectively, and for that reason relatively few scientists studying cyclodextrin inclusion complexes with spectroscopic probes have attempted to use theory. Given the state of the art developments in both hardware and software, our prognosis is that more scientists will soon make such attempts to integrate theory and experiment.

D. Studies in Molecular Recognition

The most prevalent use of molecular modeling (related to cyclodextrins) is to help determine the shapes and the energies of these macrocycles and of their inclusion complexes; the second most common application of molecular modeling related to cyclodextrins is directed toward understanding how molecular recognition takes place in these systems. Here we summarize what has been done to date in this regard. Many of the studies described earlier in this review have molecular recognition as the rationale for the scientific study, but those papers do not explicitly state what the forces are that lead to recognition. We have already described many of these papers, albeit under the aegis of subheadings such as “Energetics of Binding” and “Structural Analysis of Inclusion Complexes” so in this section we present the results of studies whose major goal is to explain molecular recognition in cyclodextrin systems explicitly using computational chemistry.

Tabushi and Mizutani[120] examined the nature of the force field operating in molecular recognition by cyclodextrins with the aim of sorting out the contributions of polar (electrostatic) and nonpolar (dispersion) terms. Their calculations were done on *p*-nitrophenol and *p*-iodoaniline inclusion complexes of α-cyclodextrin. The interaction energies were computed with an empirical force field having a Coulombic term and a van der Waals term so that each could be quantified and compared to the other. The van der Waals component was found to be an overwhelming contributor to the total intermolecular energy in both cases. For charged cyclodextrins interacting with oppositely charged guests, however, the Coulombic component dominates the interaction as expected. The finding that neutral cyclodextrins binding to neutral guests, even if they are polar, is being dominated by dispersion forces rather than electrostatic forces was in complete disagreement with many proposals at that time. It certainly was a finding in opposition to the conclusions of Kitaigawa et al., whose work was cited earlier, but agrees with Matsui, however (vide infra). Tabushi and Mizutani also elaborated the role of compensating entropy changes in these inclusion complexes, focusing especially on entropy losses arising from removal of rotational degrees of freedom of guests inside the cyclodextrin cavity.

The molecular recognition properties of cyclodextrins binding with fullerenes, a deceptively simple type of guest molecule, has been investigated in detail. For example the binding of C_{60}, a highly hydrophobic and water-insoluble compound, with γ-cyclodextrin was studied spectroscopically by Andersson et al.[133] One of the problems encountered with these highly symmetric molecules is that ring currents in hexagons are offset by those in neighboring five-membered rings giving rise to unpredictable NMR chemical shifts. Moreover, the recognition properties of cyclodextrins binding to these systems are difficult to study because there exist multiple states of association where 2:1 and 1:1 complexes are in equilibrium with uncomplexed states and those equilibria are all affected by subtle changes in environmental conditions. Molecular modeling was done to gain some insights into the nature of these equilibria and the structures of the complexes. In a related study by Kim and Jeon[139] the AMBER force field was used to better understand the kinetics of inclusion for the 2:1 fullerene complexes (a high-energy barrier to inclusion exists in these systems), and again the dispersion forces were dominating the associations. The binding of C_{70} to γ-cyclodextrin was also investigated computationally.[132]

Most published studies of molecular recognition involve experimental and computational work where substituent groups of varying sizes, charges, polarizability, hydrophobic content, directionality, etc., are strategically placed around a core substructure to probe host−guest recognition factors. For example, Eliseev and Schneider[127] evaluated the molecular recognition of nucleotides, nucleosides, and sugars by aminocyclodextrins, illustrating how both salt bridges and lipophilic interactions can lead to simultaneous differentiation of (a) the nature and location of phosphate groups, (b) the nucleobase involved, and (c) the presence or absence of hydroxyl groups in the furanoses involved. Force field calculations revealed why fewer than anticipated salt bridges were participating in several complexes as well as delineating the number and types of intermolecular hydrogen bonds for other complexes. Another example is the collaborative study of Evanseck and Kaifer[140] concerning the observation and interpretation of anomalous binding of inorganic anions to cyclodextrins in water. The measured binding constant of hexafluorophosphate anion with β-cyclodextrin was 1 order of magnitude larger than had been previously reported, and to better understand this in addition to the structure of the complex, semiempirical molecular orbital calculations using the PM3 Hamiltonian were carried out. The enhanced binding of the ion compared to perchlorates and triflates was found to come from the PF_6 octahedral symmetry that allows it to form three close-contact hydrogen bonds to the cyclodextrin in contrast to the other ions which can form only two such interactions.

Cyclodextrins have many uses, one of which is as a medium for chemical separations, especially chiral separations.[141−151] For many years separation scientists have been aware of the ability of cyclodextrins to selectively bind guest molecules, and many uses of cyclodextrins for separations now exist. The cyclodextrins can be used in chromatography as mobile phase additives (MPA) where they are added to the mobile liquid phase component of a chromatographic column and where selective complexation of analytes gives rise to differential retention times.

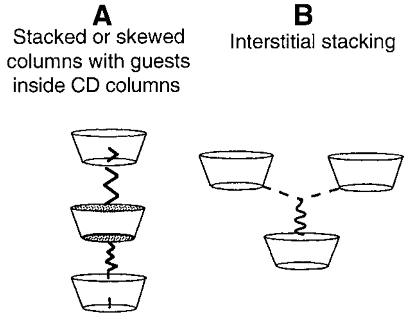
Alternatively they can be adsorbed or chemically bound to an immobile part of the chromatographic column thus becoming the stationary phase that can also differentiate binding of analytes. Because these molecules are inexpensive, easy to modify, and come in varying sizes, they have been adopted for use in planar, gas, liquid, and super- and subcritical fluid chromatographies, as well as in membrane separators, and they are now finding widespread use in capillary electrophoresis.[152] As scientists were developing these stationary phases they were also investigating how those cyclodextrins differentiate between various kinds of analytes. In other words they were probing aspects of molecular recognition, and several of those investigators relied heavily on computational chemistry to better understand where and how cyclodextrins discriminate between isomers.

Armstrong, for example, used molecular graphics to explain why cis and trans isomers of tamoxifen are separated on a β-cyclodextrin column.[153] In a book chapter he further showed how molecular graphics can reveal information concerning the molecular recognition properties of cyclodextrins to differentiate between *o*-, *m*-, and *p*-substituted aromatic rings, cis/trans diastereomers, and even enantiomers.[154] No energy calculations were done in those papers, however. Arnold, Lillie, and Beesley, in contrast, used the MM2 force field to calculate the interaction energies between ortho, meta, and para isomers of several disubstituted benzenes and compared those computed interaction energies with experimental retention times measured on a β-cyclodextrin column.[155] They found very high statistical correlations between computed interaction energies and retention times, but only within a series of isomers, suggesting other noninclusion factors are important in separations.

Not all studies focusing on cyclodextrin stereoselectivities were being done by separation scientists. Ueoka and his group, for example, were exploring the catalytic abilities of cyclodextrins and found rate constants for deacylation of diastereomeric peptide esters.[156] The large stereoselectivity was attributed to preferential binding and favorable accommodation of the substrates in the cyclodextrin cavities. The authors constructed CPK mechanical models to examine this conjecture, and their preliminary molecular mechanics calculations verified that the more rapidly hydrolyzed DL diastereomer is several kcal/mol more stable than the LL diastereomer upon binding. These examples all focus on the ability of cyclodextrins to recognize stereoisomers other than enantiomers. Cyclodextrins, being chiral, have the ability to discriminate between optical isomers, and much attention has been directed toward understanding this aspect of cyclodextrin molecular recognition.

Fotiadu, Fathallah, and Jaime,[101] for example, computed the binding energies of both enantiomers of *cis*-decalin inside a β-cyclodextrin using molecular mechanics. The relative binding energies were consistent with the earlier NMR study of Dodziuk,[157] who found nonisochronous ^{13}C NMR chemical shifts for the two diastereomeric inclusion complexes coexisting in solution. Another example focusing on chirality is the β-cyclodextrin inclusion complex of CI-933 studied by Amato et al.[122] Molecular modeling with both *R* and *S* enantiomers binding to the cyclodextrin was carried out. Side-by-side comparisons of the energies and the geometries of the most stable diastereomeric structures derived from molecular mechanics were presented. These authors also carried out molecular dynamics simulations of those complexes, and the side-by-side presentation of trajectories showed the relative movement of the enantiomers' center of mass along the *x*, *y*, and *z* axes. Amato also presented composite distributions (histograms) of distances between important host−guest protons in these complexes, thus making comparisons of enantiomer binding easy for the reader to visualize.

Chart 1



A theoretical study of enantiodifferentiation in solid-state cyclodextrins was undertaken by Lipkowitz et al.[158] To accomplish this the authors searched the Cambridge Structural Database for enantiomerically pure guests trapped in the same cyclodextrin host; i.e., one crystalline inclusion complex had been grown with the *R* enantiomer and the second inclusion complex grown with the *S* enantiomer. For each complex the intermolecular energy between the guest molecule and its corresponding cyclodextrin environment was computed (note that a single guest could be surrounded by several adjacent cyclodextrins). The authors used both the MM2 and AMBER force fields to cross-validate their results. The guest molecule was then moved 100 Å from the cyclodextrin lattice, and the energy of the system was computed again. The difference in energy between the bound and the free states is an enthalpy of binding, ΔH, and the contributions to this total energy arising from hydrogen bonding terms, from electrostatic terms, and from van der Waals terms were tabulated. The difference in binding enthalpy between the *R* guest, in its own unique lattice environment, and that of the *S* guest, in its own unique lattice, is the enantiodifferentiating enthalpy, $\Delta\Delta H$. The authors found two binding motifs for these chiral guests in the lattice. One motif had stacked columns of cyclodextrins with guests embedded along those stacks (Chart 1A). In the other motif the guest is partially inserted in a cyclodextrin cavity but protrudes into the interstitial region between two or more neighboring cyclodextrins (Chart 1B). For the latter situation there exists extensive intermolecular contact between guest molecules with the exterior of neighboring cyclodextrins. Contrarily only interior contact exists in the former case. The authors found Chart 1B situations to be more enantiodiscriminating than

Chart 1A, opening up the possibility that enhanced enantioselection could take place on the exterior of the cyclodextrin rather than on the interior. Unfortunately a very small number of examples were investigated making this hypothesis speculative at best but an intriguing hypothesis nonetheless that is certainly worth testing.

The interaction energy of heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin complexed with *R*- and *S*-flurbiprofen has been studied in detail by Leherte, Latour, and Vercauteren.[159] The approach this group used, that is worth reading about because of what it can reveal concerning anisotropic interactions but will not be explained in detail here, is to carry out a topological analysis of electron density maps to quantify the steric complementarity of the host−guest systems. To accomplish this the following three steps are performed: (1) Generate an electron density map at some predefined resolution; this is done by reconstructing density maps from the original crystal structures. (2) Define regions where the gradient (curvature) of electron density is zero, i.e., critical points, that are connected to atomic peaks in the density. (3) Compute peak volumes and steric interactions, the latter of which is done with a probing sphere. It was found from the 3D contour maps that both *R*- and *S*-flurbiprofen reside in regions of minimal energy but that the accessible volume for the *S*-enantiomer is greater than for *R* and that steric interactions favor slightly the *R* isomer. To confirm this the authors carried out molecular mechanics calculations because a different conclusion had been reported earlier by Lipkowitz.[158] The latter authors' calculations were done in the solid state where extraneous guest molecules like water were removed. Using the CFF91 force field Leherte, Latour, and Vercauteren similarly found the same result under those same conditions, but when the waters of hydration found in the crystal structure were retained in the calculation, a reversal of computed selectivity was noted. From this, then, one concludes that there is no such thing as "extraneous" waters and that all molecules should, perhaps, be included in the calculations of this kind. The interactions considered in that paper represent the shape compatibility of anisotropic electron density zones.

The most extensive computational studies of enantioselective binding and chiral recognition in cyclodextrins came from scientists who were interested in creating, testing, and using cyclodextrins for chiral separations by chromatography. The development and use of cyclodextrins initially centered on liquid chromatographies but soon expanded to gas chromatography as well. Both are described below.

Armstrong had constructed a variety of covalently linked cyclodextrins and demonstrated their ability to resolve a wide range of drugs, agrochemicals, food additives, and the like, all containing a diverse range of organic functionality. It was also in his nature to examine the physical chemistry of these new chiral stationary phases (CSP) and ultimately to use molecular modeling tools to derive models for how they selectively bind one enantiomer in lieu of another. For example in a paper showing how a β-cyclodextrin column was able to resolve enantiomers for nine classes of drugs, he also used molecular mechanics calculations to energy minimize the diastereomeric complexes of several of those inclusion complexes to explain the hydrogen bonding between host and guests that lead to chiral recognition.[99] Hydrogen-bonding patterns were deemed to be one of the key features of cyclodextrins' ability to discriminate between these otherwise identical mirror image isomers.

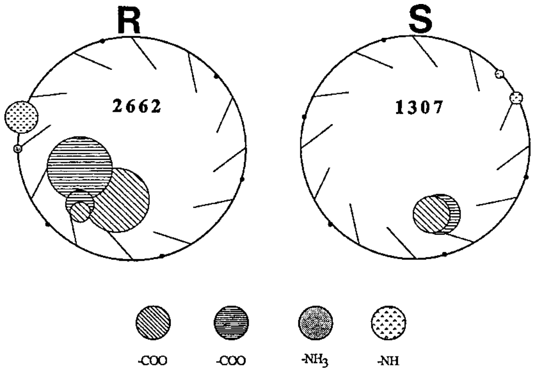


Figure 12. Graphical representation of the intermolecular hydrogen bonds for (*R*)- and (*S*)-tryptophan with α-cyclodextrin. The large circle represents the macrocyclic host. The small black dots on that circle are the acetal linker oxygens (O_4 in Figure 3), and the lines attached to the circle represent the unidirectional C_2 and C_3 hydroxyl groups. The crosshatching indicates the atoms or groups on the tryptophan that are forming the intermolecular hydrogen bonds. The size of the crosshatched circle corresponds to the number of hydrogen bonds formed during the molecular dynamics simulation. The centers of those crosshatched circles are placed at the mean positions of the hydrogen bond contacts. Taken with permission from ref 82.

One of Armstrong's findings was that tryptophan and related molecules could be resolved on an α-cyclodextrin column[160] where the *R* enantiomer is more tightly bound to the column and thus has a longer retention time than the *S* antipode. Lipkowitz, Raghothama, and Yang also examined this system in great detail.[82] They used NMR methods to study the aqueous inclusion complexation of tryptophan by α-cyclodextrin, and they carried out molecular dynamics simulations to assess where and how chiral discrimination takes place on this chiral host. All of the simulation results were in accord with the NMR data as well as with the chromatography data. A graphical representation of the intermolecular hydrogen bonds from that paper is presented in Figure 12. In this cartoon the large circle represents the cyclodextrin. The small black dots on the ring represent the acetal linker oxygens, and the unidirectional lines inside the circle represent the C_2 and C_3 hydroxyl groups that were found to be most important in hydrogen bonding to that zwitterionic guest. The crosshatched circles represent the location of the intermolecular hydrogen bonds, the type of crosshatching corresponds to different groups on the host giving rise to the intermolecular hydrogen bonds, and the diameter of those circles is proportional to the number of intermolecular hydrogen bonds arising from those groups. Two important findings are embedded in the cartoon. First, there are twice as many intermolecular hydrogen bonds when the longer retained *R* enantiomer binds than when *S* binds (∼2600 vs 1300). In the original paper the authors analyzed the type of hydrogen bonding taking place and found that when the *R* enantiomer binds there exist numerous simultaneous, "multiple-contact", hydrogen bonds in contrast to the *S* enantiomer that almost always forms a single intermolecular hydrogen bond with the cyclodextrin. So, there exist more, and stronger, hydrogen bonds for the longer retained *R* isomer than for the *S* isomer. The second feature is that the analyte molecule becomes highly localized once it is affixed to the interior of the cyclodextrin. This finding allowed the authors to modify, slightly, Armstrong's original chiral recognition model.

Much information gathered over the years concerning cyclodextrin molecular recognition came from different groups of scientists, particularly chromatographers, physical organic chemists employing NMR spectroscopy, and physical chemists using absorption spectroscopy and calorimetry to assess the kinetics and thermodynamics of binding. Much of the data thus published is one-dimensional, e.g., many molecules were examined on a given type of chromatographic column or chemical shifts were presented for a class of compounds but not both in the same paper. Infrequently one could find multifaceted publications implementing a broad spectrum of experimental probes together with theory to explain how cyclodextrins work. One example of this is the work of Rüdiger et al.,[96] who combined NMR, calorimetry, and molecular modeling approaches. Lipkowitz also wanted to evaluate chiral discrimination on β-cyclodextrin CSPs by using chromatography, NMR spectroscopies, and molecular dynamics simulations. This in fact was presented in a paper with Stoehr,[161] but it became apparent that only a very limited set of molecules could be studied in such detail this way because those probe molecules had to (1) form inclusion complexes large enough to be observed, (2) be well enough resolved on a chromatographic column over a wide temperature range so van't Hoff plots could be generated, (3) have assignable carbons or protons that upon complexation give rise to nonisochronous chemical shifts, and (4) have high-caliber molecular mechanics parameters available for the molecular simulations. These constraints pose a serious problem, thus making multifaceted, detailed investigations of this kind difficult and rare.

The major impetus for creating these (and other types) of chiral stationary phases came from the pharmaceutical industry. Mandates were being set forth for pharmaceutical companies to consider enantiomers as being completely different drug entities, requiring them to be obtained in pure forms for testing.[162] A number of chromatographers thus started generating new, derivatized cyclodextrins for this purpose. One example is from Kuroda and his pharmaceutical collaborators,[163] who prepared a perphenyl carbamate derivative of β-cyclodextrin that was capable of separating the drug atenolol. These scientists carried out extensive NMR studies of host–guest complexation on a soluble analogue of their CSP. They also used molecular mechanics calculations and molecular dynamics simulations to compute free energies of analyte binding and to better understand the mode of complexation for comparison with their NMR data (see discussions above on regioselectivity of guest orientations).

Other molecular modeling calculations of cyclodextrins focusing on chiral separations by liquid chromatography exist. Durham and Liang,[164a] for example, modeled the inclusion complex of (*R*/*S*)-methylphenobarbitone with β-cyclodextrin, which was present as a chiral mobile phase additive in their chromatography experiments. Durham further used molecular mechanics to compute $\Delta\Delta H$ and predict the chiral discriminating chromatographic behavior for several drug and nondrug analytes binding to β-cyclodextrin.[164b] Another modeling study was by Tesarová in collaboration with Smolková-Keulemansová, one of the first people to successfully use native cyclodextrins for liquid chromatographic resolutions of enantiomers. Their modeling work attempted to find correlations between the structure of dihydropyridine calcium antagonists and their retention behavior and enantioseparation on the β-cyclodextrin stationary phase.[165] Another computational evaluation of chiral separations by cyclodextrins in an aqueous environment was published by Copper et al., who separated derivatized amino acids by cyclodextrin-modified capillary electrophoresis and used Boltzmann weighted, molecular mechanics energies to predict elution orders.[166] Another application directed toward better understanding the cyclodextrin-modified micellar electrokinetic capillary chromatography separations of benzophenone isomers has also been published.[73]

All of the above examples focused on computational chemistry related to cyclodextrin CSPs or cyclodextrin additives in solution. A large investment in time and money has also been directed toward using cyclodextrins in gas chromatography, and many of the researchers instrumental in developing and/or using those CSPs were also using molecular modeling tools to understand exactly what was going on inside those chiral columns. For example, König's group had developed a series of cyclodextrin-based CSPs for gas chromatography.[143] Heptakis(3-*O*-acetyl-2,6-di-*O*-pentyl)-β-cyclodextrin is one of the CSPs engineered by König's group that is now marketed as Lipodex D. A paper describing the chiral chromatograpic separation of methyl 2-bromopropionate, methyl lactate, and methyl mandelate on this CSP along with NMR studies of a soluble analogue binding to those substrates was published.[167] The authors computed the averaged interaction energies of the methyl 2-bromopropionate using molecular dynamics simulations and predicted the *S* enantiomer to be the more stable complex, a result in agreement with the observed retention orders as well as induced NMR chemical shifts arising from inclusion complexation. A description of the relative orientation of guest inside the cyclodextrin cavity was provided, but the authors indicated in that paper that the simulation times used were too short to be meaningful. In a follow-up paper Köhler et al.[168] extended those studies by addressing conformational features of the guest and the cyclodextrin, the orientation of the guest embedded in the host cavity, and details of the geometry of the host−guest complex. The simulation times were much longer than in the preliminary report but as we shall point out later these times are still too short to satisfactorily sample the phase space needed to make this a predictive method. Another group preparing and evaluating the molecular recognition of derivatized cyclodextrins for gas chromatography is that of Koen de Vries, who published a paper showing the synthesis and utility of octakis-(3-*O*-butyryl-2,6-di-*O*-pentyl)-γ-cyclodextrin.[169] Using this CSP along with several other commercially available derivatized cyclodextrin-based CSPs, the authors carried out temperature studies to find the enthalpic and entropic contributions to the differential free energies of complexation for several chiral esters, alkanes, substituted benzenes, and styrene oxide. The authors were cognizant of the fact that multiple minima exist on the complexes' potential energy surface and that a molecular dynamics sampling method would be most suitable for computing the interaction energies. Truncated versions of those CSPs were used to reduce the computing times required in the modeling. Calculations on styrene oxide were done, and discussions concerning the orientation of the guest inside those cavities were given along with rationalizations for the relative abilities of those CSPs to separate the oxirane enantiomers.

Kobor, Angermund, and Schomburg[170] also prepared unique CSPs for gas chromatography based on derivatized β−cyclodextrins. In addition to using permethylated β-cyclodextrin, a well-known and fully explored CSP that will be described below, the authors prepared a 2,3-dimethyl-6-(*tert*-butyldimethylsilyl)-β-cyclodextrin CSP with the aim of narrowing the wide, secondary rim of the cyclodextrin cavity and to completely block entry of guests from the primary side of the macrocycle. Chromatographic and molecular modeling experiments were carried out on limonene, a lipophilic chiral hydrocarbon, and the more polar 1-phenylethanol. These authors also used a truncated version of the CSP in their modeling to reduce the computing times required. They too used molecular dynamics to compute the interaction energies rather than molecular mechanics, but they carried out Monte Carlo docking experiments first. The authors found the elution sequence to correlate nicely with the average energy difference between diastereomeric complexes, but their results seem inconclusive because these energy values depend on which conformer of CSP is considered. Discussions ensued focusing on the intermolecular forces giving rise to chiral discrimination, the role of rigidity of cyclodextrin in molecular recognition, and on other aspects of host−guest complexation.

Another paper where chiral separations were done using gas chromatography and where the results were predicted using molecular modeling was published by Cozzini et al.[171] Chiral lactones and prolines were separated on 2,6-di-*O*-methyl-3-*O*-trifuoroacetyl derivatives of β- and γ-cyclodextrins as well as on permethylated cyclodextrins. The authors carried out conformational analyses of the 20 analytes studies and docked the low-energy conformers into the cyclodextrin cavity for energy minimization using molecular mechanics. Most of the predictions agree with experimental retention orders, but there exist enough incorrect predictions to come to the conclusion that manual docking and simple energy minimization of diastereomeric complexes is not a foolproof way to predict elution orders in these systems.

The use of the modified cyclodextrin heptakis(2,3-di-*O*-methyl-6-(*O*-*tert*-butyldimethylsilyl))-β-cyclodextrin described above for resolving aroma-related dihydrofuranones has also been studied computationally by Beier and Höltje.[172] These authors used the CVFF force field in their work and carried out high-temperature MD simulations, annealing the cyclodextrin from 1000 to 0 K to locate low-energy structures. The structure at the end of the annealing cycle was saved and used in another annealing cycle with the objective of generating a collection of different low-energy cyclodextrin structures. For all low-energy host shapes so derived, a molecular interaction potential was evaluated using (i) a methyl group probe to discern the most favorable van der Waals binding regions and (ii) a hydroxyl probe to locate the hydrogen bonding regions. Then a similar type of molecular interaction potential is performed on the guest molecule. The complementary regions of host and guest molecules located this way are aligned as best as possible as the guest is "docked" in the host cavity. This way the host−guest stabilizations are maximized. These initial binary, diastereomeric complexes are then subjected to molecular dynamics simulations at 380 K, a temperature corresponding to the gas chromatograph operating temperature, and structures were saved along the trajectory for analysis. In addition to the determination of averaged interaction energies, which agreed with known experimental retention orders, predictions were made for unknown systems. Hydrogen bonding patterns were also assessed; generally the more retained enantiomer has a greater number of hydrogen bonds. The authors conclude that inclusion is necessary for discrimination and that the flexibility of the CSP is a very important feature contributing to chiral recognition (induced fit enantioselective binding).

The most popular CSP used in gas chromatography appears to be permethyl-β-cyclodextrin, depicted in Figure 13. There have been several computational studies published with the intention of understanding the mechanism of chiral recognition in this and related CSPs. In one of these studies, Reinhardt et al.[173] were interested in understanding why differences in elution orders of terpenes occurred on permethylated α-, β-, and γ-cyclodextrins. They also wanted to understand the chiral selectivity expressed by the β-cyclodextrin (only when α-pinene elutes before tricyclene on the various CSPs studied was chiral discrimination noted to take place). The authors' aim was to evaluate a very large number of host−guest structures by systematically moving the hydrocarbons through the cyclodextrin cavities using

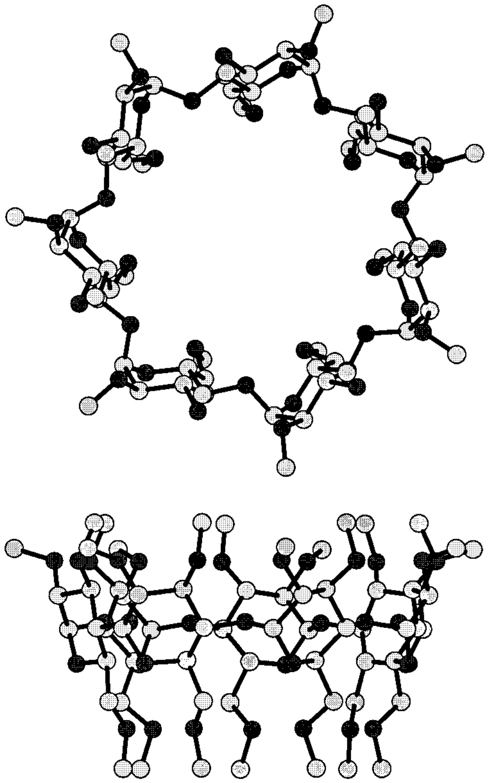


Figure 13. Top: View looking into the permethyl-β-cyclodextrin chiral cavity. Bottom: Side view illustrating the typical conical shape of these molecules. The more open end is the 2° rim, and the narrower end is the 1° rim. Dark gray tones represent oxygen atoms, and light gray tones are carbons. Hydrogen atoms omitted for clarity.

a grid search strategy we described earlier in this review. Using a rigid, symmetric cyclodextrin, the analyte was moved along the major axis of the host in 1 Å increments while rotating the guest so that 1296 positions were sampled at each point. Eventually 27 216 starting positions were sampled, but typically only 500−1500 structures were kept (based on an energy threshold criterion) for further molecular mechanics calculations. The force field used for that study was the Tripos force field found in SYBYL. The number of retained low-energy configurations differed substantially when the permethylated α-, β-, and γ-cyclodextrins were compared to one another and also when the ratios of pinene to tricyclene complexes were compared in the β-cyclodextrin (in which chiral recognition takes place). Detailed discussions concerning the number and types of complexes in the three permethylated cyclodextrins were presented, and eventually binding energies of (1R)-α-pinene were compared to (1*S*)-α-pinene. Both the retention orders and relative energetics of binding were found to be consistent with experiment. Several conclusions concerning molecular recognition in these systems are as follows: (1) An optimal host diameter is required for retention of hydrocarbons of this size. (2) Because the authors found very little change in conformation of the cyclodextrin upon energy minimization, “induced-fit” structural effects are negligible. However, the energies of the system change dramatically suggesting induced-fit binding is important (discussed by both Zimmerman and Lipkowitz below). (3) The chiral discrimination for pinene separations can be traced to differences in dispersion forces, a sentiment echoed below by Lipkowitz.

Black, Parker, Zimmerman, and Lee[174] presented a molecular modeling study of α-pinene and three chiral derivatives of 2,3-isopropylidene-1,2,3-cyclohexanetriol derivatives that they had resolved on permethylated β-cyclodextrin and native α-cyclodextrin. They used the CVFF force field and like their predecessors made the assumption that binding takes place on the interior of the cyclodextrin. Two computational strategies were compared. One involved using only rigid guests and rigid hosts, while the other used the low-energy structures from those searches for further molecular mechanics energy minimizations to generate relaxed structures. This way one could compare the two computational strategies directly for their predictive abilities and also assess the significance of induced-fit binding effects on chiral discrimination. The rigid body docking experiments involved defining an imaginary cylinder within the host cavity through which the guests were systematically translated and rotated to sample configurations. A Boltzmann average of the resulting interaction energies derived this way was then computed. The low-energy structures found from this search were then used for full molecular mechanics energy minimizations. The authors found that the rigid body docking grid scan technique gave four of the five retention orders incorrectly. This problem exists even though they used Boltzmann averaging rather than just the lowest energy structures and even when taking great care to systematically scan the binding site with small guest translation and rotation increments (0.25 Å and 12° per axis, respectively). Using the fully relaxed structures and energies gave results more in agreement with experiment, although two computed energy differences were inconclusive in their predictions. Like Reinhardt et al., these authors found small structural changes in the energy-relaxed cyclodextrins and they allude to the significance of induced-fit changes in chiral discrimination by cyclodextrins. The authors conclude by saying that rigid body grid searches introduce an unacceptable error into the chiral recognition calculations and that their results support previous assertions that induced fits are important in inclusion complexation and may be relevant to chiral discrimination. Preliminary reports of an improved method for modeling enantioselective binding using rigid body docking followed by partial geometry optimizations are noted.[175]

The most extensive study of chiral recognition on permethyl-β-cyclodextrin, the most commonly used CSP in gas chromatography, was done by Lipkowitz’ group in Indianapolis, IN. In their studies[176] they compared rigid body Monte Carlo sampling methods with flexible molecular dynamics techniques and found the rigid body approach to inconsistently predict retention orders. They interpreted this as meaning induced-fit structural changes during host−guest interaction are important not only for enhancing inclusion complexation but also for chiral discrimination. Two key questions were posed in that study. First, where in or around the cyclodextrin do analytes tend to bind? It is well recognized that one of the dominant driving forces for host−guest inclusion complexation is the hydrophobic effect, but in gas chromatography, such aqueous environments are absent (though often the CSP is dissolved in moderately polar siloxane polymer matrixes). *A priori*, then, one might not expect inclusion complexation in the gas phase. This issue was brought into focus by Berthod, Li, and Armstrong,[177] who presented their results of an exhaustive, extrathermodynamic study of gas-phase binding using a wide range of analytes on related CSPs. They found clear evidence for two modes of binding, one mode corresponding to encapsulation (interior binding) and the other to exterior binding. Second, how does enantiodifferentiation arise? In particular, what are the intermolecular forces holding the complexes together and what are the forces most responsible for chiral discrimination?

The simulation protocol developed was somewhat unusual compared to the other studies described in this review, but it is a protocol that is robust, meaning any analyte could be treated, and one that almost always predicted the correct retention orders. What the authors wanted to accomplish is to simulate the binding of enantiomeric analytes to CSP molecules as those analytes migrate through the chromatographic column. It is not possible to simulate the entire chromatographic column or even a closely spaced set of cyclodextrin molecules for the analytes to interact with, given the current modeling tools we have to work with. How, then, can one sample the various intermolecular interactions between analyte and CSP? The approach they took was to use a single CSP molecule with a single analyte molecule and carry out molecular dynamics simulations on those systems. In reality the analyte molecule binds to the CD but then dissociates and moves downstream to another CD where it again binds. To effect this simulation with a single selector (the CSP) and a single selectand (analyte) they allow the molecules to bind, dissociate, and rebind multiple times by placing a reflective wall around the diastereomeric complexes. To accomplish this they used a flat-bottom potential having no restraining forces until the analyte molecule moves 20 Å from the cyclodextrin. At that point a 100 kJ/mol/Å restraining force is applied which pulls the analyte back toward the CSP where it can further associate. Effectively, then, what they have accomplished is to allow the analyte to randomly collide with the CSP in all possible conformations, orientations, and positions as it would in the real system.

Two other points were raised by the authors concerning the simulations. First, very long simulation times, on the order of nanoseconds rather than picoseconds, are required, and second, one must average over multiple trajectories to ensure a large volume of phase space is being sampled for good statistical averaging. Accordingly the authors used five trajectories for each enantiomer. Those trajectories were started with the analytes placed in different positions and orientations in and around the cyclodextrin as depicted in Figure 14. Note that, in this figure, had one started with the guest docked as in the upper left panel, a typical starting point used by most people carrying out MD simulations on such molecules, one would have predicted the incorrect retention order before 1000 ps; only after 1 ns time is the order reversed and the correct prediction made. Averaging over multiple trajectories is thus recommended.

By the averaging of five trajectories, each being 5 ns in length, a 25 ns simulation for *R* and a 25 ns simulation for *S* analyte binding is accomplished. Lipkowitz studied a wide range of analytes including simple hydrocarbons such as α-pinene and limonene to more polar analytes such as simple esters and alcohols. To address the question of where analytes tend to bind the authors placed the cyclodextrin on a three-dimensional grid. Eight neighboring grid points define a small volume element, and the number of times an analyte's center of mass passed through that volume element was tallied over the entire simulation period. This was done for both *R* and *S* enantiomers. Regions of high density correspond to the most probable binding site for substrates. An example of this is presented in Figure 15 for both enantiomers of limonene. Evident in these plots is the fact that the analyte prefers to bind to the interior of the cyclodextrin (because the cyclodextrin collapses around the analyte to maximize the van der Waals attractions) and there exists a penchant for association to the narrower but more flexible primary rim of the cavity for this particular analyte. This trend was evident for most but not all volatile guests studied.

The authors evaluated the number of intermolecular hydrogen bonds for those guests capable of forming hydrogen bonds to the cyclodextrin, and they described which oxygens on the CSP were most involved in hydrogen bonding. Then, rather than considering the total system's energies (and/or the component energies, e.g., stretch, bend, torsion, etc.) as have others, the authors projected out the intermolecular energy components responsible for host−guest complexation. They found the short-range van der Waals forces to be dominating the attractions rather than the long-range electrostatic forces, but for polar molecules such as alcohols a significant contribution from the latter arises. Then, by comparing the intermolecular forces for *R* versus *S* analyte, the authors were also able to define the intermolecular force responsible for chiral discrimination.

The conclusions from that paper were the following: (1) The preferred binding site for small volatile analytes is the interior of the cavity, with rapid shuttling between the primary and secondary rims and low-energy excursions in to and out of the host cavity. (2) The dominant forces holding the diastereomeric complexes together are the short-range dispersion forces. (3) The enantiodiscriminating forces responsible for chiral recognition are also the short-range van der Waals forces, and these forces are typically 1−2 orders of magnitude smaller than the binding forces. A second paper extending these studies has appeared.[178]

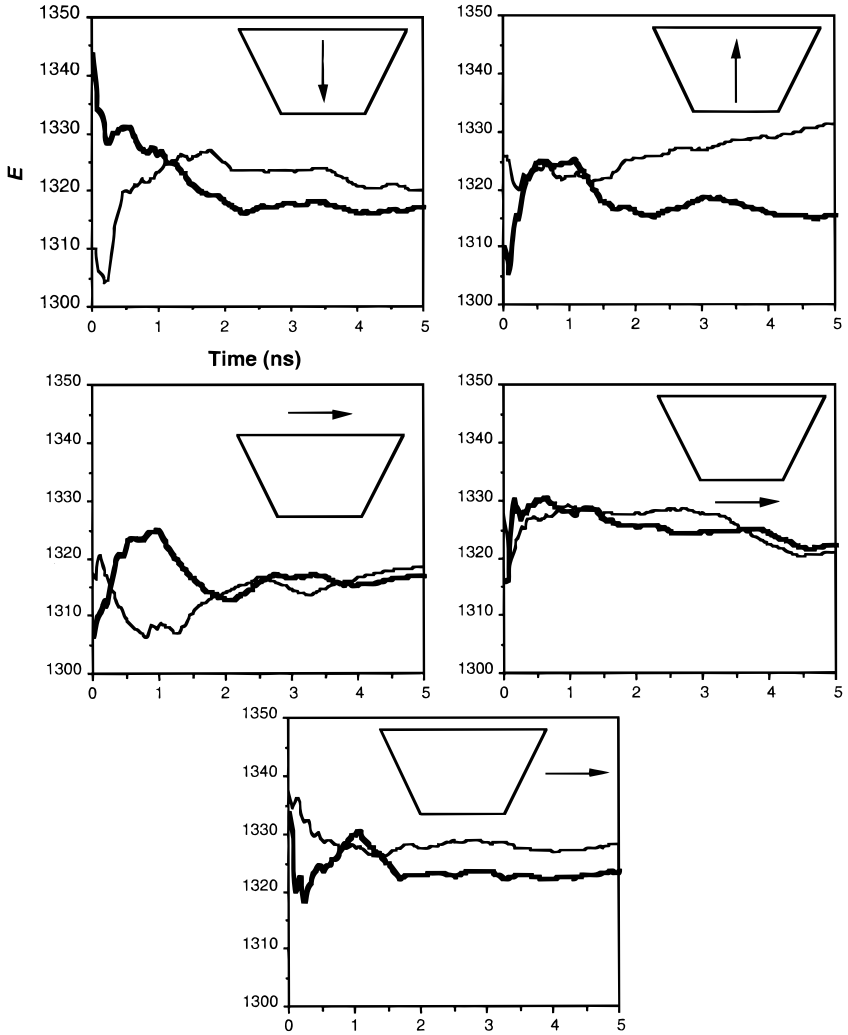


Figure 14. Representative molecular dynamics trajectories for a small analyte molecule binding to permethylated β-cyclodextrin. The conical insert within each frame is a caricature of the host. The arrow corresponds to a bond vector on the analyte used for purposes of alignment. The different trajectories correspond to different alignments of the guest (up/down/horizontal) and different positions (inside/outside) with respect to the host. Thick lines: (*S*) enantiomer. Thin lines: (*R*) enantiomer. Note that these energies being plotted are running averages and that the simulation times are in nanoseconds. The longer retained enantiomer in this case (experimentally and computationally) is the (*S*) isomer. Averages over multiple trajectories are required for successful predictions of analyte retention orders. Taken with permission from ref 176.

Knowing where analytes tend to bind in or around a cyclodextrin is important, but this constitutes only part of what leads to effective chiral separations. Another aspect that is critical for effective resolutions is knowing which region of the CSP is most discriminating. This is especially important because if the preferred binding site differs from the site that is most highly discriminating, one is relegated to an inferior region of chiral selection leading to loss of discriminatory power or even no recognition at all. This can be conceptualized by considering a cyclodextrin, or any other chiral host–guest complexer for that matter, where if the preferred binding site exists on the interior of the host but the most chiral discriminating region is on the exterior of the host, one loses discriminatory power.

This is a general issue that seems not to have been discussed in the literature and one that is important enough to play a major role in, e.g., the design of chiral catalysts, improved chiral stationary phases for chromatography, or any other area of science involving chiral discrimination. Having a priori knowledge of which region of a host is most discriminatory is especially useful because one could then devise techniques to force the substrate to bind at that less-favored but more discriminatory site. In terms of chiral chromatography with, for example, cyclodextrins, this could be as simple as adding to the mobile phase a competing substrate that binds exclusively to the interior of the cyclodextrin thus forcing the guest to the less favored and more discriminating exterior of the cyclodextrin. For other systems more complicated means of forcing the substrate to an alternative site could be envisioned.

This issue of finding and using the most enantiodifferentiating region of a molecule for asymmetric induction or for chiral recognition is something that was recently published by Lipkowitz, Coner, and Peterson.[176] To define which part (or parts) of the molecule are most discriminating toward a given analyte they (1) placed the cyclodextrin's center of mass at the origin of a Cartesian coordinate system,

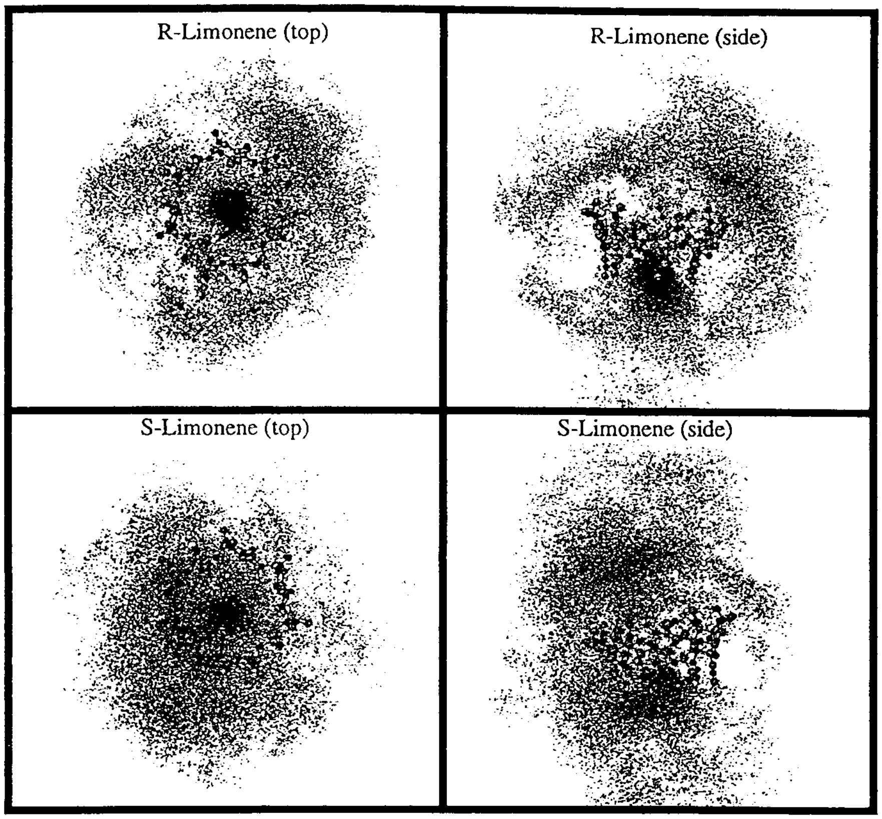


Figure 15. Position of limonene center of mass relative to the permethylated β-cyclodextrin's center of mass. Illustrated here are 50 000 points for each enantiomer sampled from uniform time periods along the molecular dynamics trajectory (25 ns). Top: (*R*) enantiomer. Bottom: (*S*) enantiomer. Two views of the distribution of points are given with the "left" views having the secondary hydroxyl groups proximal to the reader. Both views show the propensity for interior binding. Original plots are color coded to indicate the intermolecular energy at each point. The interior points are generally of lower energy than the exterior points. Taken with permission from ref 178.

(2) embedded the cyclodextrin into a 3-dimensional grid, (3) positioned the analyte's center of mass at each grid point and then computed, using the AMBER* force field, the intermolecular energy between selector and selectand for a large number of unique orientations per grid point, and (4) made isodensity contour maps of differences between Boltzmann weighted energies for various *R* vs *S* probe molecules. Grid points having zero or small energy differences correspond to regions that are nondiscriminating while those grid points showing large differences between the enantiomeric probes are deemed most enantiodiscriminating.

For permethylated β-cyclodextrin, the most popular chiral stationary phase used in gas chromatography, the authors found the most enantiodifferentiating regions are at the interior rather than the exterior of the macrocycle. Both the van der Waals and the electrostatic components of this enantiodifferentiation are found inside the cyclodextrin, but the (minor) electrostatic component is less localized to this region, having sites outside the cavity. Seven representative analytes were investigated in that study, ranging from nonpolar to polar in nature and containing a diversity of organic functionality. In all cases the regions of maximum chiral discrimination correspond, roughly, to the preferred binding site for those analytes. An example of their contour plots is given in Figure 16. The authors conclude that, in the case of permethylated β-cyclodextrin, Nature places the analytes in the vicinity of highest chiral discrimination, perhaps explaining the popularity of this molecule as a CSP in chromatography.

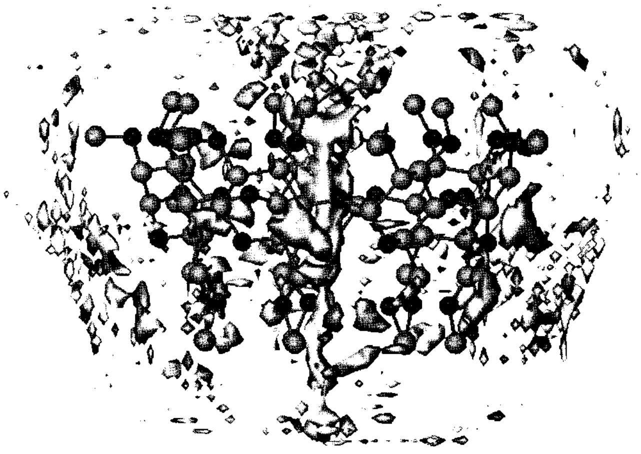


Figure 16. Regions of chiral recognition between a symmetric host, permethyl-β-cyclodextrin, and α-pinene. The cyclodextrins and their gray-tone color codes are the same as in Figure 13. Inside the macrocycle the region of greatest discrimination is localized near the (wider) secondary rim. At all levels of chiral discrimination the inside of the macrocycle is most cognizant of differences between *R* and *S* guests.

VI. Summary and Prospectus

In this review we summarized computational chemistry as it pertains to cyclodextrins. Both quantum-based techniques and application of empirical force field methods have been used for this purpose with most applications being molecular mechanics. A significant number of these applications have been directed toward understanding the shape(s) of cyclodextrins, especially for comparison to those structures derived from X-ray crystallography. Assessing cyclodextrin structural features such as geometry, charge distributions, lipophilicity patterns, and so on represents the largest percentage of published papers where molecular modeling tools have been applied to issues in cyclodextrin chemistry. Most of those papers provide information that is static, usually presenting global minima from geometry optimizations using quantum mechanics at the semiempirical levels of theory or with molecular mechanics. However, dynamical aspects of cyclodextrin's structures in solid, liquid, and gas phases have also been assessed. It is clear from most of these studies that cyclodextrins are deceptively simple looking molecules because of their inherent symmetries. But in terms of computational chemistry there exist many internal degrees of freedom making structure prediction both time-consuming and difficult. Also covered in this review was a discussion of the energetics of host−guest binding. In this regard the computational tools used were both quantum- and force field-based. Another widely used application of computational chemistry in this field involves assessing the structure and dynamics of guest−host complexes. Again quantum- and force field-based tools have been used to evaluate this, but most studies use the latter, relying on grid-based searching strategies to map out where in the cyclodextrin interior the guest tends to reside. Some of these applications have been to explain observed chemical reactions taking place inside the cavity as well as to rationalize the catalytic abilities of the cyclodextrin's microenvironment. Most studies, though, have been directed toward understanding the regioselectivity of host−guest binding using relatively simple polar guests as probes. Related to this are the many applications of molecular modeling tools that have been used to help scientists understand their spectroscopic data. In this vein most applications have been to help interpret NMR data, especially Overhauser enhancements from ROESY spectra, by providing working models related to averaged locations and orientations of included guests. Finally, we provided examples from the literature where computational chemistry has been used to explain the molecular recognition of cyclodextrins. In particular we brought forth the fact that most of these studies have been carried out by scientists interested in the ability of cyclodextrins to selectively bind stereoisomers including diastereomers but more interestingly enantiomers. The enantiodiscriminating abilities of cyclodextrins have been studied especially by separations scientists interested in the chromatographic properties of cyclodextrins, and most of those studies used molecular mechanics and molecular dynamics to compute differential energies of analyte binding and to describe the forces responsible for chiral recognition.

The question to ask at this point is "how valid are these calculations in general"? From this author's perspective most of the calculations described here were done by nonexperts who introduced significant flaws into their calculations so as to jeopardize the conclusions drawn from their calculations. In particular we note that most scientists make major omissions in their modeling, leaving out for example solvent, buffers, and counterions. Moreover they are prone to making comparisons between energies or energy differences of a single minimized structure that is, at best, an enthalpy for comparison to experiment where free energies are being measured. Similarly, even when Boltzmann averaging has been done the results are sometimes questionable because of the limited number of configurations sampled in the statistical averaging. All is not bad, however. There exist a significant number of papers reported in this review that have carefully evaluated structural, energetic, and dynamical aspects of cyclodextrins, and it is easy to spot these papers in the literature.

Why is it that so many computational studies are not done as well as they should be? The answer to this question comes in two parts. First, the user of the computational tool is usually not an expert in the field of molecular modeling and is prone to introducing errors and misinterpreting the computed results. Until a decade ago the users of these programs were the same scientists who generally developed the software; they were cognizant of what the programs could do and what they could not do. Those programs were usually not "user-friendly" so most scientists not involved in theory tended to avoid them. However, with the advent of user-friendly, menu-driven software, everybody could begin using molecular modeling tools and great abuses in molecular modeling became prevalent. The second reason for the work not being as good as one wishes is because the software and the computing machinery was not as good as needed. In particular the computing machinery, even a decade ago, was by today's standard meager. One was often limited to carrying out quantum mechanical calculations on very small to medium sized molecules; cyclodextrins were giant molecules to a computational chemist at that time, and clearly no geometry optimizations could be done. The empirical force fields implemented in MM, MC, and MD algorithms were also not very good. They were undergoing development, and many of the parameter sets associated with those force fields were not thoroughly tested or they were ad hoc guesses. This is not meant to denigrate cyclodextrin scientists. Indeed, the abuses alluded to in this review could have been in any area of chemistry, and in fact a review on the application of molecular modeling in synthetic chemistry[203] concluded with many of the cautionary concerns being expressed here. There have been so many inadvertent uses and misinterpretations of molecular modeling that this author has prepared a tutorial on the pitfalls to avoid when doing molecular modeling, especially when using molecular mechanics.[204] It is a pedagogical summary of problematic issues in computational chemistry that is well worth reading before one applies molecular modeling tools to problems as complex as those associated with cyclodextrins. Also, several well written books on the topic of computational chemistry now exist and should be read before beginning such calculations.[205−207]

So, what is the prognosis for the future of computational chemistry as it relates to cyclodextrins? Actually it is astonishingly good. First, computing hardware is nowadays stellar. The typical machine on your desk, once beefed up with extra memory and disk space, is comparable to a super computer several years ago! These machines are capable of handling simulations of systems containing thousands of particles, e.g., cyclodextrins in aqueous environments, and for very long simulation times, i.e., in the range of nanoseconds or more, on a single processor. Moreover, parallelized versions of the programs used for molecular modeling now allows one to take advantage of many computers (sitting on your desk and those of your colleagues) throughout your local environment. This way one can carry out multiple simulations simultaneously or break up an otherwise daunting task into a manageable chore. Second, software developments have been keeping pace with hardware developments. New algorithms in quantum theory now make it possible to carry out calculations on molecules the size of cyclodextrins as a routine matter, allowing one to obtain multiple structures and energies for statistical averaging. Likewise, new classes of force fields have been developed and tested, particularly related to carbohydrates, making the computed results far more reliable. Moreover, the user can now carry out simulations on completely solvated cyclodextrins using several types of solvent models for both quantum-based and empirical force field-based techniques. All of this portends well for the future of host−guest chemistry and molecular recognition studies, but the user must be aware of the many pitfalls that still exist and in this regard it is urged that you work collaboratively with an expert in the field of computational chemistry.

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Note Added in Proof

Since this paper was written several other reports concerning computational chemistry applied to cyclodextrin research have appeared. These are listed in alphabetical order by first author in refs 208−214.

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