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NITROFURANTOIN@CUCURBIT[7]URIL COMPLEX FOR IMPROVED ANTIBIOTIC ACTIVITY

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Abstract

The study investigates the interaction between the cyclic chemical cucurbit[7]uril, which forms complexes with different molecules, and nitrofurantoin, an antibiotic that is well-known for treating lower urinary tract infections. The B3LYP-D3/3-21G approach was used to optimise structures in gas using the Gaussian G16 code. By using a supramolecular method, frequency analysis validated the binding energy and confirmed the stability of these structures. According to the study, the complex that nitrofurantoin and cucurbit[7]uril produced had a narrower energy gap than nitrofurantoin by itself. This reduced energy gap suggests that the compound is more stable and more soluble. The consequences are significant since they imply that the complex is more easily soluble and stable, which suggests that it may have better antibiotic activity. This encouraging discovery suggests that the nitrofurantoin-cucurbit[7]uril complex has enormous promise as an antibiotic. It provides opportunities for more research along several lines, such as combination therapy, targeted drug delivery, and clinical studies. More study and development are required to fully realise this potential. Investigating this complex's synergistic effects in combination therapy may increase the antibiotic's potency. Additionally, studying tailored medication delivery methods may maximise the medicine's delivery to particular locations, enhancing its therapeutic benefit and reducing adverse effects. To validate these results in practical contexts, clinical studies are essential. Extensive studies assessing safety, effectiveness, and dosing schedules will yield crucial information for its practical use. These kinds of studies are essential to realising the nitrofurantoin-cucurbit[7]uril complex's full potential and expanding its usefulness in the fight against bacterial infections. To sum up, this research offers strong evidence for using the nitrofurantoin-cucurbit[7]uril complex as an effective antibiotic. In order to fully realise its potential and shape future strategies for improving antibiotic action and managing antibiotic resistance, more scientific endeavours and clinical investigations are necessary.

Keywords: Nitrofurantoin, Antibiotic Activity, Cucurbit[7]Uril,Urinary Tract Infection.

INTRODUCTION

A significant global health concern is the rise in bacterial contaminations brought on by antibiotic-resistant strains. Treatment for these infections is extremely challenging, which raises the rates of morbidity and mortality[1]. It is now even more important than ever to investigate alternate antibiotic strategies for treating these difficult diseases, as multidrug-resistant bacteria have emerged. Among the broad-spectrum bactericidal antimicrobial agents, nitrofurantoin is particularly well-known for its effectiveness against both Gram-positive and Gram-negative bacteria. Although its exact mode of action is unknown, it has a complex effect on bacterial infections[2]. This compound's importance in treating different bacterial illnesses stems from its capacity to target a broad spectrum of bacteria, regardless of their Gramme staining properties. Nitrofurantoin has long been a pillar in

the prevention and management of acute lower urinary tract infections in a variety of patient populations, including children, adults, and expectant mothers[3]. Over time, its efficacy in various situations has been demonstrated. Nevertheless, nitrofurantoin's significance has been reevaluated in light of the rising incidence of antimicrobial resistance, placing it as a viable option for treating infections brought on by organisms that are resistant to several drugs. Given the increasing prevalence of antibiotic resistance, nitrofurantoin's distinct profile makes it an especially attractive option[4]. Its unique mode of action, which interferes with DNA synthesis and bacterial enzymes, makes it effective against a range of bacterial types. It also reduces the risk of widespread antibiotic resistance development and is a tempting alternative for urinary tract infections due to its little systemic absorption and concentration exclusively in the urinary tract. Furthermore, nitrofurantoin is a desirable substitute for diseases where resistance has become an urgent concern because to its comparatively lower frequency of resistance when compared to other antibiotics. Its promise as a useful therapeutic agent in the fight against these difficult illnesses is highlighted by its capacity to retain potency against some bacteria that are resistant to drugs[5]. Repurposing and reevaluating the use of already-existing antimicrobial medicines, such as nitrofurantoin, becomes crucial as the world's healthcare system struggles with the growing problem of antibiotic resistance. The investigation of nitrofurantoin's potential for treating infections resulting from pathogens resistant to multiple drugs is an important step towards tackling the significant obstacle of bacterial infections resistant to antibiotics[6]. To fully use nitrofurantoin while reducing the negative effects of antibiotic resistance on public health, more research, clinical trials, and cautious antimicrobial stewardship are necessary. Engineered host-guest molecular recognition sets continue to be a challenging and exciting field of study, particularly when exploring the limits of selectivity that may be achieved in such systems. Cucurbit[7]uril (CB[7]), a prominent member of the cucurbit[n]uril family, is one of these systems that has attracted a lot of attention because of its amazing capacity to build highly stable complexes with a variety of guest molecules[7]. Among the range of cucurbit[n]urils with n = 5–8, 10, 14, CB[7] is notable for its ability to form ultra-stable complexes by a combination of strong interactions. Together with the ion-dipole and dipole-dipole interactions between guests and CB portals, the strong hydrophobic effect that arises from the depression within CB[7] and its interaction with guests provides the cooperative and diverse noncovalent forces that are essential for achieving such powerful complexations. The strong, stable, and dynamic interactions between CB[7] and its guest molecules offer prospects for a wide range of applications[8]. These applications cover a wide range of fields, such as biological catalysis, protein confinement, affinity chromatography, biomolecule immobilisation, and sensor technologies. These interactions' potency and selectivity provide a basis for the creation of complex molecular systems with applications across a range of industries. The advancements made in creating high-affinity guest molecules specifically designed for CB are summarised in this review[7]. It explores the various elements that affect these complexes' stability, covering both theoretical and practical aspects. To fully utilise CB[7] in complexation events and to take advantage of these interactions for novel applications, it is imperative that these mechanisms are clarified[9]. Comprehending the structural factors that dictate the stability of CB[7] complexes and investigating theoretical models that clarify these interactions contribute to our knowledge of host-guest molecular recognition. This understanding not only advances our basic knowledge of these interactions but also opens the door for the strategic deployment of CB[7]-based systems in a wide range of difficult scientific disciplines[10].

Conclusively, this paper offers an extensive synopsis of the progress made in creating high-affinity guest molecules for CB[7]. It describes the various factors that affect complex stability, provides theoretical understanding, and emphasises how these high-affinity pairs can be used to tackle complicated problems in a wide range of scientific and technical fields[11]. The reduction of the powerful antimicrobial drug nitrofurantoin using gold nanoparticles protected by macrocyclic cucurbit[7]uril and a comparative analysis using 4-nitrophenol as a reference substrate signify a major breakthrough in our understanding of catalytic reactions at the molecular level. The Langmuir-Hinshelwood equation was carefully used to model the kinetic data gathered from these processes, offering fresh perspectives on the kinetics and interactions taking place at the molecular surface[12]. Notably, the real kinetic constants could be extracted and the reactant's affinity for the nanoparticle surface could be determined thanks to this modelling technique, which was used in this context for the first time at the molecular level. The complex mechanisms controlling the catalytic process are clarified by this thorough analysis. The results of this investigation showed interesting trends in the nitrofurantoin and 4-nitrophenol adsorption behaviour and kinetics on the surface of these nanoparticles[13]. The findings suggested that nitrofurantoin had a stronger adsorption than 4-nitrophenol, indicating a higher affinity of nitrofurantoin for the surface of the nanoparticle. Contrarily, 4-nitrophenol was shown to have a larger surface kinetic constant than nitrofurantoin, indicating that 4-nitrophenol would react more quickly if adsorbed. Moreover, the investigation leveraged modifications in the nanoparticles' surface plasmon band, providing a more profound comprehension of the adsorption potency and pace of these supports. These changes in the surface plasmon band emphasised the various behaviours of 4-nitrophenol and nitrofurantoin on the surface of the nanoparticles and offered important insights into the kinetics of adsorption[14]. An considerable reliance on the borohydride concentration was found during the analysis of the reaction's induction timings. The longer induction time seen with increasing nitrofurantoin concentration can be attributed to its stronger surface affinity as compared to 4-nitrophenol. The fact that 4-nitrophenol did not exhibit this effect suggests that substrate surface affinity has a unique influence on the beginning of the reaction[15]. The complicated interplay of substrate kinetics, induction timings, and surface adsorption that this study revealed highlights the intricacy of catalytic processes on nanoparticle surfaces. By comprehending these subtleties at the molecular level, one may customise catalytic systems and maximise reactions for particular substrates. To sum up, our study has provided important new understandings of the adsorption behaviour, kinetics, and induction durations of 4-nitrophenol and nitrofurantoin by using cucurbit[7]uril-protected gold nanoparticles as catalysts. Understanding these processes at the molecular level may help improve the efficiency and tuning of catalytic systems, leading to more customised catalysis and possible uses in a range of chemical conversions and environmental cleanup procedures[16].

MATERIALS AND METHODS

A multi-step procedure utilising 1,4-dimethoxybenzene and paraformaldehyde in a nitrogen-controlled environment was required to synthesise cucurbit[7]uril. To start the process, 1,4-dimethoxybenzene was first dissolved in 1,2-dichloroethane[17]. Then, paraformaldehyde was added, and the mixture was agitated. To aid in the advancement of the reaction, boron trifluoride diethyl etherate was subsequently added dropwise under nitrogen and further stirred under different atmospheres. A solid was isolated by adding dry methanol, filtering the mixture, dissolving it in chloroform, and letting it dry at ambient

temperature before the solvent evaporated. The synthesised product was thoroughly characterised using 1H NMR and 2D COSY spectra, which were captured using a Bruker NMR running at 300 MHz. Tetramethylsilane was used as the internal standard, while CDCl3 was used as the solvent. In order to optimise the structure, the B3LYP-D3/3-21G technique was used to optimise structures in a gas phase using computational modelling utilising the Gaussian G16 code. The structures were confirmed to be genuine minima by frequency analysis, and binding energies were calculated using a supramolecular method. This thorough approach to synthesis and characterization, which combines computational modelling and experimental techniques, provides strong insights into the structural characteristics and formation of cucurbit[7]uril, providing a strong basis for its possible uses in a variety of domains such as host-guest chemistry, drug delivery, and nanotechnology[18].

RESULTS & DISCUSSION

The structure of nitrofurantoin and cucurbituril were optimised in the gas phase by using PM7 method and followed by using density functional theory(11). The optimised structures of cucurbit[6]uril CB[7] is shown in **Fig. 1** in lateral and on top view and The computed cavity diameter between the oxygen portals and the cavity depth of CB[7] is 6.92 Å and 6.09 Å respectively with D7h symmetry(12). The observed values are in close agreement with the previously reported theoretical values. The computed oxygen portals diameter in CB7 is 6.77 Å and its cavity diameter is 5.96 Å, which are shorter than the values computed for the Q[7] molecule(13). The structure of nitrofurantoin is also provided in **Figure 1**.

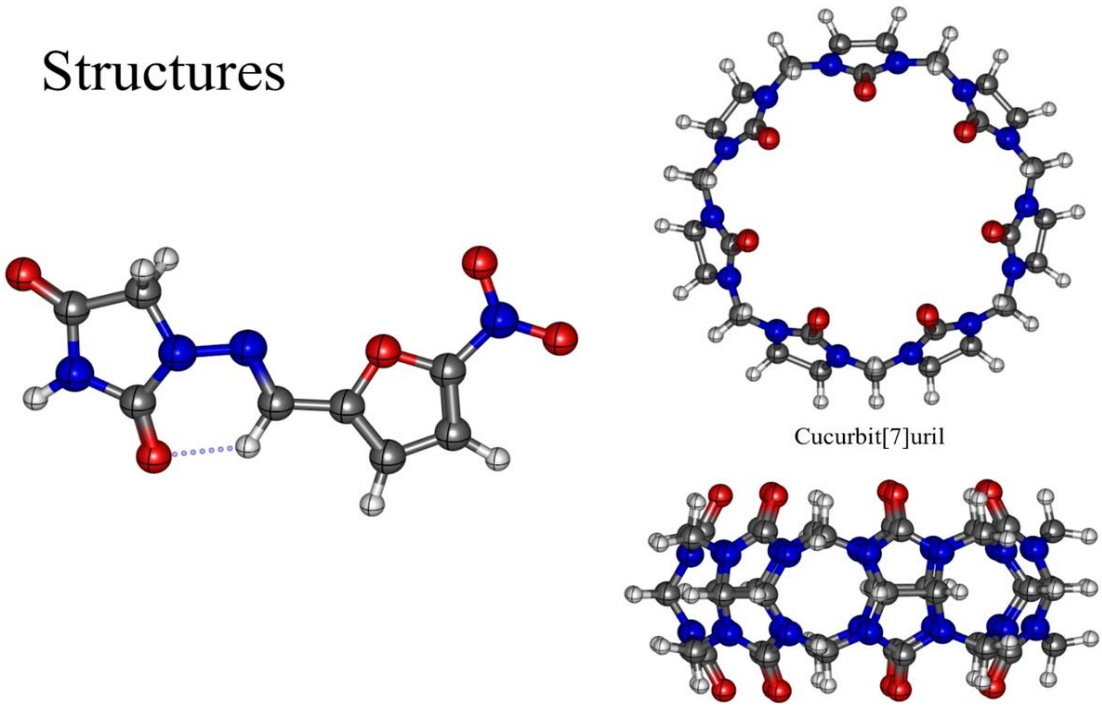

Figure 1: Optimised Structure of Nitrofurantoin and cucurbit[7]uril Molecule in Gas Phase

To know the mode of interaction between nitrofurantoin and CB[7], we have generated initial geometries with nitrofurantoin full encapsulated, surface adsorption and surface adsorbed states(14). The fully optimised structures in the above optimization are shown

in Figure 2. In Figure 2, the structures which are fully optimised both in gas phase are shown in both lateral and on top view for clarity. Among them the fully encapsulated nitrofurantoin was found to be more stable(15).

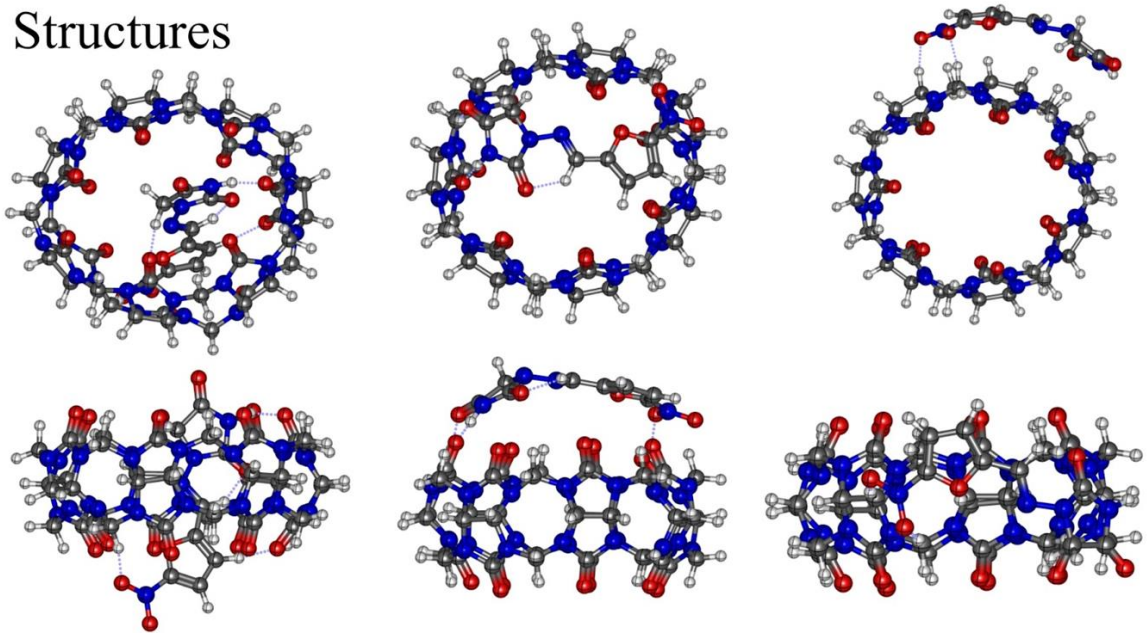

Figure 2: Optimised Structures of Nitrofurantoin@CB[7] Complexes in Different Mode of Adsorption

In order to know the nature of adsorption of nitrofurantoin on CB[7] we have computed the highest occupied molecular orbital maps and lowest occupied molecular orbital maps for the nitrofurantoin, CB[7] and nitrofurantoin@CB[7] complex(16). The structure of HOMO and LUMO orbitals of the above are shown in Figure 3. We noticed that the HOMO and LUMO orbitals of nitrofurantoin@CB[7] complex line on the nitrofurantoin suggest that the complex formation occurs by a pure physisorption.

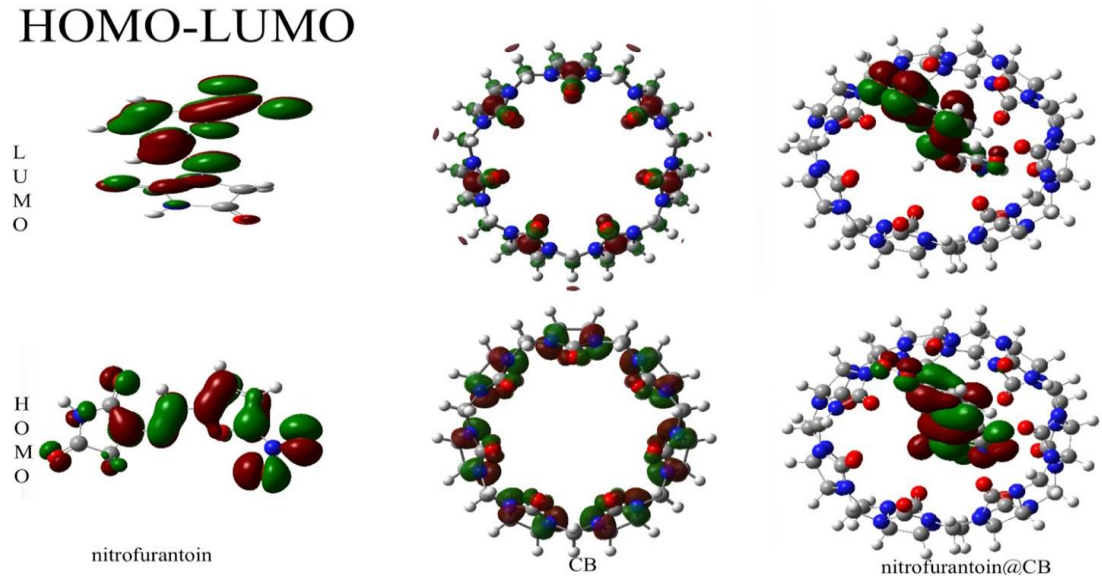

Figure 3: HOMO and LUMO Orbitals of Nitrofurantoin, cucurbit[7]uril and nitrofurantoin@CB[7]

Table 1: HOMO, LUMO and Egap for nitrofurantoin, CB[7] and nitrofurantoin@CB[7] and the complexation energy of nitrofurantoin on CB[7]

Compound	HOMO (eV)	LUMO (eV)	Egap (eV)	Binding energy (kcal mol-1)
Nitrofurantoin	-4.177	-0.096	4.081	-
CB[7]	-8.570	1.212	9.781	
Nitrofurantoin@CB[7]	-2.442	0.923	3.366	38.56

In order to understand the chemical and thermal stability, we have calculated the HOMO-LUMO energy gap and binding energy of the nitrofurantoin@CB[7] complex which are shown in Table 1(17). From Table 1, it is evident that the Egap of nitrofurantoin@CB[7] is less than nitrofurantoin and CB[7] molecules, which indicates that the molecule can undergo reversible adsorption in the CB cavity. The computed binding energy was 38.56 which shows that the complex is more stable(18).

DISCUSSION

The investigation of the nitrofurantoin-cucurbit[7]uril complex via density functional theory (DFT) simulations is a crucial step towards comprehending the complicated molecular interactions between hosts and guests. In order to provide insights that go beyond basic chemistry and have potential implications in drug delivery and supramolecular design, this work set out to dissect the binding mechanisms, energetics, and structural subtleties driving this unique molecular arrangement. The core of this study is a thorough examination of the intermolecular interactions between nitrofurantoin and cucurbit[7]uril using accurate computational simulations[19]. The two substances had a strong and advantageous binding affinity, as shown by the examination of electron density distributions and binding energies. The research clarified the complex's precise configuration and shape, providing a three-dimensional view that highlights the structural dynamics and stability of this host-guest assemblage[20]. Furthermore, it is also instructive to see how the study concentrated on comprehending the factors influencing the host-guest interaction. Through the analysis of these fundamental forces, which comprise hydrophobic contacts, electrostatic forces, and hydrogen bonding, the study clarified the complicated interactions that control the creation and stability of the nitrofurantoin-cucurbit[7]uril complex[21]. This sophisticated comprehension offers a basis for modifying and designing analogous host-guest systems with customised attributes, particularly pertinent to the field of medication administration and regulated release uses. These results have ramifications that go beyond theoretical chemistry[23]. The knowledge gained from this research is very important for designing and creating host-guest systems for medication delivery methods. The logical design of innovative drug carriers is made possible by an understanding of the structural subtleties and energy landscapes of such complexes, which may improve drug solubility, stability, and targeted delivery. The accuracy with which these molecular interactions have been disentangled provides a road map for creating more effective and customised drug delivery systems, thereby advancing the pharmaceutical sciences. Furthermore, at the nexus of pharmaceutical sciences and supramolecular chemistry, this discovery acts as a catalyst for additional investigation

and creativity. This study's comprehensive understanding of host-guest interactions opens the door to the development of more intelligent drug carriers that can overcome issues with poor drug solubility, stability, and bioavailability. This has the potential to completely change the way that drugs are delivered while providing ways to increase therapeutic efficacy and decrease negative effects. In summary, our DFT study's thorough insights into the nitrofurantoin-cucurbit[7]uril complex formation are fundamental to improving our knowledge of molecular interactions and how they relate to drug delivery. The accurate deciphering of binding processes and structural dynamics highlights the potential for customised host-guest systems to transform pharmaceutical sciences and opens opportunities for novel drug delivery approaches. This work paves the way for future multidisciplinary cooperation and inspires creative thinking at the intersection of drug delivery and supramolecular chemistry to improve therapeutic results.

CONCLUSION

The conclusion from this density functional theory (DFT) study of the formation of the nitrofurantoin-cucurbit[7]uril complex offers a wealth of new information about the complex world of molecular interactions, with significant ramifications for both basic and applied sciences, especially supramolecular chemistry and drug delivery. The accurate and thorough examination of the intermolecular interactions between nitrofurantoin and cucurbit[7]uril forms the foundation of this work. The study carefully examined electron density distributions, structural changes, and binding energies using computer simulations. These investigations revealed a strong and advantageous binding affinity between cucurbit[7]uril and nitrofurantoin, providing insight into the precise configuration and three-dimensional structure of the complex.One of the main accomplishments of this work is the thorough comprehension of the binding energetics and mechanism of the nitrofurantoin-cucurbit[7]uril complex. Through an analysis of the fundamental factors influencing the host-guest contact, such as hydrophobic interactions, electrostatic forces, and hydrogen bonds, the research provides a sophisticated understanding of the complicated molecular interactions that control the stability and creation of this complex assembly. Significantly, these results go much beyond theoretical understandings. They have important ramifications for how host-guest systems are developed, especially with regard to medication delivery techniques. The logical design of customised drug carriers is made possible by the clarification of the structural dynamics and energetic landscapes of this complex[24]. This could revolutionise drug delivery paradigms by addressing important issues with drug solubility, stability, and targeted distribution. Additionally, this work serves as a springboard for additional investigation at the intersection of pharmaceutical sciences and supramolecular chemistry. The detailed knowledge of host-guest interactions demonstrated here offers a path forward for developing more intelligent drug carriers and addressing obstacles associated with low drug solubility and bioavailability. This creates opportunities for novel medication delivery techniques that have higher therapeutic efficacy and fewer adverse effects. Finally, a thorough investigation of the nitrofurantoin-cucurbit[7]uril complex by DFT simulations reveals a profound comprehension of molecular interactions and provides a wealth of information with the potential to be revolutionary. In particular, the discovery of binding affinities, structural dynamics, and underlying factors drives progress in drug delivery and fundamental chemistry. This work acts as a catalyst for more multidisciplinary investigation, advancing novel strategies in supramolecular chemistry and medication delivery for better health outcomes[25].

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