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MODELING AND OPTIMISATION OF COMLEXITY BY THE *β*-CYCLODEXTRIN OF AN ORGANIC POLLUTANT MODEL: m-METHYL RED

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Abstract. Studies of cyclodextrin chemistry using quantum chemical methods are mainly adopted to investigate the formation of the inclusion complex causing changes in the physicochemical properties of the cyclodextrin guest. In this paper, we conducted a computational modeling study of the inclusion complexes of *β*-cyclodextrin (*β*-CD) with m-Methyl Red (m-MR) by using parametric method 6 (PM6), the semi empirical molecular orbital calculations and the natural bond orbital method (NBO). The inclusion process is carried out by maintaining the coordinates of the *β*-CD fixed and by displacing the guest molecule. The different relative positions between m-MR and *β*-CD are measured with respect to the distance between the reference atom (N) in the guest molecule and the origin of the coordinates from the equatorial plane of *β*-CD. The m-MR/*β*-CD (B) inclusion complex has a lower negative value of ΔG compared to another m-MR/*β*-CD (A) complex, highlighting the spontaneous behavior of the inclusion process. In addition, during the process of inclusion, the complexation energy is negative, which allows us to affirm that the complexation of m-MR in the *β*-CD is thermodynamically favorable. Among two directions A and B, the minimum energy generated from the PM6 was obtained in the orientation B and the guest molecule is partially encapsulated in the cavity of *β*-CD. In the NBO analysis, the stabilization energy is also usually used to characterize the hydrogen bond interaction between a lone pair (LP(Y)) of an atom Y and an anti-bonding orbital (BD*(X-H)).[1]

Keywords: cyclodextrin, m-Methyl Red, inclusion complex, PM6, NBO analysis.

1. Introduction

Supramolecular chemistry is a central theme not only in chemistry, but it overlaps other disciplines including, physics and biological sciences.[1] Supramolecular chemistry is the study of systems involving aggregates of molecules or ions held together by non-covalent interactions,[2] such as electrostatic interactions, hydrogen bonding, dispersion interactions, and solvophobic effects.[3] Supramolecular chemistry aims at developing highly complex chemical systems from components in interacting by noncovalent intermolecular forces.[4] Many metabolically important compounds, such as lipid-soluble vitamins and hormones, have very low solubility in aqueous solutions.[5] Various techniques have been used to solubilize these compounds in tissue culture, cell culture, or other water-based applications.[6] A frequently used approach is to use cyclodextrin as a "*carrier*" molecule to facilitate the dissolution of these compounds.[7] Cyclodextrin are a family of cyclic oligosaccharides consisting of a macrocyclic ring of glucose subunits joined by *α*-1,4 glycosidic bonds.[8] They are widely used in foods, cosmetics, pharmaceuticals, and agrochemicals products[9] due to their excellent ability to form molecular inclusion complexes with volatile or labile substances and to stabilize them.[10]

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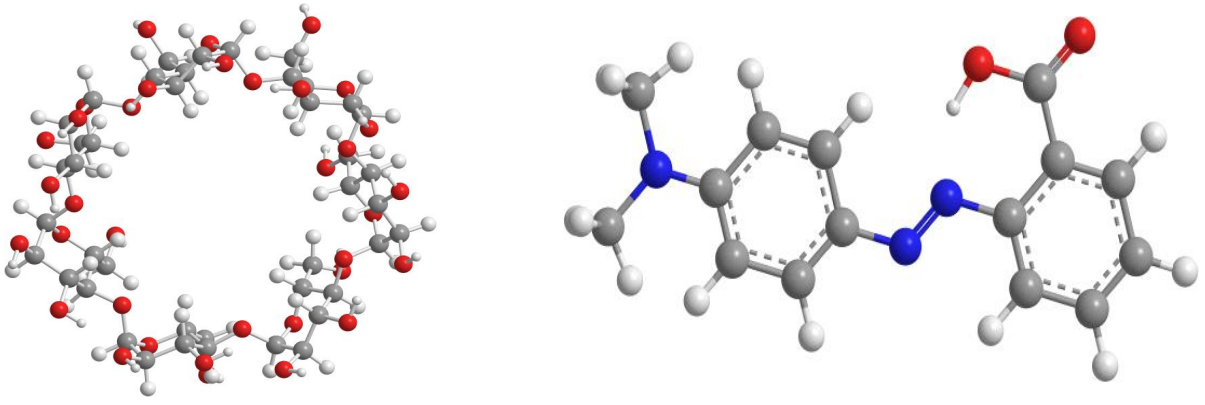
One of the first studies of cyclodextrin was published by Villiers in 1891.[11] Three cyclodextrines, namely, α-CyD, β-CyD and γ-CyD have six, seven and eight glucose units, respectively.[12] Cyclodextrin possess the overall shape of a hollow truncated cone, the narrow rim bearing primary hydroxyl groups and the wide rim secondary hydroxyl groups.[13] However, the high solubility of cyclodextrin in aqueous medium significantly limits its application in the removal of organic pollutants from water. Numerous experimental and theoretical studies have been conducted in recent years to better predict and understand the structures, properties, and molecular interactions of supramolecular systems.[14] A combination of experimental and theoretical approaches has been found to be very effective in solving problems related to the formation of inclusion complexes.[15] The formation of the inclusion complex causes changes in the physico-chemical properties of the guest molecules, in particular, stability in water and stability in solution. For this it is important to determine its stability in solution.[16] Molecular modeling is used to simulate molecular systems, quantum mechanics (QM), molecular dynamics (DM), and molecular mechanics (MM).

In recent years, the QM/MM association seems to be very promising.[17] There are many experimental studies concerning the complex β-cyclodextrin and Methyl Red.[18] Khouri *et al.*[8] proposed an inclusion model of the m-MR/β-CD, and according to the obtained results, they confirm the formation of the inclusion complex with a 1:1 stoichiometry.[19]

Therefore, in the present study, we propose a theoretical study of the m-MR/β-CD complex using a set of computational methods. Specifically, an attempt was made to determine the optimal geometric structure and the nature of the intermolecular interactions between host and guest molecules. These methods are also used to describe the changes experienced by m-MR following complexation, as well as some electronic and thermodynamic properties. .Recently developed semi-empirical methodologies augmented with dispersion and hydrogen bonding corrections such as PM6-DH$^+$, PM6-DH2, PM6-D3H4 and PM7 are improved, thus allowing a better description of noncovalent interactions, especially hydrogen-bonding.[20]

2. Calculation Methodology

All calculations were performed using Gaussian software 09.[21] The initial structure of β-CD (Fig. 1) was constructed with CS Chem3D Ultra (version 10, Cambridge software) of crystal structure[22] and fully optimized by the semi empirical PM6, while the initial structure of acid m-Methyl Red (m-MR) was constructed by the Hyperchem module manufacturer[23] optimized with the PM6 method.[24]

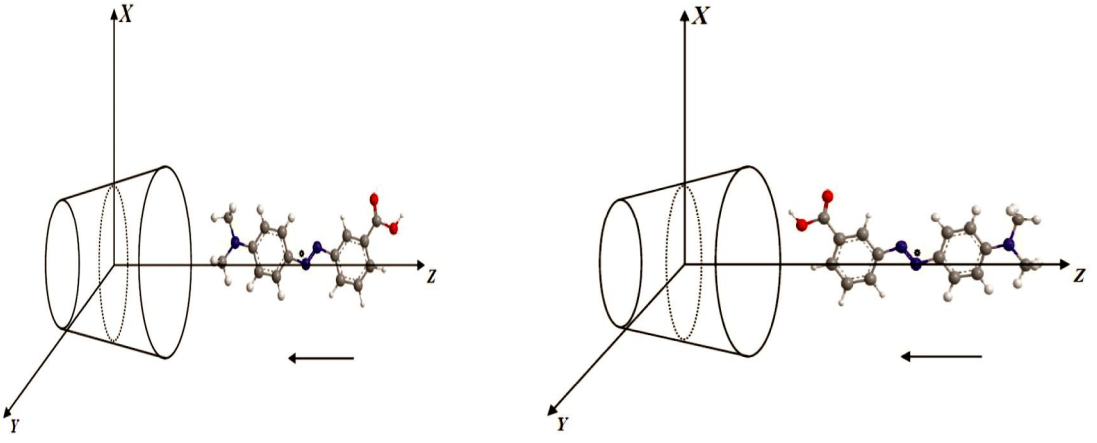


a) b)

Fig. 1. The geometric structures of the β-CD (a) and m-MR (b) optimized by PM6

In the present study, the inclusion process was conducted according to the method proposed by Liu *et al.*,[7] for which the glycosidicoxygens of the host molecule (β-CD) are placed in the XY plane, and their center is defined as the center of origin coordinates of the total system[25]. The inclusion process is carried out by maintaining the coordinates of the β-CD fixed and by the simultaneous translation of the guest molecule placed on the axis OZ. The different relative positions between m-MR and β-CD are measured with respect to the distance

between the reference atom (N) in the guest molecule and the origin of the coordinates of the equatorial plane of *β*-CD. We have considered two inclusion orientations to get into the cavity of the *β*-CD (Fig. 2). The m-MR located at the distance of 9 Å from the origin of the Cartesian coordinates is manually brought closer to the cavity of the *β*-CD along the axis OZ, in steps of 1 Å up to the point from 10 Å. After locating the minimum in the translation, the molecule (m-MR) was rotated around the OZ axis by 30° angle from 0° to 360° to explore more conformational space. At each position, the system is optimized without restriction using the semi empirical PM6 method. Thus, it is possible to locate the absolute minimum. It should be noted that the use of these local minimums makes it possible both to plot the curves of the complexation energy as a function of the distance between the reference atom and the center of the *β*-CD along the axis OZ.



a) b)

Fig. 2. Coordinate system used to define the inclusion process orientation A (a) and orientation B (b)

3. Results and Discussion

The complexation energy is calculated according to Eq. (1):[26]

$$\Delta E_{\text{complexation}} = E_{\text{complex}} - (E_{\text{guest}} + E_{\beta\text{-CD}}) \quad (1)$$

where $E_{\beta\text{-CD}}$ is the energy of *β*-CD before complexation; E_{guest} is the energy of the guest molecule before complexation; E_{complex} is the energy of the complex.

3.1. Search for the Minimum

The overall minimum was carried out by the semi empirical method PM6 because a large number of theoretical studies on the inclusion complexes were carried out with this approach, which proved to be adequate for the treatment of macro molecules. The inclusion process is illustrated in Fig. 3. For the orientation A, the minimum is located at the point Z = 5 Å, position for which the molecule FF is totally encapsulated in the cavity of the *β*-CD (*E* = -77.91 kJ/mol). For model B, the minimum is located at the distance Z = 2 Å, the complexing energy is -91.31 kJ/mol. We note that in the process of inclusion, the complexation energy is negative, which allows us to affirm that the complexation of m-MR in the *β*-CD is thermodynamically favorable.

The structures that correspond to the minimum energy in orientations A and B obtained with PM6 are presented in Fig. 4. For orientation B, the guest molecule is partially encapsulated in the cavity of *β*-CD.

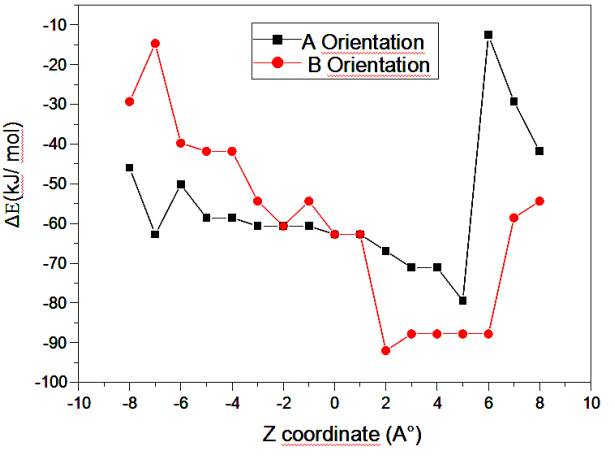


Fig. 3. Stability energies of the inclusion complexation of m-MR into *β*-CD at different positions calculated by PM6 method

a) b)

Fig. 4. The energy minimum structure obtained by the PM6 calculation: Orientation B (a) and Orientation A (b)

The complexing energies are equal to -77.78 kJ/mol for the A orientation and -91.16 kJ/mol for the B orientation. There is an energy difference of 13.38 kJ/mol between two orientations. In general, the complex with the most negative energy value is considered the most favored (orientation B). The energies of the HOMO and LUMO are important parameters in the calculations of quantum chemistry. HOMO represents the ability to donate an electron and LUMO represents the ability to gain an electron. The energy gap between the HOMO and LUMO ($E_{HOMO} - E_{LUMO}$) is one of the most important stability factors for chemical species.[13] The stability of chemical products is directly related to the $E_{HOMO} - E_{LUMO}$ energy gap and, moreover, the large energy gap values tend to have high stability. The calculated results are reported in Table 1. The $E_{HOMO} - E_{LUMO}$ energy gap for the B orientation was obtained larger than the other complexes, suggesting that this complex is more stable. For the most stable complexes, the physical parameters such as the electronic chemical potential (μ), hardness (η), stability (S), and electrophilicity (ω) are determined according to the formulas below:

$$\mu = (E_{HOMO} + E_{LUMO})/2 \quad (2)$$

$$\eta = (E_{HOMO} - E_{LUMO})/2 \quad (3)$$

$$S = 1/\eta \quad (4)$$

$$\omega = \mu^2/2\eta \quad (5)$$

Table 1. Characteristic energy values of the most stable structures of the complexes m-MR/β-CD

	m-MR	β-CD	Orientation A	Orientation B
E, kJ/mol	31.78	-6551.08	-6597.22	-6610.62
$E_{complexation}$			-18.61	-21.81
E_{HOMO}, eV	-4.561	-10.757	-4.844	-4.694
E_{LUMO}, eV	-3.872	16.796	-3.732	-3.539
$E_{HOMO} - E_{LUMO}$, eV	-0.689	-27.553	-1.112	-1.155
μ	-4.2165	3.02	-4.288	-4.116
η	-0.3445	13.77	-0.556	-0.577
S	-2.90275	-3.02	-1.798	-1.731
ω	-25.80387	0.33	-16.535	-14.671

The values of the m-MR/β-CD complexes differ from the isolated guest molecules and the host as shown in Table 1. The value of m-MR molecule (-4.2165 eV) is lower than that of β-CD (3.02 eV), so the m-MR acts as electron acceptors in the inclusion complexes. The electrophilicity of the components was calculated using Eq. (1). The polarity of the CD cavity is also considered before and after the formation of the most stable inclusion complexes. The polarity of the cavity of the CDs changed after the inclusion of the guest in the cavity.[27] Finally, based on the results of the PM6 semi-empirical study, all inclusion complexes showed high dipole moment values compared to the isolated guest molecule, while for CDs the values were higher or inferior. This indicates that the polarity of the CD cavity has changed after complexation. From these results, we can conclude that the values of the dipole moments show a strong correlation with the complexing behavior of the m-MR molecule.

3.2. Thermodynamic Analysis of the m-MR/β-CD Complexation Process

To study the thermodynamic parameters of the complexation process, the thermodynamic calculation was carried out at the pressure of 101 kPa and the temperature of 298.15 K by the PM6 method. Thermodynamic quantities: enthalpy variations (ΔH), Gibbs energy changes (ΔG) and entropy contributions (ΔS) are shown in Table 2. All these values for all inclusion complexes are more negative than the corresponding isolated species. The negative energy variation (ΔG) of inclusion complexes means that inclusion is a spontaneous process at room temperature. The m-MR/β-CD (B) inclusion complex has a lower ΔG negative value (-11.43 kJ/mol) than another m-MR/β-CD (A) complex, which shows that its inclusion process is more spontaneous.

Table 2. Thermodynamic parameters for β-CD, m-MR, complexes A and B calculated by the PM6 method

	m-MR	β-CD	Orientation A	Orientation B	Results of experimental study[8]
H, kJ/mol	753.06	-3513.20	-2828.77	-2844.15	–
ΔH^0, kJ/mol	–	–	-68.63	- 84.01	-88.90
G, kJ/mol	575.66	-4047.95	-3475.71	-3483.69	–
ΔG^0, kJ/mol	–	–	-3.42	-11.41	-88.95
S, kJ/mol	595.01	1793.42	2170.42	2151.88	–
ΔS^0, kJ/mol	–	–	-218.02	-236.58	1.67

3.3. Geometric Parameters

In Table 3 we present the geometrical parameters (bond lengths and dihedral angles) of the m-RM molecule before and after complexation, calculated by the PM6 method for the most stable structures in the A and B complexes. For the m-MR complexed results, it is clear that the geometric structure is completely altered. This alteration is very significant through the large variation of the dihedral angles of m-MR which has undergone a great distortion to adopt a specific conformation leading to the formation of the most stable complex. These conformational changes in the guest molecule are dictated by steric adaptation.

Table 3. Geometrical parameters of m-MR before and after inclusion in β-CD, bond distances, bond angles and dihedral angles calculated by PM6 method

m-MR		Orientation A	Orientation B
1		2	3
Bond lengths, Å			
C(148)-C(149)	1.4776	1.4748	1.4748
C(148)-O(155)	1.2100	1.2173	1.2173
C(148)-O(156)	1.3827	1.3745	1.3745
C(149)-C(150)	1.4018	1.3995	1.3995
C(149)-C(154)	1.4039	1.4063	1.4063
C(150)-C(151)	1.4071	1.4073	1.4073
C(151)-C(152)	1.4083	1.4054	1.4054
C(151)-N(157)	1.4446	1.4401	1.4401
C(152)-C(153)	1.3965	1.3990	1.3990
Bond angles, grad			
H(182)-C(167)-H(181)	108.5193	107.6621	107.6621
H(182)-C(167)-H(180)	107.5888	107.0528	107.0528
H(182)-C(167)-N(165)	110.8950	111.1982	111.1982
H(181)-C(167)-H(180)	107.5888	108.5297	108.5297
H(181)-C(167)-N(165)	110.8950	113.0605	113.0605
H(180)-C(167)-N(165)	111.2137	109.1291	109.1291
H(179)-C(166)-H(178)	108.8397	108.4506	108.4506

Continuation of Table 3

1		2	3
H(179)-C(166)-H(177)	107.4802	107.2849	107.2849
H(179)-C(166)-N(165)	110.6484	108.7985	108.7985
H(178)-C(166)-H(177)	107.4802	107.4848	107.4848
Dihedral angles, grad			
O(155)-C(148)-C(149)-C(154)	180.0000	-177.1513	-177.1513
O(155)-C(148)-C(149)-C(150)	0.0000	2.5989	2.5989
O(156)-C(148)-C(149)-C(154)	0.0000	2.7286	2.7286
O(156)-C(148)-C(149)-C(150)	180.0000	-177.5212	-177.5212
C(149)-C(148)-O(156)-H(172)	180.0000	-179.7470	-179.7470
O(155)-C(148)-O(156)-H(172)	0.0000	0.1476	0.1476
C(154)-C(149)-C(150)-C(151)	0.0000	1.3686	1.3686
C(154)-C(149)-C(150)-H(168)	180.0000	-178.7730	-178.7730
C(148)-C(149)-C(150)-C(151)	180.0000	-178.3848	-178.3848
C(148)-C(149)-C(150)-H(168)	0.0000	1.4736	1.4736

3.4. Natural Bond Orbital (NBO) Analysis

The donor-acceptor interactions for hydrogen bonds, donate from a filled orbital of the electron donor to an empty orbital of the electron acceptor were performed using NBO 3.1 program implemented in the Gaussian 09 package. In the NBO analysis, the stabilization energy ($E^{(2)}$) is used to characterize the interaction between occupied Lewis-type NBO orbitals and formally unoccupied non-Lewis NBO orbitals which act as the delocalization trend of electrons from the bonding (BD) or nonbonding orbitals (LP) to the anti-bonding orbitals (BD).[28] So, the stabilization energy ($E^{(2)}$) is also usually used to characterize the hydrogen bond interaction between a lone pair (LP(Y)) of an atom Y, and an anti-bonding orbital (BD*(X-H)). The stabilization energies $E^{(2)}$ of two models calculated using R m062x /6-31G(d, p) single point methods in vacuum and in water are shown in Table 4. The interactions are in detail: (i) the m-MR plays the role of donor, the important intermolecular hydrogen bond is observed between LP(2) O75 and σ^*(1) C159-H174 with energy equal to 27.54 kJ/mol, and (ii) on the other side, when the m-MR is an acceptor, the important H-bond is formed between σ(1) C160-H177 and σ^*(1) O69-H141 with energy of 25.87 kJ/mol.

Table 4. Donor-acceptor interactions and stabilization energies $E^{(2)}$ calculated for A model

Donor	Acceptor	$E^{(2)}$ B3LYP/6-31G(d, p), kJ/mol
β-CD proton donor and m-MR proton acceptor		
σ(1) C29-H109	σ^*(1) C158-H171	18.47
σ(1) O69-H141	σ^*(1) C160-H177	19.26
LP(1) O56	σ^*(1) C163-H178	06.47
LP(2) O56	σ^*(1) C163-H178	14.67
LP(1) O67	σ^*(1) O148-H182	14.54
LP(2) O67	σ^*(1) O148-H182	19.47
LP(2) O75	σ^*(1) C159-H174	27.54
m-MR proton donor and *β*-CD proton acceptor		
σ(2) C155-C158	σ^*(1) C21-H100	10.49
σ(2) C155-C158	σ^*(1) C33-H114	06.81
σ(1) C158-H171	σ^*(1) C29-H109	15.59
σ(1) C160-H177	σ^*(1) O69-H141	25.87
σ(2) C165-C166	σ^*(1) C12-H52	04.51
LP(1) O148	σ^*(1) C30-O68	04.80
LP(1) O149	σ^*(1) C36-H117	06.10
LP(1) O149	σ^*(1) O47-H128	12.20
LP(2) O149	σ^*(1) C36-H117	11.16
LP(2) O149	σ^*(1) O47-H128	09.94

4. Conclusions

In this work, we used quantum chemistry methods to model inclusion complexes. The methodology adopted through the PM6 approach has allowed us to rationalize the electronic structure and the geometry of the m-MR/*β*-CD complexes, for which we have found that the substantial structural changes of the m-MR molecule are at the origin of its encapsulation in the *β*-CD. The results confirm that the complexation energy of the B complex in is much more favorable than that of the A complex. The calculated negative values of the enthalpies Δ*G*, Δ*H* and Δ*S* indicate that the formation of the inclusion complex m-MR/*β*-CD is a spontaneous process. The study of chemical reactivity has allowed us to observe that m-RM is more electrophilic than *β*-CD. The higher the electrophilic index, the more electrophilic the system and the greater the energy of stabilization. Based on this reasoning, we can conclude that complex B is the most stable and the most electrophilic. The HOMO-LUMO energy gap of each complex suggests a substantial change in the electron structure of the host molecule. The HOMO-LUMO gap of the B complex is larger, so it is more stable and less reactive. The results indicate that, compared to its initial geometry, the m-MR molecule undergoes a substantial changes in certain bond lengths and dihedral angles after complexation, so that it can adopt a specific conformation within the cavity and the molecular host allows it to form a stable inclusion complex.

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МОДЕЛЮВАННЯ ТА ОПТИМІЗАЦІЯ СКЛАДНОСТІ ЗА *β*-ЦИКЛОДЕКСТРИНОМ МОДЕЛІ ОРГАНІЧНОГО ЗАБРУДНЮВАЧА: МЕТИЛ М-ЧЕРВОНИЙ

Анотація. *Проведено моделювання адуктів β-циклодекстрину (β-CD) з м-метиловим червоним (m-MR) за допомогою параметричного методу 6 (PM6), напівемпіричних молекулярних орбітальних розрахунків та методу натуральної орбіталі (NBO). Показано, що реакція приєднання відбувається внаслідок підтримання фіксованих координат β-CD та переміщення гостьової молекули. Різні положення між m-MR та β-CD вимірюються щодо відстані між еталонним атомом (N) гостьової молекулі та початком координат екваторіальної площини β-CD. Встановлено, що адукт m-MR/β-CD (комплекс B) має нижче негативне значення ΔG порівняно з іншим m-MR/β-CD (комплексом A), що підкреслює спонтанну поведінку процесу приєднання. Крім того, під час приєднання енергія комплексоутворення є негативною, що дає можливість стверджувати, що комплексоутворення m-MR у β-CD є термодинамічно вигідним. Встановлено, що мінімальну кількість енергії PM6 отримують в орієнтації B, а гостьова молекула частково інкапсульована в порожнині β-CD. За допомогою NBO аналізу проведено характеристику взаємодії водневих зв'язків між одинокою парою (LP(Y)) атома Y та антизв'язуючою орбіталлю (BD□(X-H)).*

Ключові слова: *циклодекстрин, м-метиловий червоний, адукт, PM6, NBO аналіз.*