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Understanding ligand-receptor non-covalent binding kinetics using molecular modeling

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Abstract

Kinetic properties may serve as critical differentiators and predictors of drug efficacy and safety, in addition to the traditionally focused binding affinity. However the quantitative structure-kinetics relationship (QSKR) for modeling and ligand design is still poorly understood. This review provides an introduction to the kinetics of drug binding from a fundamental chemistry perspective. We focus on recent developments of computational tools and their applications to non-covalent binding kinetics.

Keywords

Residence Time; Enhanced Molecular Dynamics; Brownian Dynamics; Drug Discovery; Host-guest

2. INTRODUCTION

Traditionally, a dominant criterion for selecting drug candidates is ligand-protein binding affinity, the thermodynamic property that describes how tight a ligand can bind to its target protein. This criterion has been used with the understanding that a drug must have strong affinity to successfully compete with the natural substrate binding to the same target. However high affinity does not always lead to a successful drug because candidates solely selected by strong binding affinity may have unexpected *in vivo* clinical efficacy (1). One important fact from the studies is that the drug efficacy correlates with dissociation rate constant better than the equilibrium constant which is the ratio of association and dissociation rate constants (2). These experiences over the past decades have led researchers to realize that the kinetic properties of a drug candidate, more specifically, how fast the drug associates into the binding site and how long it stays there, sometimes is equally important to its thermodynamic properties (2–5). Despite the comprehension of the importance of the kinetics in drug design, a concrete recipe of kinetic effects remains as an open question due to the intrinsic difficulties of this issue. Experimental investigation of drug-protein binding is usually done by *in vitro* studies (6, 7), mutagenesis (8, 9), and structural biology (10, 11).

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Computational modeling is a powerful tool to study drug-protein binding kinetics. It is capable of describing molecular systems with atomistic details while exploring the motions of the systems at femtosecond to microsecond time-scale. These advantages have resulted in high applicability to the drug discovery field in the recent years. However, the computationally determined kinetics is sometimes faster than experimental values. In some scenarios, where the binding kinetics are calculated using rigid body approximation (12), the slow conformational changes of the protein and the ligand are ignored and thus the kinetics is overestimated. In other scenarios, where flexible systems are studied using explicit solvent model. Two factors make the kinetics faster than experimental values. First, the commonly used non-polarizable force field tends to underestimate the hydrogen bonds between charged residues in the protein and water molecules and thus accelerates the protein conformational changes (13). Second, the kinetics of long timed events are usually extrapolated from simulations of short transitions (14), resulting in large errors. Therefore, the theoretical methods generally overestimate the kinetics of protein-ligand binding, and researchers continue to develop new strategies and tools to provide more accurate calculations.

Thermodynamic properties and specific interactions that increase drug-binding affinities have been widely applied in structure-based drug design (15–17). For example, scientists can successfully design tighter binders by reducing conformational entropic penalty or by introducing new hydrogen bonding (18–20). However, a rationality of the effects that significantly alter the association/dissociation rates has not yet been established. For the past few years, attempts (4, 21–23) have been made towards developing this rationality, but difficulties have slowed down the pace of developing systematic strategies for designing inhibitors with desired binding kinetics. Drug-protein binding/unbinding usually involves conformational changes that occur on the timescale of microseconds (21) or even longer. High energy barriers to binding and rough free energy surfaces naturally contribute to slow association/dissociation rates, which sometimes may be on the scale of seconds or even days. Both of these assert challenges to contemporary computational power in sampling the dynamics of drug-protein binding, which can only simulate conformational changes in the microsecond range (22, 24–26). Furthermore, even if the conformational changes are sampled, the extraction of kinetics, or probability of state transitions, remains as the second obstacle before rationalized design of drugs. Therefore development of more advanced sampling methods and kinetic models is a necessity in the drug design field.

Among the attempts towards determining drug binding kinetics with computational tools, several categories of methods can be distinguished. Stochastic methods sample both equilibrium and non-equilibrium states and thus provides insights into non-covalent interactions (27–39). Normal mode or contact map based kinetic network models also reveal some large scale motions of proteins (39–42). Another major category is molecular dynamics (MD) based methods (43–46), which not only sample conformational changes and the association/dissociation of the ligands, but also provides straightforward and insightful information on the kinetics in the time domain. Therefore numerous efforts have been spent on MD-based methods despite of the current timescale limitation in those methods.

Here we review the recent development of computational methods for investigating non-covalent binding kinetics. The review starts with an introduction on non-covalent ligand-

receptor binding kinetics from a fundamental chemistry perspective. We will also discuss conformational sampling methods and kinetic models. Several examples of investigated systems are reviewed.

3. BACKGROUND FOR NON-COVALENT BINDING KINETICS

The protein-drug binding process can be demonstrated by a two state model composed of free and bound states, which represent the abstract process of binding with all the intermediate steps represented by a single energy barrier. The rate of association and dissociation are characterized by the rate constants k_{on} and k_{off}, respectively. A representative association process is shown in the equation below (where R stands for the receptor, and L stands for the ligand). The forward process is a second order process because of the two associating molecules. On the other hand, dissociation, the reverse process of association, is a first order process. The two rate constants are related to the equilibrium constant (K_{eq}) and further to the binding affinity (ΔG) by the equations below. Faster association or slower dissociation leads to a larger equilibrium constant, which implies a stronger drug binding to the target protein. The recently defined residence time (t_R) (2, 3, 5) is directly related to the dissociation rate constant, which can be rigorously derived from the first order kinetics of the dissociation.

$$\mathrm{R+L} \leftrightarrow RL$$
$$\mathrm{K}_{eq}=\mathrm{k}_{on}/\mathrm{k}_{off}$$
$$\Delta\mathrm{G}=-RTInK_{eq}$$
$$\mathrm{t}_{\mathrm{R}}=1/\mathrm{k}_{off}$$

It is noticeable from the equations that the equilibrium constant is the ratio of the two rate constants. Therefore, even if two drugs have the same binding affinity to their target protein, binding kinetics can be significantly different from one another (Figure 1). In addition, the binding affinity can be tuned by changing either the association or dissociation rate without affecting the other. However, this is not necessarily achievable in practice considering the complex environment of the binding pathway. From the perspective of chemistry, non-covalent binding kinetics share the same concept as that for the transition state theory widely used for chemical reactions, in which the rates are governed by energy barriers. In Figure 1, two systems with exactly the same binding affinity are shown in the plot of free energy versus reaction coordinate. Despite having the same binding affinity, the energy barriers are different for association and dissociation processes, thus resulting in different values for k_{on} and k_{off}.

In real protein-drug systems, the actual binding free energy profile is much more complicated than the single barrier model. This results from the convoluted conformational changes, intramolecular and intermolecular interactions, solvent effects, and changes of entropy involved in the association/dissociation pathways. Firstly these details reshape the free energy profile by introducing multiple small barriers that can be overcome by thermal fluctuation energies rather than one single dominant insurmountable high barrier. Secondly, the rough free energy surface also creates a series of stable or metastable intermediate states, which may in turn contribute to the slow kinetics by constant back and forth transitions. Due

to the presence of the rough free energy surface, k_{on} and k_{off} are simply a net effect from the complex network of transitions between multiple conformational minima, which requires more sophisticated treatment than a two state model.

4. SIGNIFICANCE IN CONSIDERING BINDING KINETICS IN CLINICAL EFFECTIVENESS OF DRUG CANDIDATES

Kinetic properties may modulate protein function and drug activity, and are recognized as a critical differentiator and predictor of drug efficacy and safety (47–52). For example, for inhibitors binding to bacterial enoyl-ACP reductase, slow binders are preferred, with binding kinetics that correlate with the *in vivo* efficacy of compounds tested in an animal model of tularemia infection. In contrast, no correlation was found between K_{eq} and *in vivo* efficacy (51, 52). Another recent example is agonists binding to adenosine A_{2A} receptor. The adenosine A_{2A} receptor belongs to the superfamily of G-protein-coupled-receptors (GPCRs) and a number of its ligands have been developed with several therapeutic applications. Although ligand-protein binding affinity was traditionally the primary guidance for drug development targeting GPCR, studies showed that the residence time of agonists binding to adenosine A_{2A} receptor, not binding affinity, has positive correlations to functional efficacy (53). Another GPCR, the muscarinic M3 receptor, also showed a correlation between ligand binding residence time and agonist efficacy (54).

Kinetic properties may also contribute to developing drugs that have decreased susceptibility to protein mutations or have increased specificity to their target proteins. For example, compared with other HIV-1 protease inhibitors with the same ΔG, darunavir, a very slow binder, is a more potent inhibitor of viral replication with high barriers to resistance (55). The area that has prospect to utilize correlations between kinetics and pharmacodynamics is kinase inhibitor design. Inhibitors binding to the DFG motif of kinases, either binding to DFG-in or DFG-out conformations, have been associated with fast/slow binding kinetics (56, 57). Potent and selective inhibitors have been designed that target p38 MAP kinase for chronic obstructive pulmonary disease (COPD), with an emphasis on slow protein dissociation kinetics to deliver prolonged lung p38 inhibition (58). Compared with experimental assays for kinetic profiling, thermodynamic equilibrium constants, K_d or K_i, or IC50, are relatively easy to measure. However, experimental methods for determine drug binding kinetics are becoming faster and less expensive; therefore, a greater understanding of molecular determinants of binding kinetics is crucial to further assist structure-based drug design.

5. COMPUTATIONAL TOOLS FOR SIMULATING DRUG-PROTEIN BINDING KINETICS

5.1. Conventional molecular dynamics simulations

Conventional molecular dynamics, a standard and robust technique which has been well established in the past century, is a method that describes a molecular system with harmonic approximations and evolves the coordinates of the atoms in the system with time under the government of classical mechanics.

In a typical force field model for protein systems, for example the AMBER force field (43, 59), the potential energy of molecules is described by harmonic bond and angle terms, a cosine dihedral torsion term, a Lennard-Jones van der Waals (vdW) term and a Coulombic electrostatics term. In other force fields, additional terms or other functional forms may be used for more detailed description of molecular systems. In general a classical force field model is unable to capture breakage or formation of a bond (i.e. a hydrogen transfer, or strong quantum effect like electron transfer), but it is capable of modeling the local or allosteric conformational changes and non-bonded interactions.

$$\begin{aligned} \mathrm{V}(\mathrm{r}) = & \sum_{bonds} \mathrm{k_b}(\mathrm{r}-\mathrm{r_0})^2 + \sum_{Angles} \mathrm{k}(\mathrm{a}-\mathrm{a_0})^2 \\ & + \sum_{torsions} \sum_{\mathrm{p}} \frac{1}{2}\mathrm{V_n}\left[1+cos\left(\mathrm{p}\theta-\varphi\right)\right] \\ & + \sum_{\mathrm{j}=1}^{\mathrm{N}-1} \sum_{\mathrm{i}=\mathrm{j}+1}^{\mathrm{N}} \mathrm{f}_{ij} \left\{ \mu_{ij} \left[\left(\frac{\mathrm{r}_{0ij}}{\mathrm{r}_{ij}} \right)^{12} - \left(\frac{\mathrm{r}_{0ij}}{\mathrm{r}_{ij}} \right)^{6} \right] + \frac{\mathrm{q_i q_j}}{4\pi\mu_0 \mathrm{r}_{ij}} \right\} \end{aligned}$$

$$\frac{\mathrm{F}_{XI}}{\mathrm{m_i}} = \frac{\mathrm{d}^2\mathrm{x_i}}{dt^2}$$

In classical mechanics, the motion of a system is governed by Newton's equation. Integration of force along time is done by the finite difference numerical method, and the coordinates of atoms in the system are updated correspondingly so that the motion of the system is produced. At each step the force on each atom is calculated and the atom coordinates are updated by integrating Newton's equation with the calculated force. Certain methods (60–65) that simulate a heat bath environment are applied to ensure the thermodynamic stability of the isolated system. In an all-atom simulation, the integration time step is usually limited to 1 or 2 femtoseconds due to the fast motion of hydrogen atoms. This results in the shortcomings of the conventional MD method, which limits the timescale that it can practically achieve. Without accelerating techniques, the timescale that conventional MD can reach is limited to microseconds with contemporary hardware (22, 24–26) leaving a large gap to the timescale of protein motion of interest. However despite the limitations of timescale of conventional molecular dynamics, there have been important discoveries and progress over the past years.

Since the first atomistic MD for a protein was performed in 1977 (66), MD has been used to investigate the behavior of proteins, regardless of the timescale limitation of MD (67). To extend the time range while retaining a reasonable atomistic level description of the system, many studies were performed with an implicit solvent model. Implicit water models are well known to significantly speed up slow dynamics (68–70). This allows the study of allosteric effects or slow conformational changes in microsecond or even millisecond time scale with limited computational resources. However, it has been known that water molecules play crucial roles in protein dynamics (71–75) due to the importance of viscosity, hydrogen bonds, and water bridges in protein dynamics. As a result, although MD simulations using

implicit water models can provide important information, in some cases, it may fail to capture certain dynamics from direct correlation with explicit water molecules.

Recently, computational speed has grown rapidly with the introduction of parallel computing based on graphic processor unit (GPU) computing techniques and specialized computing machines. This enabled study of the complete drug binding process of a transition state analogue to purine nucleoside phosphorylase (PNP) by microsecond level MD simulations with the aid of machine learning (22) on GPUs (76). Peptide recognition by protein domain was studied by microsecond MD simulation with parallel computing (77). The dewetting effect of a protein pocket was also investigated by GPU accelerated MD (78). The effect from N-myristylation and ligand binding to the catalytic subunit of protein kinase A was also studied by GPU accelerated MD simulation (79). With the Anton machine (24, 80) it is possible to study the protein dynamics on a millisecond timescale (81).

Besides the increasing computational power, various modeling techniques have been developed to accelerate simulations and/or to sample rare events during ligand binding processes. Reseeding techniques attempt to avoid equilibrium traps in MD simulations by detecting trapped simulations, stopping them, and restarting the dynamics from more promising thermodynamic states. The choice of restart condition in reseeding techniques is carried out by various methods including RMSD (82), principal component analysis (PCA) (83), conformational clustering (84), progress index (85), and free energy (86).

5.2. Enhanced molecular dynamics simulations

Considering the current limitation of conventional MD at the millisecond timescale, conventional MD itself is under question as to its practical applicability. Therefore a wide diversity of MD variants has been developed over the past decade.

The first class of such MD variants relies on the fact that the conformational changes happen slowly due to high free energy barriers, and aims to lower the energy barrier or smooth the potential energy surface itself. The most obvious approach is to coarse grain the atomistic model into a residue bead model (87–89), but this method loses the atomistic details and can only provide a reference about the overall motions of the system. Other early works used the locally enhanced sampling technique that focused on residues important to binding to accelerate dissociation pathways (90, 91). Hyperdynamics was the first implementation of an algorithm to raise the potential energy well of the dihedral torsions so that the conformational changes happen much easier than the original model (92). Accelerated MD (93) was built on similar principals. Similarly its natural variant RaMD-db (94) aims at accelerating the most relevant portion of the system. Regarding the force field, a softcore force field was developed to allow easier motion at the region of interest intrinsically (95). A scaled potential was used to estimate the kinetics of ligand dissociation (96). Recently, a Gaussian accelerated MD (GaMD) method was developed by using Gaussian functions to boost the conformational transition in protein systems, in a way similar to accelerated MD (97), so that the Gaussian functions alleviate the potential energy wells.

A second group of MD variants enhance sampling by employing additional forces that pull a ligand from its binding site. This group includes steered MD (98, 99) and target MD (100)

methods, which drive the conformational change to or away from some predefined states. A popular method in the past decade for enhanced sampling is metadynamics (92, 101, 102). Instead of using Gaussian functions to systematically alleviate the potential energy surface of the system, it utilizes the Gaussian functions to raise the potential energy surface of the readily sampled regions so that the sampling evolves to unvisited, originally high energy portion of the potential energy surface, such as an energy barrier. However, collective variables must faithfully reproduce the reaction coordinates and distinguish the states of interests efficiently, which limits the applicability of metadynamics. Another method related to metadynamics is known as self-guided Langevin dynamics (SGLD) (103, 104). It distinguishes from metadynamics in that it needs no pre-knowledge of the system. It accumulates the random force on the system for a directional force and enhances the low frequency motion of the system by applying that additional force back to the system.

There exist several other important related computational methods. LowModeMD (105) embeds low frequency modes from normal mode analysis into the velocity of MD simulations to allow low frequency transitions to happen. Transition interface sampling (106) is based on the idea of the transition path sampling method and allows intensive sampling at the transition interface, and extracts the kinetics from the direct probability measurement. Replica exchange molecular dynamics (REMD) (107, 108) was developed on the idea that in high temperature or low interaction ensembles the system evolves with a faster speed than room temperature ensemble.

5.3. Brownian dynamics simulations

Bimolecular association kinetics are of particular interest to the study of biochemical systems due to the ubiquitous nature of protein-protein and substrate-receptor association events *in vivo*. Computational methods to characterize the kinetics of molecular association processes have been in development for many years. Brownian dynamics (BD) has been a common approach to simulating the diffusional encounter of a ligand and receptor system for several decades. The most direct way to determine association kinetics with BD is to perform many simulations of a model system at a specific concentration and calculate the rate of association through the inverse of the average association time of a specific pair of molecules. However, this approach suffers from a lack of computational practicality due to the dilute nature of many biological and experimental conditions, and suffers from problems of convergence due to the rare-event nature of binding processes. The “NAM” method, named after the authors Northrup, Allison, and McCammon, established the means to estimate the second-order bimolecular association rate constant of a substrate-receptor pair through BD simulations (109–111). In this scheme, many replicate substrate simulations start from a distance b from a molecular receptor, and through the propagation of Brownian motion either the substrates diffuse away from the receptor and escape at an exit distance q, or “bind” by diffusing to the target receptor and satisfying a binding criterion. The fraction of trajectories resulting in binding events is used to scale the analytical approximation of diffusion limited association from the distance b. A spherical recombination probability is also included to account for the small fraction of substrate that diffuse beyond the exit radius q before returning to, and binding with, the receptor. While this method focuses on the relevant configuration space, the primary challenge with this approach is still to sufficiently

sample configuration space to accurately describe the probability of the encounter of a ligand to the active site of a receptor. This approach typically requires the simulation of many thousands of Brownian trajectories for a reaction probability to converge.

Algorithms have been formulated to bias or weight BD trajectories in such a way as to accelerate the sampling of rare events. The biased BD method proposed by Zhou *et al.* introduces a biasing force to the BD simulation, increasing the probability of substrate-active site encounter leading to faster convergence (112). Trajectories are then statistically weighted in an attempt to remove the effect of the biasing force from the results. The Weighted-ensemble Brownian dynamics (WEB dynamics) approach, proposed by Huber and Kim, attempts to efficiently sample the bimolecular configuration space by replacing a single instance of one molecule with an ensemble of psuedoparticles with variable statistical weights (113). These pseudoparticles are distributed evenly into bins that are located along a reaction coordinate. The statistical weights of particles are assigned according to the Boltzmann distribution, giving particles in regions of higher energy lower statistical weights. This allows for additional sampling of regions of low probability, such as the top of a free energy barrier, without over-weighting rare events (114). This method has proven to accurately determine association rate constants relative to the NAM method. The algorithm itself has also found use in the Brownian dynamics of protein folding (115).

The University of Houston Brownian Dynamics package (UHBD) and the MacroDox package were early expressions of the “NAM” method and related algorithms using flexible chain molecular models, and enabled a large body of computational studies (116–126). BrownMove contains similar functionality and also includes flexible definition of molecular structure (127). The Simulation of Diffusional Association (SDA) package additionally applies the “NAM” method to determine protein-protein association rates under rigid-body constraints (128, 129). SDA has been used extensively for this purpose, and has been modified to accommodate the investigation of protein-DNA and protein-RNA association (130–137). Similarly, BrownDye is designed as general purpose rigid-body bimolecular association rate calculation software, with support for standard and weighted BD simulations, and is capable of lending insight into subtle processes such as substrate channeling (118, 138–140). Also operating under the rigid-body approximation, GeomBD specifically focuses on simulating and characterizing intermediate substrate transfer processes in multi-receptor systems, calculating first-order rate constants for each intermediate transfer step in a series of receptors (141, 142). Large all-atom molecular constructs and nanostructures such as DNA origami scaffolds can be included in GeomBD simulations through parallel acceleration and precomputation of potential grids.

5.4. Other computational approaches

Milestoning is a multi-scale method for determining the association rate constant of a bimolecular system (143, 144). It brings together Brownian dynamics (BD) and molecular dynamics (MD) by dividing the configuration space around a receptor into a diffusive BD region and a detailed MD region. The MD region is further divided into concentric spherical “milestone” states surrounding a defined binding surface. Combining statistically derived

information from both BD and MD simulations, a bimolecular binding probability and a second order association rate can be calculated.

Continuum methods offer a deterministic alternative to the explicit simulation of particles in molecular and Brownian dynamics for determining bimolecular association kinetics. Continuum methods describe diffusional processes in terms of probability distributions through the solution of partial differential equations, such as the Smoluchowski or diffusion equations (145). Through these solutions, binding processes can be kinetically evaluated. Continuum methods are significantly faster than BD methods and do not suffer from issues of convergence. However, continuum methods require spherical approximation of substrate/ligand molecules. The SMOL program is a modern biomolecule-specific continuum method for determining bimolecular association rate constants (146). It utilizes adaptive meshing and the finite element method, via FEtk (147), to solve the steady-state Smoluchowski equation (SSSE), arriving at results similar to those of comparable BD simulations.

Determining the pathway through which a substrate binds to a molecular receptor has been the subject of many studies and the focus of many computational methods due to the relevance in determining both thermodynamic and kinetic properties of a substrate-receptor pair. Approaches such as the adaptive biasing force methods calculate a potential of mean force in order to determine the free energy change along a reaction coordinate, through which an equilibrium constant can be calculated ($K_{eq} = k_{on}/k_{off}$) (148–151). The Hopping Minima (HM) method was designed to determine binding or unbinding pathways for substrate-receptor systems, relying on thorough conformational sampling of a bimolecular host-guest system and normal mode calculations of the minima in internal coordinates (152). Normal modes of each minimum are used to generate a large set of coordinated substrate-receptor motions. Pathways are then constructed through the combination of a series of coordinated motion trajectories. The results of the HM method can be used as a physically based reaction coordinate for guided dynamics methods and potential of mean force calculations. The HM method is compatible with the second generation Mining Minima software, thus the free energy change along the minima of the binding pathway can also be evaluated (153).

6. EXAMPLES OF MODELING OF LIGAND-RECEPTOR BINDING KINETICS

6.1. Ligand-cyclodextrin: direct sampling for association and dissociation pathways

With contemporary sampling techniques, it is still extremely computationally expensive to sample a full association or dissociation pathway for a ligand binding to a protein. Protein systems usually have more than 10,000 atoms and the association and dissociation rate constant, k_{on} and k_{off}, of protein-ligand systems need microsecond to second MD simulations. It is even more difficult to sample multiple association/dissociation events to obtain ensemble properties. As a result, using classical MD simulations to calculate k_{on} and k_{off} of protein-ligand systems is currently impractical. Nonetheless, with smaller host-guest systems such as β-cyclodextrin-ligand complexes, MD simulations are applicable to sample multiple association and dissociation events within reasonable computational time. Small molecules binding to β-cyclodextrin usually have weak binding affinities, i.e. 1-propanol (ΔG=−0.88 kcal/mol) (154), 1-butanol (ΔG=−1.67 kcal/mol) (154) 1-naphthylethanol (ΔG=

−3.22 kcal/mol) (155) and 2-naphthylethanol (ΔG= 3.97 kcal/mol) (155). The k_{on} values of those complexes are on the order of 10^8 1/M s (154–156), which is an order of magnitude slower than k_{on} from a diffusion controlled association k_{on} = ~ $10^{9–10}$ 1/M s. Considering the fact that all the ligands have similar values of k_{on}, it is the difference in k_{off} values that determines their relative binding free energies.

In most cases, binding rigidifies a molecular system (157–160). However, from our MD simulations, the free β-cyclodextrin is quite flexible (Figure 2), presumably due to the single bond (α-1,4-glycosidic bond) connected glucopyranose units. Interestingly, the β-cyclodextrin molecule can become more flexible after binding to a compound described above, and the configurational entropy estimated from macrocyclic ring conformations increases by ~1–2 kcal/mol at 298K. The presence of a ligand perturbs β-cyclodextrin and the surrounding water molecules.

MD simulations also sampled various binding modes for different ligands (Figure 3). The small ligands can fit into the cavity of the β-cyclodextrin without any clashes or unfavorable vdW repulsion. Some ligands, such as 1-butanol and 1-propanol, may seem to perfectly fit into the cavity. However, the ligands are too small to occupy the entire space in the cavity to optimize the intermolecular interactions (Figure 3). Rather than gaining the attractive enthalpy, entropy gain from freeing water molecules and a more flexible β-cyclodextrin upon binding is the major driving force of binding.

Similar to a receptor, a ligand usually loses entropy during binding, including the translational and rotational entropy due to the confinement in the cavity of the host and the configurational entropy from the rigidifying the ligand upon binding. However, the MD simulation shows that those small ligands can retain most of the external entropy by tumbling and vibrating relative to the β-cyclodextrin. This is because the intermolecular attractions are not strong and the binding site of β-cyclodextrin is large enough for the ligands, comparing with most ligand-receptor binding. As a result, unlike most molecular systems, no entropic penalty is observed in these ligand-β-cyclodextrin binding.

In summary, the β-cyclodextrin and small compound binding is considerably different from a typical drug-protein system. The binding is weak and the major driving forces is entropy, and no significantly entropy loss was observed in both β-cyclodextrin and the ligand. Conventional MD simulations can sample multiple association and dissociation events. No significant conformational changes in the β-cyclodextrin are needed when compounds binding to the host, resulting in a fast computed of k_{on} which also agree nicely with experimental observations.

6.2. Drug-protein binding: sampling with microsecond long MD simulations

The pathways of drug binding to G-protein-coupled receptors (GPCRs) (Figure 4) and the binding mechanism were investigated by conventional MD on the specialized ANTON machine to carry out microsecond simulation length MD simulations (161). In this work, a total of 21 spontaneous binding events was sampled out of 82 simulations with trajectory lengths ranging from 1 to 19 μs on the binding of four ligands (propranolol, alprenolol, dihydroalprenolol and isoproterenol) to β_2 adrenergic receptor and one ligand

(dihydroalprenolol) to β_1 adrenergic receptor. One predominant binding pathway for the four ligands and one rarely visited minor binding pathway were identified from post-simulation analysis. There exist two free energy barriers along the binding pathways. The first barrier lies at the region as far as 15 Å from the entrance of the GPCR, and is believed to originate from the desolvation of the ligand and protein. The second barrier resides at the entrance to the binding site, which is from increased protein conformational energy and another partial desolvation penalty. The ligands first spent several hundred nanoseconds searching for the protein entrance and crossing the first energy barrier, and then spent a longer microsecond-level time period to finally cross the second barrier for the fully bound state. The unbinding pathway is suggested to be the reverse of the binding pathway due to the high similarity in the unique predominant binding pathway. This discovery suggested a design strategy to modify the heights of the two energy barriers according to their distinct origins. In addition to the free energy profile along the binding path, two metastable binding poses were discovered from the unsuccessful trajectories ending in bound states dissimilar to the crystal structure bound state. It is believed that the ligands would eventually undergo slow transitions to the fully bound state, but with proper engineering on the structure of the ligand, it may be possible to use these binding poses as allosteric binding sites for selective drug design. Although sampling of complete binding pathways is computationally very expensive, it will become a more routine technique with the advancements on computational resources.

6.3. Fast and slow inhibitors binding to HIV-1 protease: case study for binding pathways and mechanisms

The drug and protein binding process begins with the encounter of the two molecules by random walks that are often guided by intermolecular attractions. The internal motions of proteins may serve as a “gate” in some systems, such as the open/closed flaps of HIV-1 protease, which controls ligand–protein association (162). In addition to being a good model system for gated control ligand-protein association, HIV-1 protease is among the major antiretroviral therapy targets for AIDS treatment. The experimentally measured association rate constants of inhibitor xk263 and drug ritonavir are ~10^9 and 10^6 1/Ms, respectively. However, the two ligands bind with similar binding affinities $K_d \sim 10^{-9}$M (163). Unlike other protein systems such as kinases that have ligand binding pockets constructed by the DFG-in or DFG-out loop conformations, there is only one binding pocket for HIV-1 protease inhibitors. The binding pathways and flap motions during ligand binding processes play crucial roles in determining a fast/slow binder. Coarse-grained Brownian dynamics simulations and detailed atomistic molecular dynamics simulations have been used to study the binding processes (23, 164, 165). The MD results found that generally, charge attractions play a key role for determining binding pathways, and the number and distribution of H-bond donor or acceptor of a drug contribute to the binding kinetics. For example, the slow binder ritonavir has more H-bond donors/acceptors than the fast binding xk263. As shown in Figures 5 and 6, H-bond switches during ritonavir binding to HIV-1 protease slows down the binding process. Stable transient bridge waters can easily be found between ritonavir and HIV-1 protease that largely stabilize the intermediate states and slow down the progression of ritonavir toward the binding site. In contrast, xk263 has only a few H-bond donors/acceptors that form significantly fewer H-bonds with the protein and bridge water

molecules. The non-polar interactions between the rings of xk263 and flaps of HIV-1 protease also induce the flaps opening that accelerate ligand binding. More studies have been carried out to investigate the ligand binding to HIV-1 protease to reveal determinants of binding kinetics for fundamental research and drug design.

6.4. Cryptophane host-guest binding: other strategy to model extremely slow binding processes

Certain bimolecular binding and unbinding processes happen slowly due to high free energy barriers along the association pathway. Modeling these slow binding or unbinding pathways with dynamics techniques may be prohibitively expensive due to the unlikelihood of important transitions occurring. An exemplifying case includes the cryptophane E and cryptophane ES synthetic host molecules with trimethyl- and tetramethyl-ammonium guests (Figure 7). Cryptophane E is a cage-like molecular spheroid that is commonly used in the study of molecular recognition due to its propensity to bind atoms and small molecules (166–170). Cryptophane ES is a cryptophane E derivative in which the methoxyl gating arms are replaced by thiomethyl groups. This modification results in association and dissociation rates with the aforementioned guest molecules dropping 3 to 4 orders of magnitude despite having essentially identical changes in binding free energy (168). The rare cryptophane ES unbinding events are difficult to sample with dynamics-based methods. In addition to serving as model systems for understanding binding kinetics, chemical hosts are used as drug carriers. Therefore, the kinetics of drug-host binding is of interest for practical applications in pharmaceutical research.

The sampling of the binding processes of the cryptophane E and ES hosts to the trimethyl- and tetramethylammonium ligands has previously been modeled with the hopping minima (HM) method (152). HM is a non-dynamics method that treats a binding/unbinding pathway as a set of normal mode-based transitions between distinct host-guest conformational minimum energy states. Conformational search of each host-guest complex pair was performed with Tork, ensuring that the bound, unbound, and intermediately bound complex states were thoroughly sampled (171). Through derivation of the potential energy function at each minimum energy state, a large set of coordinated motions derived from the normal modes of the complex was created. Binding processes were modeled by combining motions representing minimum-hopping transition pathways. From the modeled binding pathway trajectories of the cryptophanes with each guest, it was observed that spatial restriction prevented facile transition of the guests through the windows of the hosts. The increased vdW radius of the sulfur atoms in the gating arms of cryptophane ES further restricted passage of guests relative to the oxygen atoms in cryptophane E. In addition, the conformations along each path highlight the importance of coordinated conformational transitions of host and guest molecules to facilitate induced-fit association processes.

7. CONCLUDING REMARKS

Computational chemistry plays an important role in understanding non-covalent binding kinetics. Molecular modeling tools will be even more important for studying binding kinetics because of recent computer hardware improvements and also the success in new

methodologies for longer timescale or large-amplitude sampling. Despite the technical varieties, most of the methods focused on three important concepts. First a reasonably detailed description of the system must be retained because examining detailed interactions is necessary to understand ligand-receptor binding kinetics. Secondly it is desirable to avoid the redundant sampling in the same region of the conformational space, which is also the major disadvantage in brute force sampling. This actually results in the many different methods which explore various techniques to reduce the redundancy in sampling. Finally, sampling efficiency can be achieved by parallelization. This could be accomplished by parallelization in algorithm and/or by replica exchange. In order to understand binding kinetics using computational methods, the first step is to search for the most popular association/dissociation pathways. Various post-analysis methods are then used to gain useful information, such as representative conformations, well defined minima, rates/probability for crossing major energy barriers, free energy profiles and key conformational changes involved in the binding processes.

The examples discussed here suggest several concepts important for studying binding kinetics. First of all, rare events are challenging to sample because of the high energy barrier and the low probability of occurrence, but it is possible to capture rare events by contemporary sampling techniques such as accelerated MD techniques. Secondly, researchers may not always need to obtain a complete sampling of one trajectory for a ligand-receptor binding pathway. The kinetic information may be extracted from combining with multiple distinct sampling of the entire conformational space and some kinetic models, for example, the MSM model. Thirdly, water molecules are crucial and may contribute significantly to the kinetic behavior for a ligand binding to a receptor. The solvent plays a role in both enthalpy and entropy, and stable bridge waters that form intermolecular H-bonding with both the ligand and receptor can directly alter binding kinetics.

With the constantly evolving hardware and methodologies, experiments and computer simulations complement with each other to bring a more complete view for complex chemical and biological events. Deeper understanding of non-covalent binding kinetics will enable more rational design of drug development.

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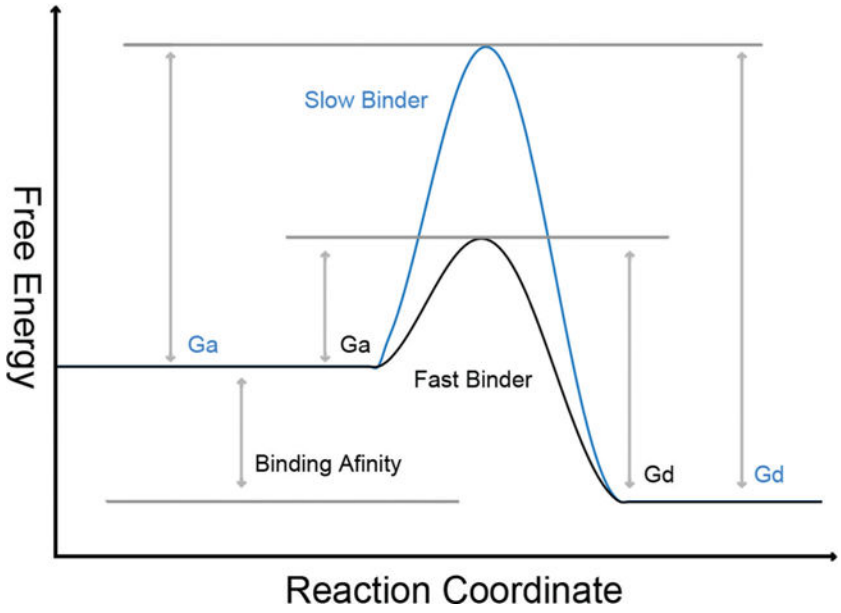

Figure 1.

Representative free energy profiles along the reaction coordinate for a fast binder and a slow binder. E_a is the activation energy of the forward process (association) and E_d is the activation energy of the backward process (dissociation).

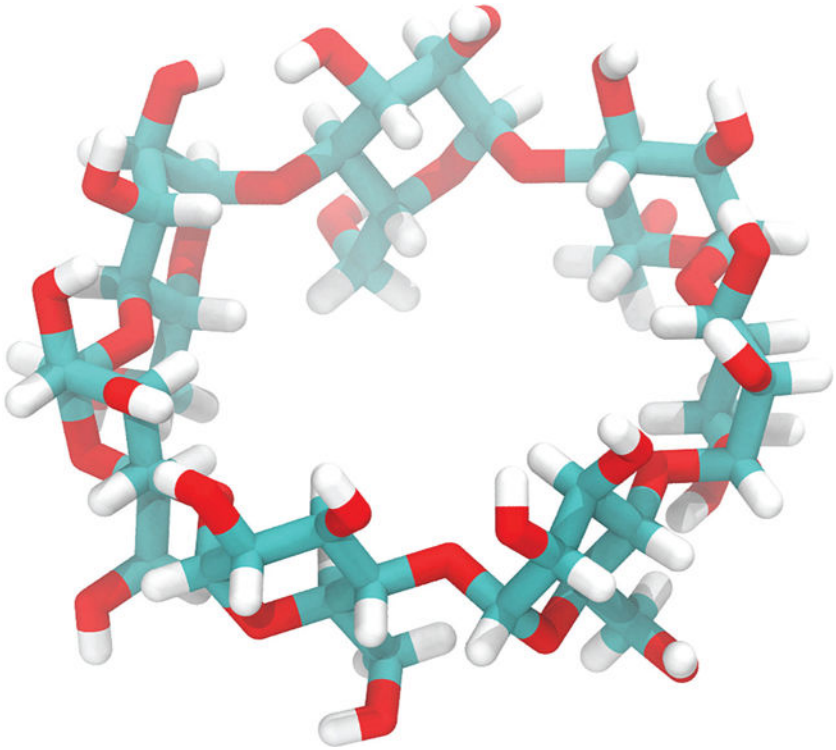

Figure 2.
The structure of β-cyclodextrin. The seven glucopyranose units are connected by α-1,4-glycosidic bonds.

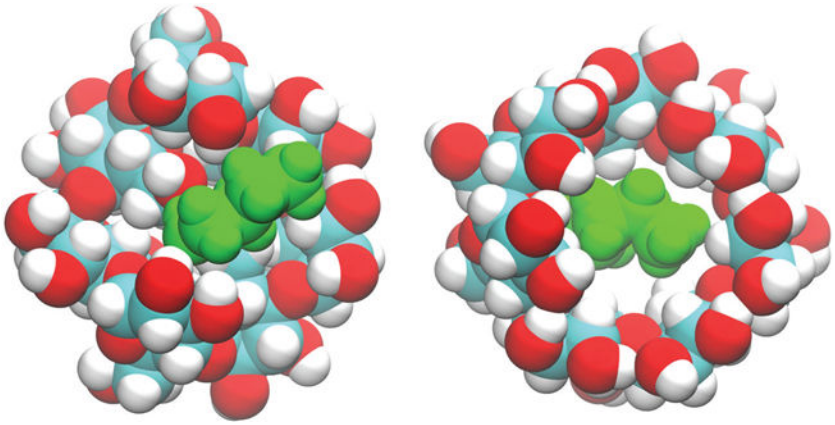

Figure 3.

The left is a superficial binding pose, and the right is a deeper binding pose with the ligand inside the cavity of β-cyclodextrin. The β-cyclodextrin is rendered with atom types while the ligand is rendered as green. In the left binding pose, the cavity of β-cyclodextrin is closed up by flipping of glucopyranose units. In the right binding pose, the cavity is open and some vacuum space is created.

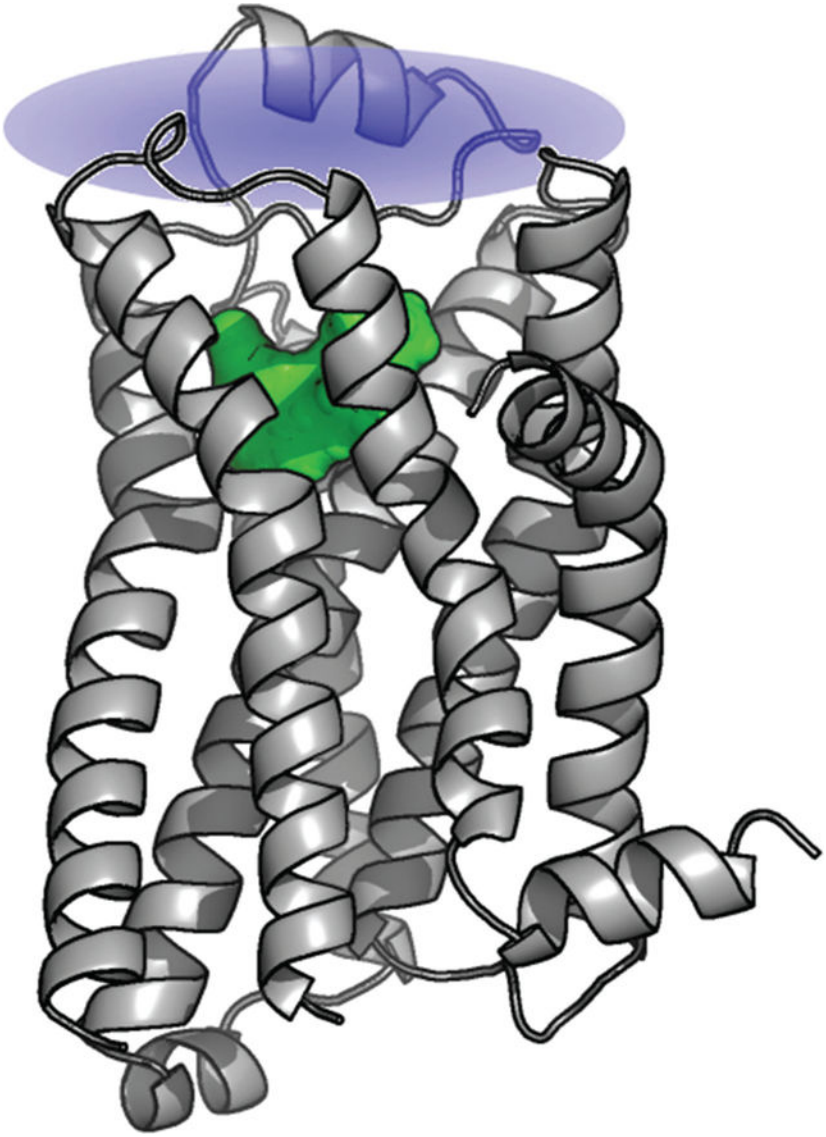

Figure 4.

Structure of the adrenergic receptor. The entrance of the binding tunnel is shown in blue. The binding site is shown in green. The first energy barrier is located above the blue sphere. The second energy barrier is between the blue and green regions.

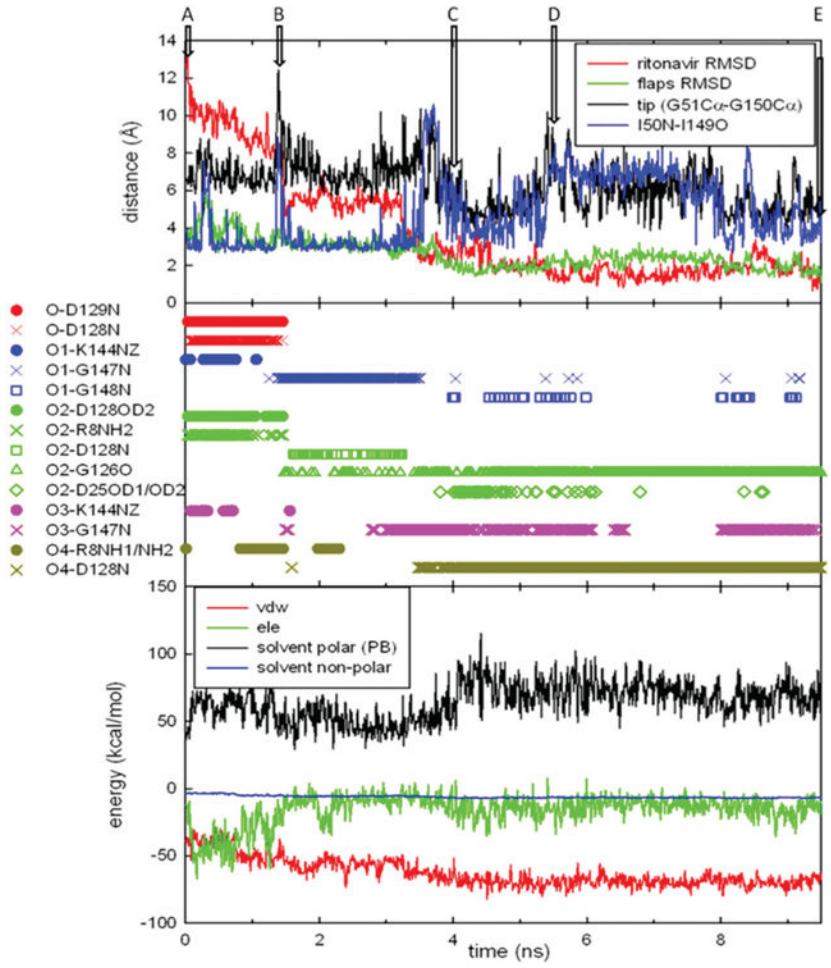

Figure 5.

Hydrogen-bond switches of ritonavir when binding to HIV-1 protease. (Top) The root mean square distance (RMSD) compared with the final bound state of ligand position (Red), the bound state of flaps (Green), and the tip distance (Black) and distance between two representative residues (Blue). (Middle) H-bond pairs between ritonavir and HIV-1 protease. (Bottom) Polar and nonpolar interactions during the binding process. The Figure is plotted using a trajectory from a 200 ns MD simulation with implicit-solvent model for ritonavir–HIVp association. Notably, the same behavior that shows similar hydrogen bond switches can be observed during binding processes in MD simulations using both implicit and explicit models.

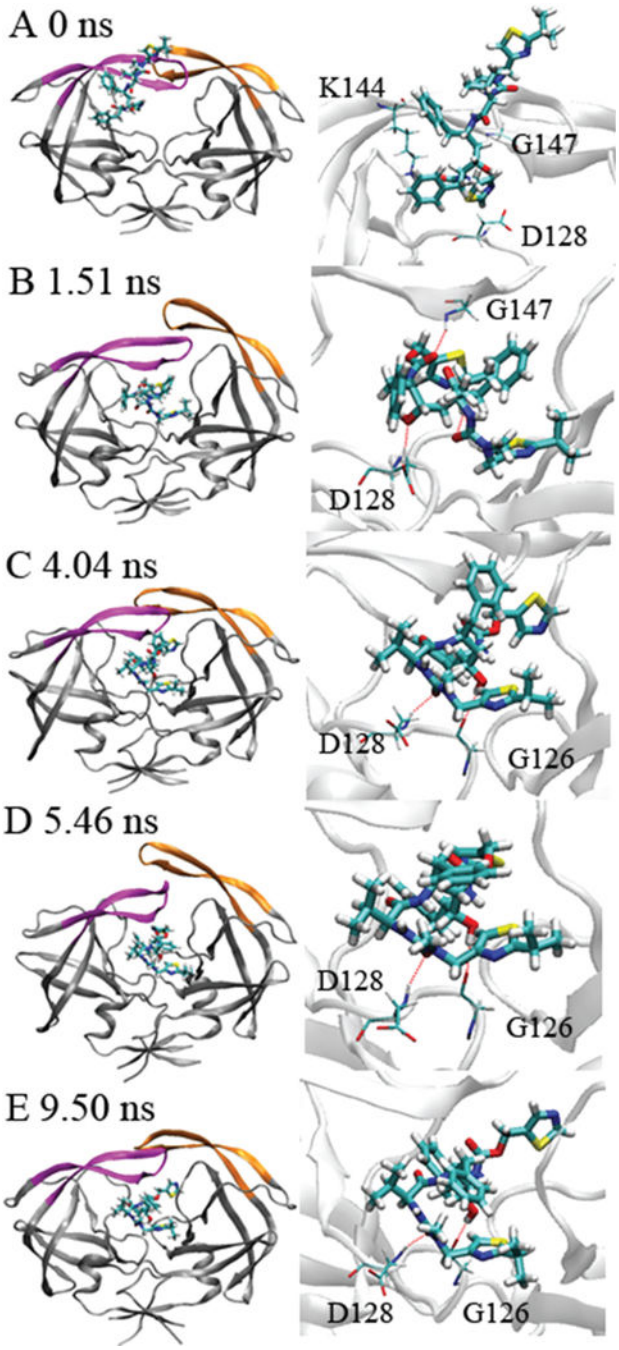

Figure 6.

Representative conformations of ritonavir when binding to HIV-1 protease. A, B, C, D, and E represent the MD snapshot for 0, 1.51, 4.04, 5.46, and 9.50 ns, respectively. The conformations are from the same 200 ns MD simulation with implicit-solvent model for ritonavir–HIVp association as in Figure 5.

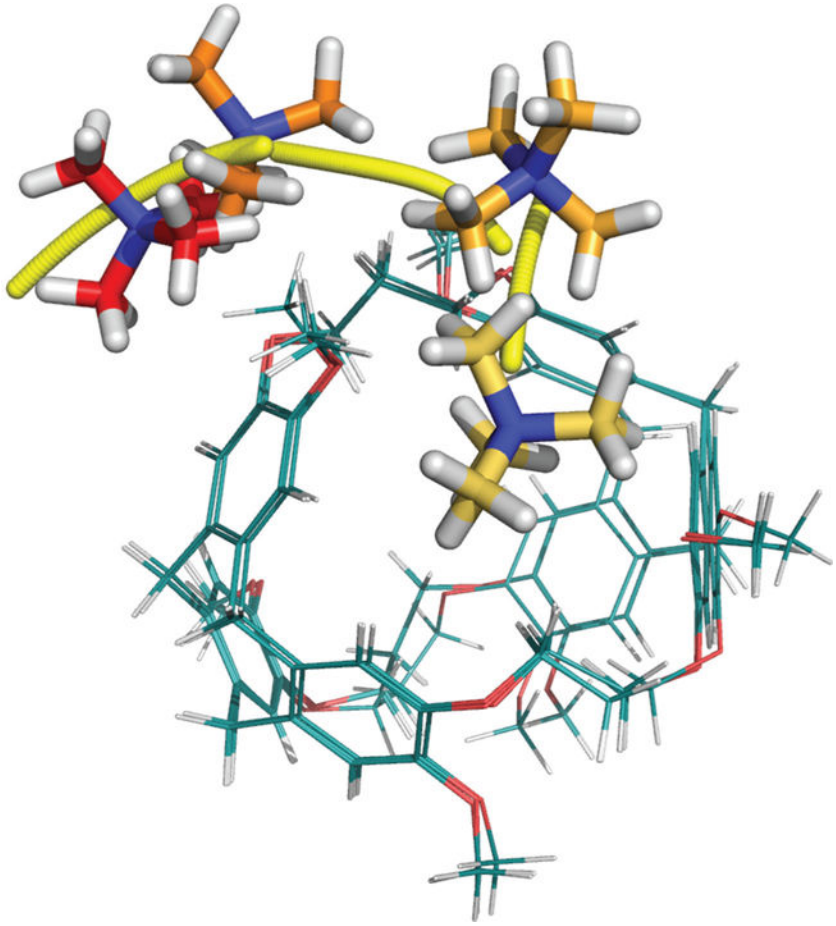

Figure 7.

Hopping Minima resulting association pathway for Cryptophane-E with Tetramethylammonium guest. Three natural motion paths, represented by yellow traces, connect four distinct minimum states. The ligand minimum states are colored, from red to yellow, according to their position along the association path. Hopping Minima provides both the translational motion of the ligand as well as the corresponding conformational changes of the host molecule.