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Original research article

Molecular Modeling of Host-Guest Complexes: A Comparative Study of β-Cyclodextrin, Calix[4]arenesulfonate, and Cucurbit[7]uril with Bicyclic Azoalkane Guests

Luckhana Lawtrakul[1, *], Sodara Thao[2]

[1] *School of Bio-Chemical Engineering and Technology, Sirindhorn International Institute of Technology, Thammasat University, Pathum Thani 12120, Thailand*
[2] *School of Integrated Science and Innovation, Sirindhorn International Institute of Technology, Thammasat University, Pathum Thani 12120, Thailand*

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ABSTRACT

This study examines the inclusion complexation of three bicyclic azoalkane derivatives (DBH, DBO, DBN) with macrocyclic hosts β-cyclodextrin (BCD), calix[4]arenesulfonate (C4S), and cucurbit[7]uril (CB7). Using molecular docking, Hartree–Fock (HF/6-31G(d,p)), and PM7/PCM methods, binding energies, orientations, and electronic properties were evaluated in gas-phase and aqueous environments. Docking revealed negative binding energies with azo groups consistently oriented toward host cavities. HF calculations confirmed thermodynamic stability, showing negative complexation energies and large HOMO–LUMO gaps. PM7/PCM analysis highlighted solvation effects, where water enhanced hydrophobic interactions and stabilized guest encapsulation, especially in CB7. Comparative results indicated CB7 consistently forms the most stable complexes, followed by C4S and BCD, due to favorable cavity size, steric compatibility, and electrostatic complementarity. Overall, the findings provide insights into host–guest recognition mechanisms, offering guidance for designing efficient supramolecular systems with potential applications in molecular encapsulation and drug delivery.

Keywords: Binding energy analysis; Host-guest complexes; Molecular docking; Polarizable continuum model; Semi-empirical calculation

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***Corresponding author:** luckhana@siit.tu.ac.th
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1. Introduction

Supramolecular chemistry, which focuses on non-covalent interactions between molecules, plays a vital role in developing advanced materials, drug delivery systems, and chemical sensors. One important aspect of this field is the study of host-guest complexes—structures where a host molecule forms a non-covalent association with a guest molecule. Understanding how these complexes form, especially the balance between structural compatibility and intermolecular forces, is essential for designing molecular systems with high selectivity and stability [1, 2]. Macrocyclic host molecules are widely studied due to their unique cavity structures and their ability to selectively bind a wide range of guest molecules [3, 4]. Each of these hosts has distinct structural and chemical features: β-Cyclodextrin (BCD) is a cyclic oligosaccharide with a hydrophobic inner cavity that is well-suited for binding non-polar guests [5]. Calix[4]arenesulfonate (C4S) contains a phenolic ring framework and sulfonate groups, enabling both π-interactions and electrostatic stabilization [6]. Cucurbit[7]uril (CB7) is a rigid, symmetric macrocycle with a well-defined cavity that facilitates strong hydrogen bonding and van der Waals interactions [7].

In this study, we perform a comparative molecular modeling analysis of these three host molecules in complexation with bicyclic azoalkane guests. Azoalkanes are particularly interesting due to their rigid structures and photoresponsive behavior, making them suitable candidates for dynamic supramolecular systems [8]. We investigated three bicyclic azoalkane derivatives as guest molecules: 2,3-diazabicyclo[2.2.1]hept-2-ene (DBH), 2,3-diazabicyclo[2.2.2]oct-2-ene (DBO), and 2,3-diazabicyclo[2.2.3]non-2-ene (DBN). To analyze the binding interactions, we used molecular docking [9] combined with quantum mechanical calculations at the HF/6-31G(d,p) level [10]. We evaluated key parameters including binding energy, structural compatibility, and energetic stability of each host-guest complex. To assess the impact of an aqueous environment on the relative stabilities of host–guest complexes, PM7 calculations [11] incorporating the Polarizable Continuum Model (PCM) [12] with water as the solvent were conducted. By comparing these systems, we aim to identify the factors that influence binding strength and host selectivity. The results of this study provide deeper insights into molecular recognition processes and can inform the design of more efficient supramolecular systems for use in drug delivery, sensing, and molecular encapsulation.

2. Materials and Methods

2.1 Molecular structure preparation

The initial molecular geometries of both host and guest molecules were obtained from X-ray diffraction data. Specifically, structures were sourced from the Cambridge Crystallographic Data Centre (CCDC): DBH (ID: 1138416) [13], DBO (ID: 1137100) [14], BCD (ID: 1107192) [15], CB7 (ID: 892884) [16], and from the Protein Data Bank for C4S (PDB ID: 9GR4) [17].

The starting geometry of the DBN guest molecule was derived by modifying the structure of DBO. Structural modifications, such as atom addition and removal, were carried out using the Discovery Studio 2020 Client program [18].

All molecular structures were optimized in the gas phase using the Hartree-Fock (HF) method with the 6-31G(d,p) basis set, implemented in the Gaussian 16

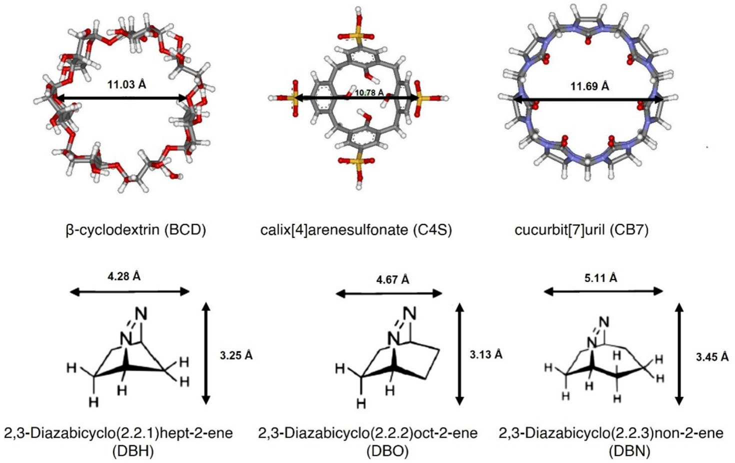

Fig. 1. Schematic representations of the three host families—β-cyclodextrin (BCD), calix[4]arenesulfonate (C4S), and cucurbit[7]uril (CB7)—alongside the chemical structures and dimensions of the bicyclic azoalkane guest molecules: DBH, DBO, and DBN. Height was measured between the $N = N$ plane and the plane of axial hydrogen atoms, while length was defined as the distance between the outermost equatorial hydrogen atoms.

software package [19]. As shown in Fig. 1, the dimensions of the host and guest molecules indicate a 1:1 molar ratio for the inclusion complex formation, which is also supported by experimental data [3]. The host diameters were measured between atomic nuclei centers, excluding van der Waals and atomic radii, based on HF/6-31G(d,p) optimized geometries.

3. Result and Discussion

3.1 Molecular docking calculation

The binding energy (ΔG) results from molecular docking calculations were negative (Table 1), indicating that the formations are entropically favorable [22]. Docking calculations showed only one orientation for all host-guest systems in this study.

Fig. 2 illustrates that the guests are positioned inside the host's cavity, with the azo group ($-N = N-$) oriented toward the center of the cavity and the C-H bonds exposed to the rim. As the size of the bi-

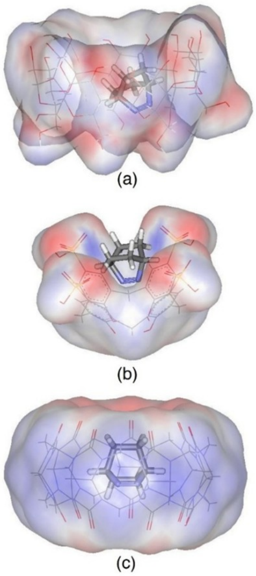

Fig. 2. Molecular docking models of the 1:1 host–guest complexes involving DBO and the three hosts: (a) DBO/BCD, (b) DBO/C4S, and (c) DBO/CB7. Host molecules are displayed as line models with a 1.4 $\mathring{A}$ probe radius; the guest molecule (DBO) is represented as a stick model.

cyclic azoalkane guests increases, the binding strength within the host's cavity also increases. CB7 forms the most stable inclusion complex with the guests, displaying the lowest binding energies: -4.52, -5.19, and -6.10 kcal/mol for DBH, DBO, and DBN, respectively. In comparison, C4S forms more stable complexes than BCD, as indicated by its lower binding energy in Table 1. Overall, the larger the size of the bicyclic azoalkane guest, the more stable the complexes formed (DBN > DBO > DBH) with all three host families.

During the docking process, the host molecules were kept fixed while the azoalkane guests were allowed to move freely. To gain more accurate insights, fully optimized geometries, where both the host and guest molecules are allowed to move freely, are necessary for further investigation.

Table 1. Calculated binding free energies (ΔG) of the 1:1 host–guest inclusion complexes obtained from molecular docking simulations.

Guest	**Host**	**ΔG (kcal/mol)**
DBH	BCD	-3.16
	C4S	-4.11
	CB7	-4.52
DBO	BCD	-3.64
	C4S	-4.58
	CB7	-5.19
DBN	BCD	-4.22
	C4S	-4.84
	CB7	-6.10

3.2 HF/6-31G(d,p) calculation

The HF/6-31G(d,p) calculations performed under ideal gas conditions provided a detailed understanding of the electronic factors influencing host–guest complex formation (Table 2). All inclusion complexes exhibited large HOMO–LUMO energy gaps, indicating that the electronic structures of the complexes remain stable and chemically inert upon complexation. The calculated complexation energies (ΔE) for all inclusion complexes were found to be negative, confirming that the host–guest interactions are energetically favorable. Among the three hosts studied, distinct differences in binding strength and guest orientation were observed, driven primarily by steric fit and electrostatic interactions. β-Cyclodextrin (BCD) formed moderately stable complexes, with ΔE values ranging from –3.77 to –4.92 kcal/mol. The host's hydrophobic inner cavity can accommodate guest molecules based on size complementarity. DBO, with a size matching the BCD cavity, was effectively encapsulated. In contrast, DBH, being smaller, was observed to shift within the cavity and favor positioning near the narrower rim (Figs. 3a–3b). DBN, however, was too bulky to be fully encapsulated and instead localized near the wider rim of the cavity (Fig. 3c). These results illustrate the sensitivity of BCD complexation to the steric dimensions of the guest molecules.

Table 2. Calculated HOMO–LUMO energy gaps (Δ|HOMO-LUMO|, in eV), total optimized energies (E, in kcal/mol), and complexation energies (ΔE, in kcal/mol) for the 1:1 host–guest inclusion complexes using HF/6-31G(d,p) under ideal gas conditions.

compound	**Δ|HOMO-LUMO|**	$E \times 10^5$	ΔE
DBH	14.03	-1.90	
DBO	13.55	-2.15	
DBN	13.44	-2.39	
BCD	16.37	-26.68	
C4S	11.63	-24.23	
CB7	15.34	-26.28	
DBH/BCD	13.95	-28.58	-4.92
DBO/BCD	13.42	-28.82	-3.77
DBN/BCD	13.41	-29.07	-4.42
DBH/C4S	11.53	-26.13	-6.61
DBO/C4S	11.12	-26.38	-6.72
DBN/C4S	11.00	-26.62	-6.24
DBH/CB7	13.55	-28.18	-7.87
DBO/CB7	13.08	-28.43	-8.10
DBN/CB7	13.03	-28.67	-6.17

Calix[4]arenesulfonate (C4S) exhib-

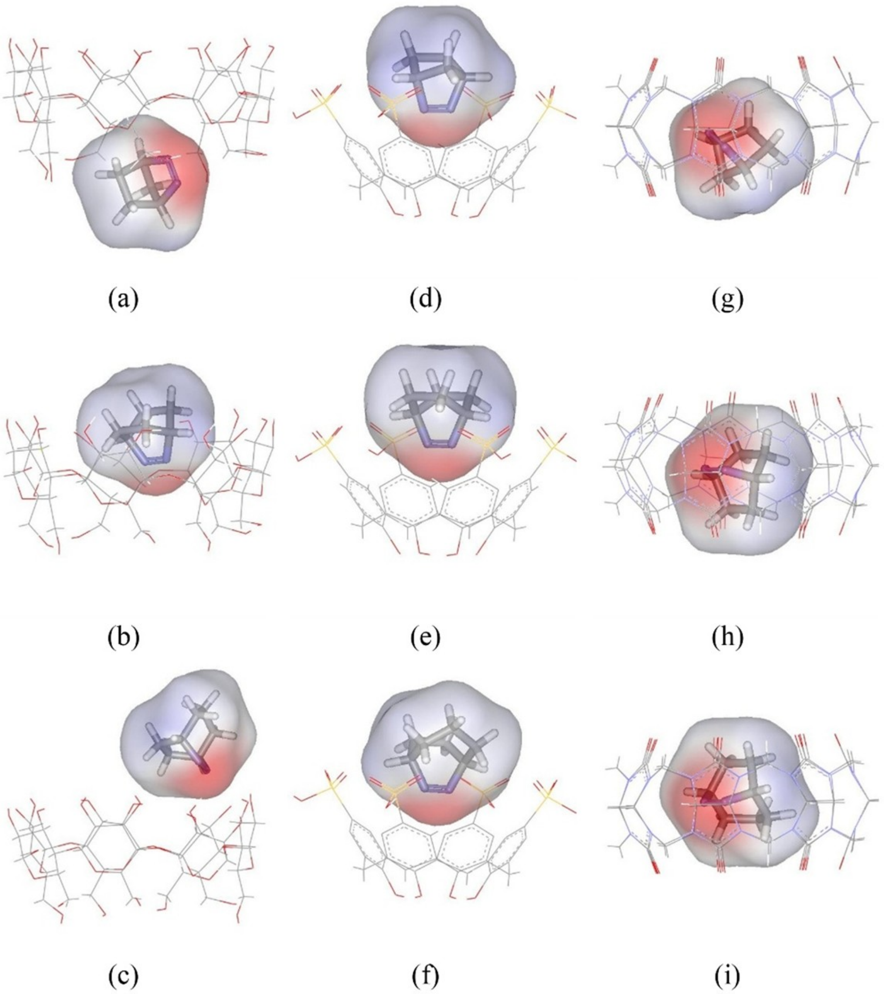

Fig. 3. Optimized structures of the 1:1 inclusion complexes obtained from HF/6-31G(d,p) calculations under gas-phase conditions: (a) DBH/BCD, (b) DBO/BCD, (c) DBN/BCD, (d) DBH/C4S, (e) DBO/C4S, (f) DBN/C4S, (g) DBH/CB7, (h) DBO/CB7, (i) DBN/CB7. Host molecules are shown as line models; guest molecules are shown as stick models using a 1.4 $\mathring{A}$ probe radius.

ited stronger host–guest interactions, with binding energies ranging from –6.24 to –6.72 kcal/mol. This enhanced affinity can be attributed to the electron-donating sulfonate groups, which may promote additional electrostatic interactions with the guest molecules. All guest azoalkanes were found to orient their azo ($–N = N–$) groups toward the interior of the C4S cavity, yet consistently remained located at the wider, upper rim of the host structure (Figs. 3d–3f). This spatial arrangement reflects a compromise between electrostatic attraction and spatial accommodation.

Cucurbit[7]uril (CB7) yielded the most stable inclusion complexes, with binding energies between –6.17 and –8.10 kcal/mol. The rigid and symmetric structure of CB7 provides a snug, preorganized hydrophobic cavity that facilitates strong van der Waals and hydrophobic interactions with the guest molecules (Figs. 3g–3i). This result highlights CB7's superior host capability due to its rigid macrocyclic structure and ideal size for binding small azoalkane derivatives.

Overall, the comparative analysis reveals that host–guest complex stability is governed by a combination of steric compatibility, cavity size, and the presence of electron-donating or polar functional groups. CB7 emerged as the most effective host, followed by C4S and BCD.

3.3 PM7 with PCM calculation

To assess the impact of an aqueous environment on the relative stabilities of host–guest complexes, semi-empirical PM7 calculations incorporating the Polarizable Continuum Model (PCM) with water as the solvent were conducted. Table 3 summarizes the computed heats of formation (ΔH_f) for each optimized structure. In this context, ΔH_f reflects the thermodynamic stability of the system; a negative value indicates an exothermic process and implies a more stable compound formed via favorable interactions, while a positive value denotes endothermic behavior. All inclusion complexes exhibited negative complexation energies (ΔE), affirming that the formation of host–guest systems is energetically favorable. These exothermic interactions suggest that the inclusion process is spontaneous under aqueous conditions. Moreover, the large HOMO–LUMO energy gaps observed for each complex signify electronic stability and chemical inertness upon complexation, which is advantageous for potential applications in drug delivery or molecular encapsulation technologies.

Interestingly, in aqueous solution, the water environment promotes the encapsulation of the three hydrophobic azoalkane guests within the nonpolar cavity of BCD, as illustrated in Figs. 4a–4c. This behavior highlights the dominance of hydrophobic interactions over steric hindrance in driving guest inclusion. Nevertheless, the binding affinities still reflect the influence of steric compatibility. Among the BCD inclusion complexes, the complex with DBO exhibited the lowest ΔE (–24.06 kcal/mol, Table 3), indicating the highest stability. In this configuration, the azo group is directed toward the narrower rim of BCD, consistent with observations for C4S and CB7 hosts (Figs. 4d–4i), where the azo groups also orient toward the interior of the cavities.

Table 3. HOMO–LUMO energy gaps (Δ|HOMO-LUMO|, in eV), heats of formation (ΔH_f, in kcal/mol), and complexation energies (ΔE, in kcal/mol) for the 1:1 inclusion complex calculated using PM7 with PCM (water solvent) to simulate aqueous-phase conditions.

compound	**Δ|HOMO-LUMO|**	ΔH_f	ΔE
DBH	10.34	47.44	
DBO	9.96	23.28	
DBN	9.95	15.92	
BCD	11.08	-1,642.68	
C4S	9.00	-690.76	
CB7	9.87	-413.33	
DBH/BCD	10.11	-1,602.15	-6.92
DBO/BCD	9.84	-1,643.46	-24.06
DBN/BCD	9.93	-1,645.55	-18.80
DBH/C4S	8.97	-659.81	-16.49
DBO/C4S	8.94	-687.18	-19.70
DBN/C4S	8.80	-694.52	-19.68
DBH/CB7	9.87	-386.17	-20.28
DBO/CB7	9.61	-413.23	-23.19
DBN/CB7	9.44	-424.35	-26.94

For the C4S host, the aqueous medium further promotes deeper insertion of azoalkane guests into its cavity (Figs. 4d–4f), enhancing host–guest interactions. The resulting binding energies ranged from –16.49 to –19.70 kcal/mol (Table 3), indicating moderately stable complexes.

In comparison, the CB7 host formed the most stable complexes, with binding energies between –20.28 and –26.10 kcal/mol (Table 3). This can be attributed to CB7's

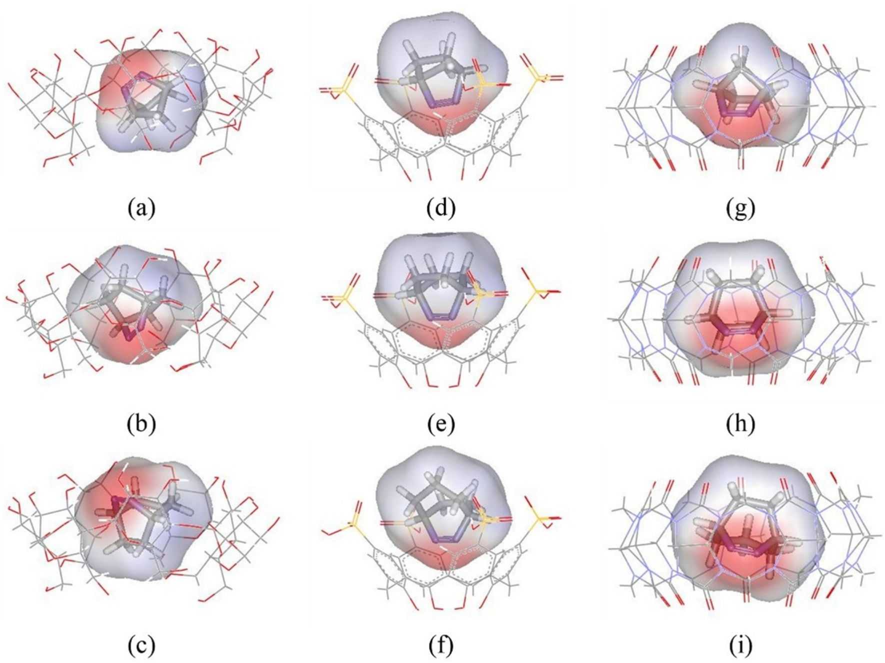

Fig. 4. Optimized structures of the 1:1 host–guest inclusion complexes obtained from PM7/PCM (aqueous) calculations: (a) DBH/BCD, (b) DBO/BCD, (c) DBN/BCD, (d) DBH/C4S, (e) DBO/C4S, (f) DBN/C4S, (g) DBH/CB7, (h) DBO/CB7, (i) DBN/CB7. Host molecules are represented as line models; guest molecules are displayed as stick models with a 1.4 Å probe radius.

rigid, symmetric architecture and its well-defined, hydrophobic cavity, which is pre-organized for efficient van der Waals and hydrophobic interactions (Figs. 3g–3i). Among the three guests, the stability trend for CB7 complexes followed the order DBN > DBO > DBH, suggesting that a larger guest size correlates with increased binding stability, likely due to enhanced surface contact and cavity filling.

In all host systems, the guest molecules were completely encapsulated within the respective cavities, exhibiting strong geometric complementarity and orientation consistency. These stable orientations reinforce the idea that size-match and cavity depth are critical for optimal inclusion. The comparative analysis across host systems underscores the significance of multiple factors in determining host–guest stability. While hydrophobic effects dominate in aqueous media, steric compatibility, cavity size, and the presence of functional groups play crucial roles in modulating complexation energetics. CB7 stands out as the most efficient host due to its symmetrical and rigid cavity, which provides a near-perfect fit for the azoalkane guests.

4. Conclusion

The computational investigation of host–guest complexes formed between three azoalkane guests (DBH, DBO, and DBN) and macrocyclic hosts (BCD, C4S, and CB7) reveals that complexation is both energetically favorable and electronically stable across all systems.

Molecular docking and HF/6-31G(d,p) calculations confirm that guest orientation and binding strength are governed by steric compatibility and cavity geometry. PM7 with PCM simulations emphasize the role of aqueous solvation in enhancing hydrophobic interactions, leading to more stable complexes, particularly with CB7. Among the hosts, CB7 emerges as the most effective encapsulant due to its rigid, symmetric cavity, followed by C4S and BCD. These findings not only deepen our understanding of host–guest interactions at the molecular level but also provide a predictive framework for designing efficient host molecules for applications in molecular recognition, encapsulation, and targeted delivery systems.

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