Computational Exploration of Functionalized Rhombellanes: Building Blocks and Double-Shell Structures

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Abstract: Double-shell covalent assemblies with the framework of the cube–rhombellane were recently proposed as potential drug delivery systems. Their potential to encapsulate guest molecules combined with appropriate surface modifications show great promise to meet the prerequisites of a drug carrier. This work reports the molecular design of such clusters with high molecular symmetry, as well as the evaluation of the geometric and electronic properties using density functional theory. The computational studies of the double-shell assemblies and their corresponding building blocks were conducted using the B3LYP/6-31G(d,p) method as implemented in Gaussian 09. The results show that the assembly of the building blocks is energetically favorable, leading to clusters with higher stability than the corresponding shell fragments, with large HOMO–LUMO gap values. In case of aromatic systems, interlayer stacking interactions between benzene rings contribute to the molecular geometry and stability. During geometry optimization the clusters preserve the high molecular symmetry of the building blocks.

Keywords: double-shell structures; DFT; cube–rhombellanes; covalent assembly; van der Waals interaction; drug delivery

1. Introduction

Over the past years great effort was dedicated to the synthesis of molecular assemblies which provide cavities that enable the encapsulation of guest molecules in a wide range of size scales. Cryptophanes [1] and carcerands [2] were the first cage-like molecular complexes based on covalent bonds. Subsequently, host molecules with space-restricted properties were assembled by metal–ligand interactions [3] or weak interactions like hydrogen bonds [4,5].

A particularly fascinating class of double- and multi-shell molecules is the spherical carbon nanostructures, known as onion or nested fullerenes. They consist of several concentric graphitic layers where a giant fullerene encapsulates progressively smaller cages. In such assemblies, weak nonbonding inter-shell interactions exist; therefore, the distance between adjacent shells plays a major role in the stability [6,7].

The hypothetical double-shell hydrocarbon called hyper-cubane [8] and its functionalized derivatives [9] were proposed and computationally investigated.

The recently proposed [10,11] cube–rhombellane 1a is a double-shell structure, designed by graph–theoretical transformation called “rhombellation” of the cube [10], which serves as a framework for chemical structures with both high complexity and symmetry, hereafter called rhombellanes. The
core of the framework is the cube, shown as green spheres in Figure 1. The surface layer of 1a is composed of six hexavalent and eight trivalent vertices, shown as red and yellow spheres, respectively. The molecular realization of 1a requires the appropriate structural fragments that can establish up to six connections with neighboring atoms. According to the purpose, six-fold rings, i.e., cyclohexane or benzene, were found to be suitable.

![Figure 1. The dual layer cube–rhombellane (a) and derived frameworks (b, c).](image)

Structure 1b represents the homeomorph of 1a, where the violet spheres (Figure 1) represent molecular linkers for the covalent binding of the two layers. In structure 1c the relative position of the four hexavalent vertices (blue spheres) in the inner shell of 1a is highlighted.

Our previous computational results on rhombellanes [12] have shown that rhombellanes are potential alternatives as drug carriers, indicated by their ADME (absorption, distribution, metabolism, and excretion) properties. To serve as a drug delivery system the molecule should possess several prerequisites, including sufficiently strong adsorptive effects towards bioactive molecules, to ensure the delivery to the target site. Therefore, further studies were performed on rhombellanes to evaluate the immobilization potential of different organic compounds. Several rhombellanes showed satisfying binding affinities towards different ligand molecules, including indirubin derivatives (ChEMBL474807 molecule) [13], oxindole derivatives [14], and cisplatin [15], investigated by molecular docking methods. The results confirmed that the distribution of the hydrogen bond donors and acceptors on the surface of rhombellanes, as well as stacking interactions between aromatic systems of both molecules, significantly contribute to the binding capacity of such systems.

These findings further motivated us to perform a systematic study to find which building blocks are suitable for the assembly of rhombellanes, from both a geometric and stability point of view. This paper presents the computational investigation using density functional theory (DFT) of both the inner (core) and surface layers and the corresponding double-shell assemblies of some rhombellanes with high molecular symmetry. Although it is not explored in this work, another important feature of this class of compounds is their hollow inside, which enables them to encapsulate metal atoms or smaller guest molecules.

2. Methods

Ground state geometries and electronic properties of the discussed structures were obtained using density functional theory. Initial geometries were fully optimized using the hybrid density functional B3LYP and 6-31G(d,p) basis set, and the Cartesian coordinates of all molecules are provided in the Supplemental Materials. To ensure that optimized structures correspond to a stationary point, vibrational frequencies were computed at the same level of theory. All calculations were performed using the Gaussian 09 computational chemistry software package [16].

The initial geometries of the double-shell clusters converged during optimization only if the input geometry was built from the already geometry optimized layers, and most importantly the linkers between the layers were positioned to maintain the molecular symmetry. For the geometry optimization, tight convergence criteria and symmetry constraints were applied. However, even...
without symmetry constraints, the structures maintained their starting point group symmetry during geometry optimization.

3. Results and Discussion

3.1. Structural Models

In the present study, only core building blocks with C–O–C linkage between carbon rings (both benzene and cyclohexane) were selected. For the surface layer we limited the selection to molecules where the aromatic rings are connected by ester or amide chemical bonds. Although several double-shell clusters were designed from such fragments, in this work only the energetically feasible rhombellanes are presented. Building of a cluster with the framework of rhombellane requires that the surface layer can easily accommodate the core fragment, and also, they must be properly oriented such that linkers can covalently bind the two layers with the least geometric strain. Both fragments have high molecular symmetry; the inner layer has octahedral ($O_h$) or tetrahedral ($T_d$), whereas due to the amide and ester bonds the surface layer has tetrahedral ($T$) point group symmetry.

3.1.1. Core Building Blocks

The molecules 2a–2f displayed in Figure 2 correspond to the core building blocks of the double-shell structures. Each structure included eight six-fold rings arranged at the vertices of a cube, which were linked by oxygen atoms, shown as red spheres in Figure 2. Structures 2a–2d were built only from cyclohexane rings, where the linking oxygen atom was connected to either equatorial or axial positions. Structure 2e consisted of eight benzene rings in an octahedral arrangement, whereas 2f contained both aromatic and cycloaliphatic rings, which were aligned at the vertices of a tetrahedron. Notice that each cyclohexane ring adopted a chair conformation. With one exception, structure 2b, the oxygen atoms pointed outwards from the carbon cluster.

![Figure 2](image_url)

**Figure 2.** Optimized geometries of the core fragments considered for the assembly of double-shell structures. To highlight the position of the aromatic and cyclohexane rings, the figure displays the perspective views of the molecules. Carbon rings are linked via an ether bond, and the red spheres correspond to the oxygen atoms. Delocalized bonds reveal the location of aromatic rings in 2e and 2f.
The aliphatic and the aromatic units found in clusters 2a–2d correspond to 1,3,5-cyclohexanetriol and 1,3,5-benzenetriol, respectively. Although in the present study only structures with etheric bonds were investigated, other linkers (i.e., C–N–C bonds) could also be considered to connect adjacent carbon rings. To preserve the high molecular symmetry, it is mandatory that the rings maintain their relative positions.

When they were part of the double-shell assembly, only four rings from the inner layer were covalently connected to the surface layer. Linkers were attached to the carbon atoms, which did not have a neighboring oxygen atom. Therefore, these rings had six connections, and they correspond to the hexavalent blue atoms from structure 1c.

The core fragments were hollow on the inside and could encapsulate smaller molecules or metal atoms, which could enhance targeted drug delivery [17].

3.1.2. Shell Building Blocks

Figure 3 shows possible candidate molecules 3a–3d, which correspond to the outer layer in the assembly of the double-shell structures. Their energy-minimized geometry (Figure 3) shows that they have a spherical shape and are hollow molecules that can accommodate guest molecules 2a–2f.

![Figure 3. Optimized geometries of the surface layers. The two types (distinct number of connections) of aromatic rings are highlighted in violet and orange, respectively. Molecules 3a and 3b are viewed along the C3 rotation axis, whereas 3c and 3d are aligned along the twofold rotation axis.](image)

Only aromatic rings were included in the carbon framework and were connected by means of amide (3a and 3c) or ester (3b and 3d) bonds. There were two symmetry distinct rings, which were connected in an alternating pattern. One type of benzene ring had three neighbors and were aligned along the threefold rotation axis (marked in violet in Figure 3), whereas those with four adjacent aromatic rings were positioned along the twofold symmetry axis (highlighted in orange in Figure 3). Structures 3a and 3b were composed of 14 aromatic rings; the removal of four three-connected rings resulted in their corresponding molecules 3c and 3d, respectively.
Covalent connection with the core layer was realized by the attachment of functional groups to the two non-substituted carbon atoms in the orange benzene rings. These aromatic rings correspond to the hexavalent red vertices from cube–rhombellane 1a; accordingly, each carbon was a junction point to a neighboring ring.

3.1.3. Double-Shell Assemblies

The covalent clusters shown in Figure 4 were designed by the connection of the corresponding core and shell fragments by means of –CH₂O– linkers. Twelve junctions linked the two building blocks by means of covalent bonds. The studied assemblies are shown in Figure 4, where the carbon framework of the inner layers is highlighted in green. Clusters 4a and 4b were achieved by joining together a core fragment 2f with shell structures 3c and 3d, respectively. Since molecule 2f included both aromatic and aliphatic rings, the linkers were attached only to the cyclohexane rings. Energetically favorable assembly between the core layer 2c and shell fragment 3a resulted in structure 4c.

![Figure 4](image-url)

**Figure 4.** Optimized geometries of double-shell cube–rhombellane structures where the core and shell building blocks are connected by –CH₂O– linkers. In each structure, the core fragment atoms are highlighted in green.

3.2. Computational Results

Each structure was energy minimized using the B3LYP functional and the 6-31G(d,p) basis set. The obtained computational results, the HOMO–LUMO energy gaps ($E_{\text{gap}}$ in eV) and heat of formations ($H_f$ in a.u.), are collected in Table 1. The heat of formation (binding energy) was evaluated as the difference between the energy of the molecule and its constituent atoms.

Comparison of the energies of structures 2a–2d with the same chemical formula indicates that structure 2c is the most thermodynamically ($H_f = -25.14$ a.u.) stable isomer. Among the cycloaliphatic isomers, 2a has the highest heat of formation (~24.9 a.u.) and also the lowest energy gap (6.14 eV), which could be explained by the repulsion between the axial hydrogen atoms connected to the carbon atoms that are part of the ether bonds. Structure 2b, where all oxygen atoms were connected in axial positions, has the highest energy gap (7.26 eV).

Aromatic clusters 2e and 2f were energetically less favorable, which could be associated with the strain of the aromatic carbon rings.

The shell molecules 3a–3d had smaller energy gaps, and the heat of formation per heavy atom was also higher. Between the amidic and esteric clusters, the former showed an improved stability. The lowest energy structure was 3c with a heat of formation per atom of −223.48 kcal/mol.
Potential drug delivery systems. The aromatic moieties through stacking interactions, as well as the
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However, due to their level of complexity, the chemical synthesis remains a great challenge.

As previously mentioned, stability of the double-shell cluster is related to the
symmetry
E
energetic feasibility and the high molecular symmetry is preserved
during geometry optimization. Two important geometric aspects were observed when building models
of rhombellanes. First, the surface layer should be large enough to easily accommodate the core
fragments, and second, the key atoms which the linkers bind covalently should be properly oriented.

The results show that all structures are energetically feasible and the high molecular symmetry is preserved
by means of density functional theory, using the B3LYP functional and the 6-31G(d,p) basis set. The

All covalent assemblies have tetrahedral (T) point group symmetries. In clusters 4a and 4b, the
aromatic rings were located above each other, with an inter-shell spacing between the carbon atoms of
3.16 Å and 3.08 Å in case of clusters 4a and 4b, respectively. The short distance suggests that a stacking
interaction exists between the two shells, the attractive van der Waals interactions between the benzene
rings has a contribution to the energy of the clusters. Notice that, in the case of graphite, the observed
spacings between two layers is 3.34–3.5 Å, whereas in the case of fullerene C
60
encapsulated inside of
C
20
, the computed inter-shell distance is only 1.95 Å [18].

Among the double-shell clusters, structure 4c was found to be the most stable assembly with the
highest energy gap (4.74 eV) and lowest energy (H
f
/N = −228.09 kcal/mol). Comparing clusters 4a and
4b with an identical number of heavy atoms, the amidic structure has a 10 kcal/mol energy gain with
respect to the molecule containing ester bonds. The HOMO–LUMO gaps of both molecules are very
close to 4 eV.

Although several other rhombellanes were built, due to geometric strain they were not energetically
feasible structures. As previously mentioned, stability of the double-shell cluster is related to the
optimal size of both layers, and the proper orientation of the covalent connection points. Obviously,
a larger surface layer could accommodate more easily the core fragments, however longer chemical
linkers are required to covalently connect the two layers.

4. Conclusions

Using the rhombellane framework, several dual-layer covalent assemblies were designed as
potential drug delivery systems. The aromatic moieties through stacking interactions, as well as the
hydrogen bond donors and acceptors groups on the surface layer, significantly contribute to the ligand
binding capacity. The immobilization of compounds with pharmaceutical potential could be further
enhanced by attachment of functional groups to the aromatic rings.

The geometry and stability of the building blocks and some covalent assemblies were investigated
by means of density functional theory, using the B3LYP functional and the 6-31G(d,p) basis set. The
results show that all structures are energetically feasible and the high molecular symmetry is preserved
during geometry optimization. Two important geometric aspects were observed when building models
of rhombellanes. First, the surface layer should be large enough to easily accommodate the core
fragment, and second, the key atoms which the linkers bind covalently should be properly oriented.
Otherwise, due to geometric strain, the assembly is not energetically favorable.

Assembly of the building blocks is favored by stacking interactions between the aromatic rings. However, due to their level of complexity, the chemical synthesis remains a great challenge.

Table 1. Symmetries, HOMO–LUMO energy gaps (E
gap
in eV), heat of formation (H
f
in a.u.), and heat of
formation divided by the number of heavy atoms (H
f
/N in kcal/mol), obtained at the B3LYP/6-31G(d,p)
level of theory.

| Structure | Formula          | N
atoms | Symm. | E
gap
(eV) | H
f
(a.u.) | H
f
/N (kcal/mol) |
|----------|-----------------|--------|-------|--------|--------|----------------|
| 2a       | C
48
O
12
H
22
     | 132    | O
h
   | 6.139  | −4.906 | −260.480 |
| 2b       | C
48
O
12
H
22
     | 132    | O
h
   | 7.264  | −25.000 | −261.466 |
| 2c       | C
48
O
12
H
22
     | 132    | T
d
   | 6.448  | −25.142 | −262.948 |
| 2d       | C
48
O
12
H
22
     | 132    | O
h
   | 6.843  | −25.041 | −261.895 |
| 2e       | C
48
O
12
H
24
     | 84     | O
h
   | 5.899  | −20.120 | −210.428 |
| 2f       | C
48
O
12
H
48
     | 108    | T
d
   | 6.200  | −22.601 | −236.371 |
| 3a       | C
108
N
24
O
24
H
60
     | 216    | T    | 2.877  | −52.610 | −211.622 |
| 3b       | C
108
O
24
H
36
     | 192    | T    | 3.914  | −47.180 | −189.782 |
| 3c       | C
72
N
12
O
12
H
48
     | 144    | T    | 3.880  | −34.190 | −223.483 |
| 3d       | C
72
O
24
H
56
     | 132    | T    | 4.201  | −31.070 | −205.949 |
| 4a       | C
132
N
12
O
36
H
96
     | 276    | T    | 3.942  | −62.110 | −216.525 |
| 4b       | C
132
O
24
H
84
     | 264    | T    | 4.020  | −59.334 | −206.849 |
| 4c       | C
192
N
24
O
48
H
180    | 444    | T    | 4.738  | −95.962 | −228.095 |
Supplementary Materials: The following are available online at http://www.mdpi.com/2073-8994/12/3/343/s1:
geometries (Cartesian coordinates) of structures 2a–2f, 3a–3d, and 4a–4c, optimized at the B3LYP/6-31G(d,p) level
of theory.

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References
1. Canceill, J.; Lacombe, L.; Collet, A. A new cryptophane forming unusually stable inclusion complexes with
neutral guests in a lipophilic solvent. J. Am. Chem. Soc. 1986, 108, 4230–4232. [CrossRef]
2. Cram, D.J. Molecular container compounds. Nature 1992, 356, 29–36. [CrossRef]
3. Sun, Q.F.; Murase, T.; Sato, S.; Fujita, M. A sphere-in-sphere complex by orthogonal self-assembly. Angew.
Chem. Int. Ed. 2011, 50, 10318–10321. [CrossRef] [PubMed]
4. MacGillivray, L.R.; Atwood, J.L. A chiral spherical molecular assembly held together by 60 hydrogen bonds.
Nature 1997, 389, 469–472. [CrossRef]
5. Liu, Y.; Hu, C.; Comotti, A.; Ward, M.D. Supramolecular archimedean cages assembled with 72 hydrogen
bonds. Science 2011, 333, 436–440. [CrossRef] [PubMed]
6. Grimme, S.; Mück-Lichtenfeld, C.; Antony, J. Noncovalent interactions between graphene sheets and in
multishell (hyper)fullerenes. J. Phys. Chem. C 2007, 111, 11199–11207. [CrossRef]
7. Casella, G.; Bagno, A.; Saelli, G. Spectroscopic signatures of the carbon buckyonions C_{60}@C_{180} and C_{60}@C_{240}:
A dispersion-corrected DFT study. Phys. Chem. Chem. Phys. 2013, 15, 18030–18038. [CrossRef] [PubMed]
8. Pichierri, F. Hypercubane: DFT-based prediction of an O_h-symmetric double-shell hydrocarbon. Chem. Phys.
Lett. 2014, 612, 198–202. [CrossRef]
9. Pichierri, F. Substituent effects in cubane and hypercubane: A DFT and QTAIM study. Theor. Chem. Acc.
2017, 136, 114. [CrossRef] [PubMed]
10. Diudea, M.V. Rhombellanic crystals and quasicrystals. Iran. J. Math. Chem. 2018, 9, 167–178.
11. Diudea, M.V.; Nagy, C.L. Rhombellane space filling. J. Math. Chem. 2019, 57, 473–483. [CrossRef]
12. Diudea, M.V.; Lungu, C.N.; Nagy, C.L. Cube-Rhombellane related structures: A drug perspective. Molecules
2018, 23, 2533. [CrossRef] [PubMed]
13. Czeleń, P.; Szefler, B. The immobilization of ChEMBL474807 Molecules Using Different Classes of
Nanostructures. Symmetry 2019, 11, 980. [CrossRef]
14. Czeleń, P.; Szefler, B. The immobilization of oxindole derivatives with use of cube rhombellane homeomorphs.
Symmetry 2019, 11, 900. [CrossRef]
15. Szefler, B.; Czeleń, P. Docking of cisplatin on fullerene derivatives and some cube rhombellane functionalized
homeomorphs. Symmetry 2019, 11, 874. [CrossRef]
16. Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Scalmani, G.; Barone, V.;
Mennucci, B.; Petersson, G.A.; et al. Gaussian 09, Revision E.01; Gaussian, Inc.: Wallingford, CT, USA, 2009.
17. Liu, Y.-L.; Chen, D.; Shang, P.; Yin, D.-C. A review of magnet systems for targeted drug delivery. J. Control.
Release 2019, 302, 90–104. [CrossRef] [PubMed]
18. Liu, F.; Meng, L.; Zheng, S. Density functional studies on a novel double-shell fullerene C_{20}@C_{60}. J. Mol.
Struct. THEOCHEM 2005, 725, 17–21. [CrossRef]