Ab Initio study and design of silicon and silicon-based nanoparticles for controlled drug delivery

Nikolaos P. Katsougrakis, George C. Sakellaropoulos, George Nikiforidis, Shanawer Niaz and Aristides D. Zdetsis

***Abstract*—**Silicon nanoparticles, which are the building blocks of porous (nano-porous and meso-porous) silicon, are characterized by biocompatibility, biodegradability, low toxicity and solubility; and they exhibit extraordinary qualities for biochemical applications for controlled drug delivery and for tissue engineering. For an efficient design and functionality of such complex systems a fundamental understanding of their biochemical properties and interactions is indispensable. The present study aims at the fundamental ab initio description and understanding at the molecular level of such interactions, which also constitute a first basic step towards a bottom up multiscalar approach for the drug delivering process, based on ab initio density functional theory (DFT). At this level our study is twofold: (1) To study the chemical and biochemical properties of silicon nanocrystals, which are the building blocks of nano- and meso- porous silicon, already used as drug carriers; and (2) to explore the possibility of ab initio designing potential new as yet untested drug delivery agents based on silicon. To this end, we employ a recently developed chemical analogy between silicon and boron "clusters" known as the "boron connection", taking advantage of the latest developments in the biomedical organoboron Chemistry. We have investigated and calculated the biochemical interaction energy of representative Si nanoparticles with selected amino acids, such as GLY (1). We have also illustrated that most of the tentative si-based nanocarriers that we have theoretically designed as borane/carborane analog structures have similar biochemical properties as their parent boron analogs, already used for drug delivery (2).

***Keywords*—**Boranes-Carboranes, Cages, Chemical analogies, Density Functional Theory, Drug delivery, Silicon-Carbon nanoparticles, Silicon nanoparticles.

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I. Introduction

NANOMATERIALS offer interesting physicochemical and biological properties for biomedical applications due to their small size, large surface area and the ability to interact in vivo with the human cells and tissues. Nanostructures may be used to deliver drugs where they are required to avoid harmful side effects [1]-[7]. Among inorganic nanostructures chosen as vehicles for drug delivery nano and nanoconstructed silicon particles have been recently emerging as promising drug delivery agents, because silicon nanoparticles can be rendered biocompatible and biodegradable [1], [2]. Current preclinical and clinical data support the hypothesis that silicon nanostructurs and nanostructered porous silicon based nanoparticles can provide the means to deliver drugs at a prolonged controlled release to specific targets1. Once optimized, these targeted nanoparticles will provide the improved treatment options. There is a variety of such silicon nanoparticles suggested for drug delivery, including silicon nanowires and even silicon fullerenes. Recently new results involving (not only nanoporous) also mesoporous silica nanoparticles (MSNs) have been shown to be a highly promising platform for intracellular controlled release of drugs and biomolecules. Despite that the application of MSNs in the field of intracellular drug delivery is still at its infancy; very exciting breakthroughs have been achieved in the last years [2], [3]. The building blocks of such silicon nanoconstructed materials are silicon nanoparticles and silicon nanocrystals7-13. In the present work, in the first part, we study the biochemical interaction of such silicon nanoparticles, including silicon cages [7], [11] with glysin (GLY), as representative amino acid. In the second part we consider cages and nanocarriers based in Boranes and Carboranes which have been designed and synthesized by the Hawthorne [14]-[21] group in order to design analogous nanostructures with Si and C, based in a chemical analogy developed by one of us, known as the "boron connection" [22]-[28]. We illustrate on one hand that the nature and magnitude of the biochemical interaction energy of GLY with representative Si nanostructures (and nanocarriers) has the right magnitude of a few kcal/mol, as the corresponding interaction energy of GLY with metal organic frameworks

(MOFs) [28], which have already been used as drug delivery agents. On the other hand, we illustrate by the isolobal analogy principle that the Si-based nanocarriers that we have theoretically designed as borane/carborane analog structures have similar biochemical properties as their parent boron analogs, already used for drug delivery.

II. Methods and Techniques

All calculations for the present work have been performed in the framework of the density functional theory (DFT) using the hybrid PBE0 functional [29] as implemented in the GAUSSIAN [30] program package.

III. Results and Discussion

A. Interaction and Functionalization of Si nanoparticles with GLY

Representative silicon nanoparticles considered in this work which include Si nanocrystals, Si nanotubes, oxygenated Si nanocrystals, Si nanotubes, and Si fullerenes are shown in Fig. 1. In this paper we focus on the 1 nm Si nanocrystal in Fig. 1. (a1) without any oxygen, and partially (or fully) oxygenated, Figs. 1.(c_1) ,1.(c_2). This particle has been synthesized and its structure can match also with a fullerene-like geometry.7 Moreover, this nanoparticle/nanocrystal is small enough that can be fully studied by ab initio methods at various (high) levels of theory with high accuracy and, even more important,

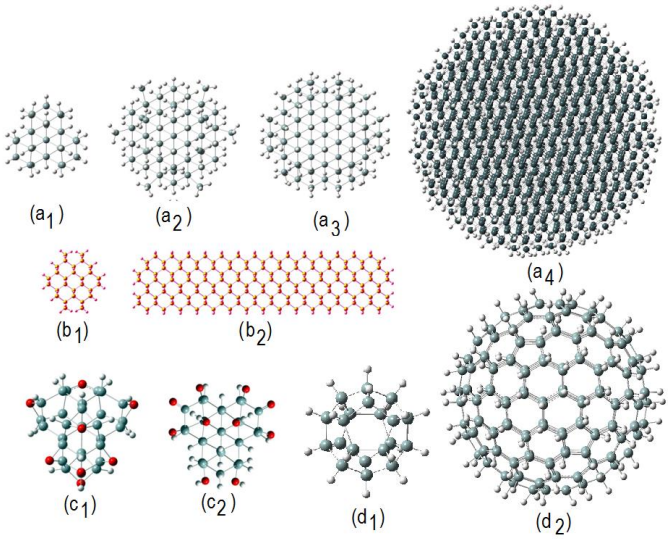

Fig. 1 Representative Silicon Nanostructures for Drug Delivery: Nanocrystals terminated by hydrogen (a_1)-(a_4); Nanotubes (b_1-b_2); Partially oxygenated nanocrystals (c_1-c_2); and Fullerenes (d_1-d_2). Structures (a_1) to (a_3) corresponds to $Si_{29}H_{36}$, $Si_{99}H_{100}$, $Si_{147}H_{100}$, and $Si_{777}H_{300}$, which is the largest nanocrystal studied here with diameter of about 32 Å. In (b_1) and (b_2) the cross section and the longitudinal view of a thin Si nanotube is shown. The partially oxygenated structure (a1), with O bridging bonds, and O double bonds is shown in (c_1) and (c_2) respectively. Structures (d_1) and (d_2) correspond to the $Si_{20}H_{20}$ and $Si_{180}H_{180}$ fullerenes.

its biochemical interaction with potential biological agents, such as amino acids, as Glycin (GLY) or potential drugs, as tamoxifen (TAM) can be further accurately examined in terms of the condition of its surface, functionalized with H, O and/or OH, which are very common in aqueous environment. The primitive interaction energy between GLY and TAM has been calculated by potential energy (PES) scan to be about 16.5

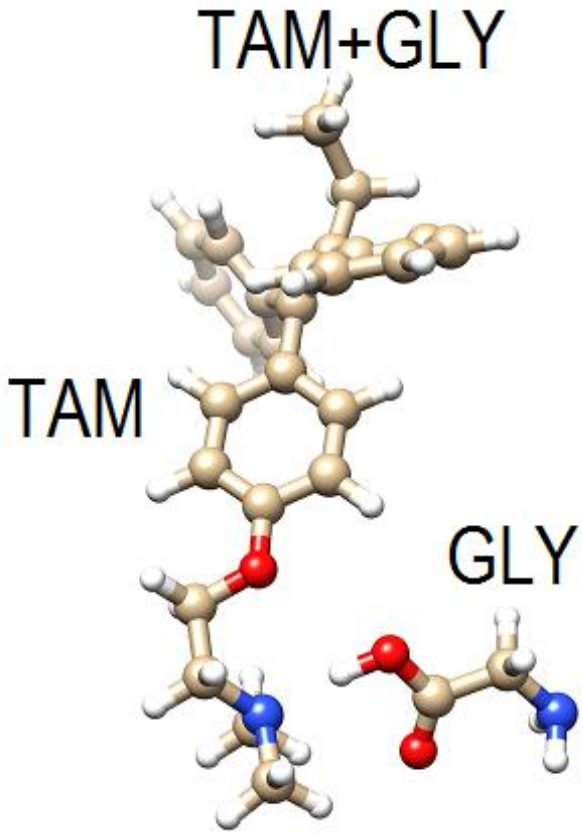

Fig. 2 Geometry of the TAM-GLY biochemical interaction at the site of maximum interaction energy.

Kcal/mole. This magnitude together with the geometry and the way of the most efficient approach of GLY, as is shown in Fig. 2, is crucial for a controlled drug delivery. By comparison to suitable metal-organic-framework (MOF) nanoparticles, which are well tested for drug delivery, this energy should be between a few (2-20) kcal/mol (see ref. 27). As it will be shown below this is indeed the case.

Another important feature is the "morphology" and charge distribution and electron localization in the frontier orbitals. Such orbitals correspond to the Highest occupied molecular orbital (HOMO), Lowest unoccupied molecular orbital (LUMO), as well as nearby orbitals below (HOMO-1, HOMO-2) and above (LUMO+1, LUMO+2). Figure 3, shows the frontiers orbitals at the maximum substitutional interaction of GLY with the 1nm (non oxygenated) 1 nm silicon nanoparticle $Si_{29}H_{36}$. The magnitude of the interaction energy (4.5 kcal/mole) and the geometry of the best approach reveal

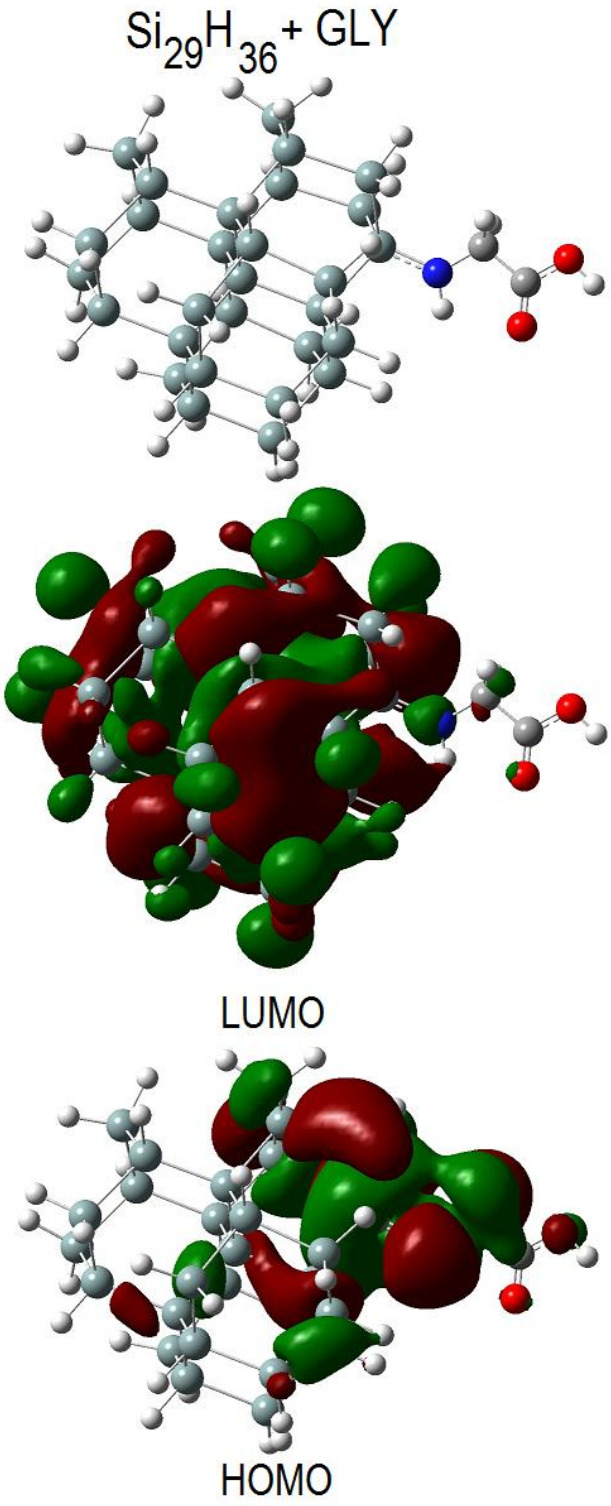

Fig. 3 Geometry and frontier (HOMO, LUMO) orbitals of the $Si_{29}H_{36}$ +1 GLY interaction at the site of maximum interaction energy.

hydrogen bonding. As we can see in Fig. 3, the HOMO orbital is mainly localized around GLY and the portion of $Si_{29}H_{36}$ in its near neighborhood, whereas the LUMO is localized at the main body of the nanoparticle.

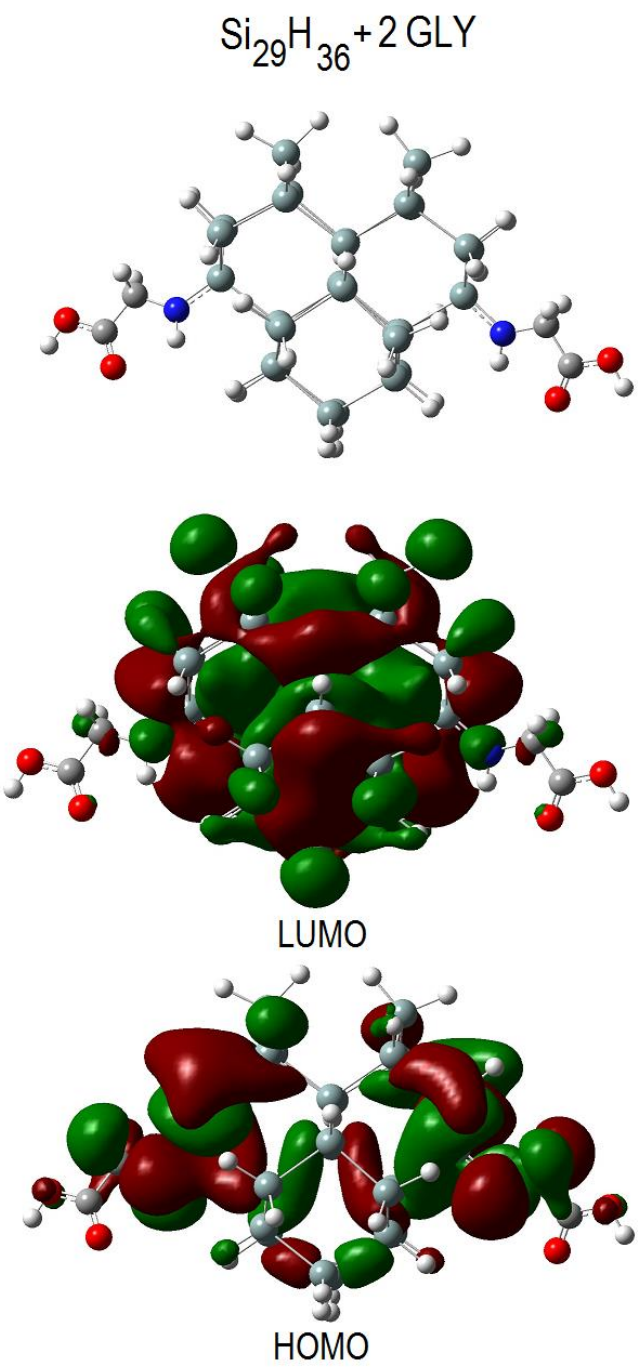

Fig. 4 Geometry and frontier (HOMO, LUMO) orbitals of the $Si_{29}H_{36}$ +2 GLY interaction at the site of maximum interaction energy.

Similar conclusions follow for the chemisorption of two GLY units on the $Si_{29}H_{36}$ nanocrystal, shown in Fig.4. The magnitude of the biochemical interaction (with each unit) is about the same (5 kcal/mole).

Since the 1nm silicon nanoparticle could have a “fullerene”

(cage) form7 we have also examined the interaction of GLY with the $Si_{28}H_{28}$ cage. As we can see in Fig. 5, although there is an energy barrier as GLY approaches the $Si_{28}H_{28}$ cage it can finally get stabilized "inside" the cage.

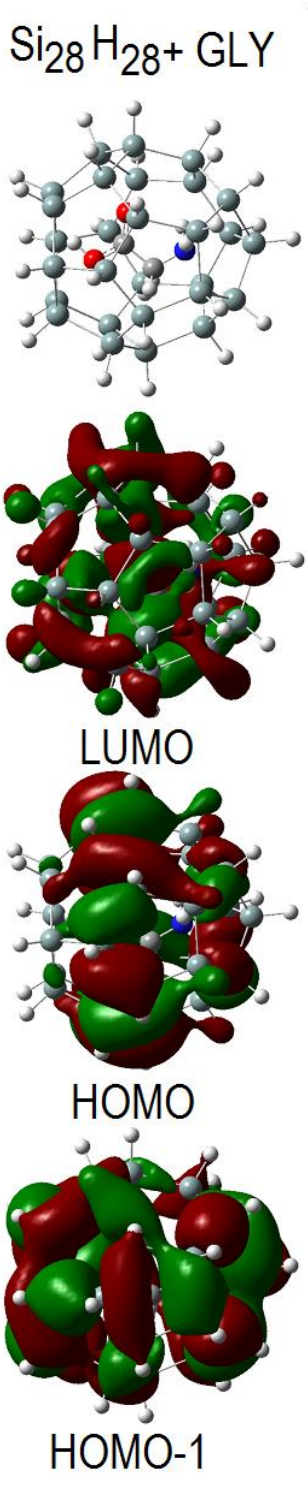

Fig. 5 Geometry and frontier (HOMO-1, HOMO, LUMO) orbitals of the $Si_{28}H_{28}$ cage nanoparticle with GLY "inside" it.

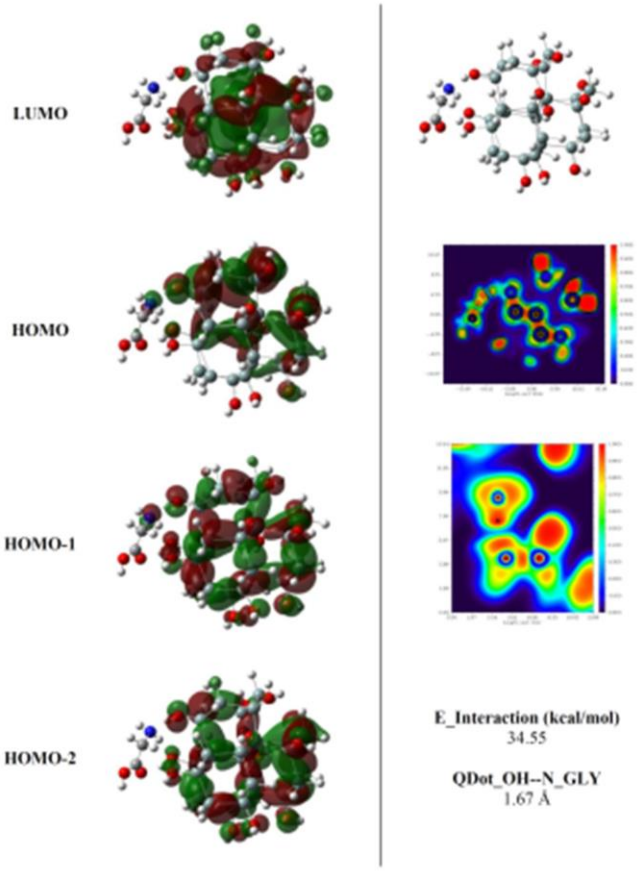

Fig. 6 Frontier orbitals (left); as well as geometry (top) and electron localization function (ELF) in the right, of the oxygenated 1nm silicon nanoparticle at the maximum interaction energy site with GLY. The ELF drawing is shown at normal (higher portion of the figure) and zoomed in (lower portion of the figure) views.

In this case, as can be seen in Fig. 5, all frontier orbitals are delocalized throughout the cage (and GLY). Finally, we have considered a representative oxygenated Si nanoparticle which also includes hydroxyl (OH) units, as shown in Fig. 6.

As we can verify in Fig. 6, we have a rather strong type of bonding, with interaction energy 34.55 kcal/mole, between a hydroxyl unit of the Si nanoparticle and the Nitrogen (blue in figure) end of GLY. This is much larger compared to the interaction energy of GLY with non-oxygenated nanoparticles. From the color code of the ELF plot it becomes clear that the ELF value of 0.4 (approx.) in the region N-OH corresponds to covalent type of bonding. This is also verified by the bond length of 1.67 Å. Thus, the hydroxyl unit in the nanoparticle is very important for strong (covalent) binding (large biochemical interaction energy), wherever is desirable. Otherwise we would have weaker hydrogen bonds (with interaction energies around 5 kcal/mole). These conclusions are very important for the design of targeted drug delivery through silicon nanoparticles and nanocomposites.

B. Ab Initio Design of Si-based nanoparticles "Suitable" for Biological Applications and/or Drug Delivery on the Basis of Chemical Analogies with Corresponding Borane / Carborane Nanoparticles.

The "boron connection" [22]-[28] is a simple efficient and physically appealing principle (or rule) based on the chemical analogy between the isoelectronic Si and BH (more accurately between the dianions Si^{-2} and $(BH)^{-2}$) moieties, developed by A. D. Zdetsis [22]-[28]. The $(BH)^{-2}$ unit is the basic ingredient of deltahedral boranes and carboranes, which are very well studied and for which there exist general topological and structural principles and building rules, based on electron count. As a result, the organoboron Chemistry is a highly developed branch of Chemistry and a wealth of extremely useful boron compounds have been developed and synthesized [14]-[22]. Among them, many useful borane and carborane compounds have been synthesized for biochemical and medical or pharmaceutical applications, including drug delivery and biolabeling. In addition, several of the developed organometallic structures have been specially designed to serve as building blocks for much larger nanostructures, a typical example of which is multidecker sandwiches. On the basis of the boron connection we have constructed several analog structures, as we can see in Fig. 7, which shows a very simple example of multidecker Sandwich [25]. In addition to this, several novel Si and Si/C compounds and structures have been theoretically designed, as the penta-coordinated Si (and C) structure of Fig. 8.

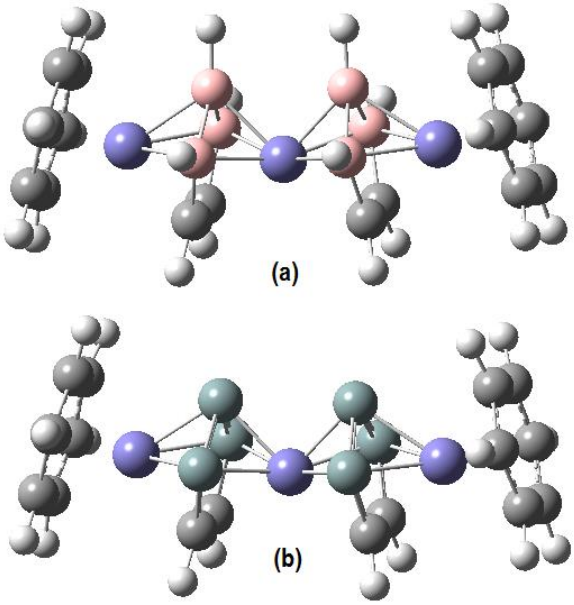

Fig. 7 A simple version of isoelectronic and isolobal Multidecker Sandwiches, based in Borane/carborane (top) and silicon (bottom), related through the "Boron connection".

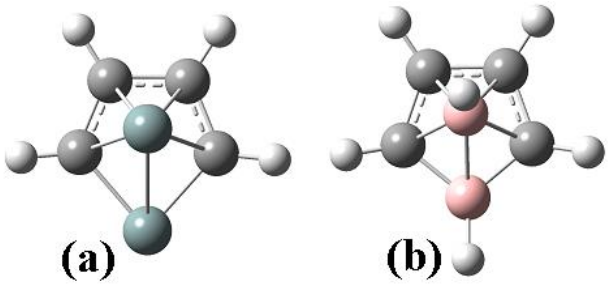

Fig. 8 Novel pentagonal structure based on Si/C (left), in full analogy to the corresponding borane based structure on the right.

Furthermore, a vast amount of biochemical research based on borane and carborane compounds for drug delivery and medical applications have been developed in particular by by M. F. Hawthorne's and his collaborators [14]-[21].

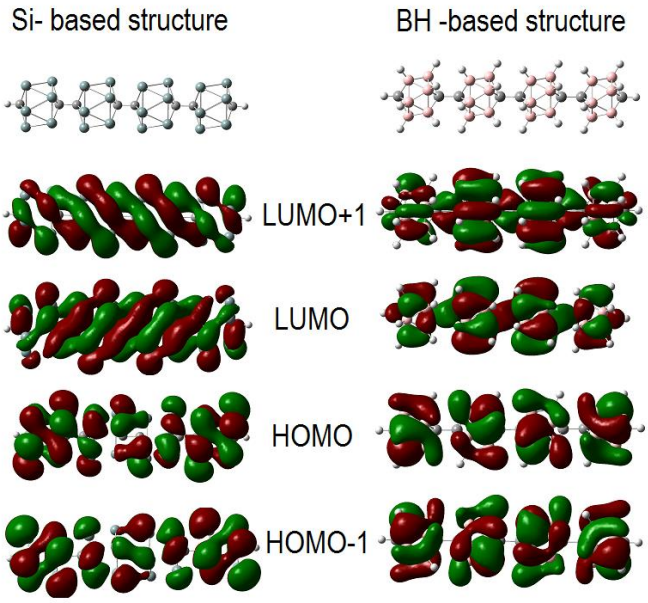

Fig. 9 Novel "designed" Si-based carborods (left) in analogy (according to the "boron connection") to the synthesized borane-based carborods.

Based on several of the Hawthorne's group theoretically developed and (experimentally synthesized) structures and compounds for biological applications and drug delivery, we have "designed" the corresponding Si based biochemical compounds for medical applications such as drug delivery. Examples of such structures are shown in Figs 9 and 10 respectively. As we can see in Fig. 9, the structure of the frontier orbitals is similar in both carborods. This feature together with the energetic similarity of the orbital energy differences is the basis of the isolobal principle in order to have chemical similarity between the two species. As a result, we expect that the chemical properties, and therefore the

biochemical or drug delivery properties, of the theoretically designed Si based compound (in this case carborod) would be similar to the initial borane/carborane-based compound, which has been already chemically (and clinically) tested. In Fig. 10 the similarity of the orbital structure is not so direct or evident in particular for the HOMO-1 and LUMO+1.

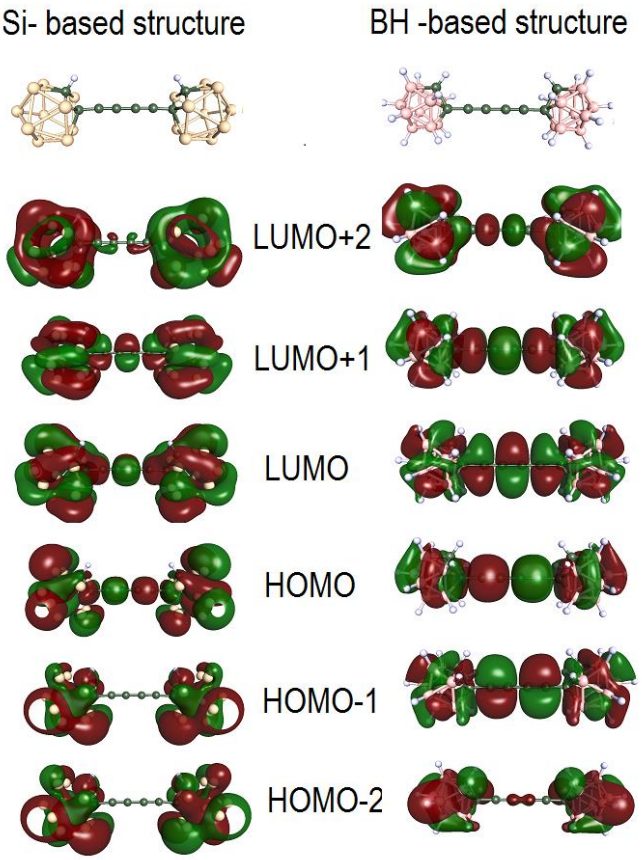

Fig. 10 Another "designed" Si-based carborod (left) in analogy (according to the "boron connection") to the synthesized borane-based carborod in the right.

However, this is not a particular problem, due to small changes in the energy ordering of the orbitals, provided the "homologous" orbitals exist in both structures, even with slightly different energetical ordering (slightly higher or lower).

Therefore, in conclusion, we have designed several (and could design more) biochemically interesting Si based nanostructures, which was a main target of the present work.

REFERENCES

[1] D.S. Kumar, D. Banji, , B. Madhavi, , V. Bodanapu, , S. Dondapati, , and A. P. Sri, "Nanostructured Porous Silicon - A Novel Biomaterial for Drug Delivery," International Journal of Pharmacy and Pharmaceutical Sciences, vol. 1, pp. 8-16, 2009.

[2] E. J. Anglin, L. Cheng, W. R. Freeman, and M. J. Sailor, "Porous silicon in drug delivery devices and materials," Advanced Drug Delivery Reviews, vol. 60, pp. 1266-1277, 2008.

[3] Y. Piao, A. Burns, J. Kim, U. Wiesner, and T. Hyeon, "Designed Fabrication of Silica-Based Nanostructured Particle Systems for Nanomedicine Applications," Advanced Functional Materials, vol. 18, pp. 3745–3758, 2008.

[4] A. B. Descalzo, R. Martinez-Manez, F. Sancenon, K. Hoffmann, and K. Rurack, "The Supramolecular Chemistry of Organic–Inorganic Hybrid Materials," Angewandte Chemie International Edition, vol. 45, pp. 5924, 2006.

[5] B. G. Trewyn, I. I. Slowing, S. Giri, H.-T. Chen, and V. S. Y. Lin, "Synthesis and Functionalization of a Mesoporous Silica Nanoparticle Based on the Sol–Gel Process and Applications in Controlled Release," Accounts of Chemical Research, vol. 40, pp. 846-853, 2007.

[6] I. Slowing, B. G. Trewyn, and V. S. Y. Lin, "Effect of Surface Functionalization of MCM-41-Type Mesoporous Silica Nanoparticles on the Endocytosis by Human Cancer Cells," The Journal of the American Chemical Society, vol. 128, pp. 14792–14793, 2006.

[7] A. D. Zdetsis "One-nanometer luminous silicon nanoparticles: Possibility of a fullerene interpretation," Physical Review B, vol. 79, pp. 195437, 2009.

[8] A. D. Zdetsis, and C. S. Garoufalis "Surface reconstruction Versus oxygen contamination in the 1 nm small silicon nanocrystals," Physical Chemistry Chemical Physics, Vol. 8, pp. 808-813, 2006.

[9] A. D. Zdetsis. "Optical properties of small size semiconductor nanocrystals and nanoclusters," Reviews on Advanced Materials Science (RAMS), vol. 11, pp. 56-78, 2006.

[10] C.S. Garoufalis, A. D. Zdetsis, and S. Grimme, "High level ab initio calculations of the optical gap of small Sillicon Quantum dots," Physical Review Letters, vol. 87, pp. 276402, 2001.

[11] A.D. Zdetsis, "High-symmetry high-stability silicon fullerenes: A first-principles study," Physical Review B, vol. 76, pp. 075402, 2007.

[12] S. Niaz, E. N. Koukaras, N. P. Katsougrakis, T. G. Kourelis, D. K. Kougias, and A. D. Zdetsis, "Size dependence of the optical gap of "small" silicon quantum dots: Ab initio and empirical correlation schemes," Microelectronic Engineering, vol. 112, pp. 231−234, 2013.

[13] S. Niaz, and A. D. Zdetsis, "Comprehensive Ab Initio Study of Electronic, Optical, and Cohesive Properties of Silicon Quantum Dots of Various Morphologies and Sizes up to Infinity," The Journal of Physical Chemistry C, vol. 120, pp. 11288–11298, 2016.

[14] M. F. Hawthorne, "Boron My Favorite Element", Journal of Chemical Education, vol. 86, pp. 1131, 2009.

[15] W. Jiang, C. B. Knobler, M. D. Mortimer, and M. F. Hawthorne, "A Camouflaged Icosahedral Carborane: Dodecamethyl-1,12-dicarba-closo-dodecarborane(12) and Related Compounds," Angewandte Chemie International Edition, vol. 34, pp. 1332, 1995.

[16] X. Yang, W. Jiang, C. B. Knobler, and M. F. Hawthorne, "Rigid-Rod Molecules: Carborods. Synthesis of Tetrameric p-Carboranes and the Crystal Structure of Bis(tri-n-Butylsilyl)-Tetra-p-Carboranes," The Journal of the American Chemical Society, vol. 114, pp. 9719, 1992.

[17] M. J. Bayer, and M. F. Hawthorne, "An Improved Method for the Synthesis of [closo-B12(OH)12]-2," Inorganic Chemistry, vol. 43, pp. 2018-2020, 2004.

[18] M. F. Hawthorne, and A. Maderna, "Applications of Radiolabeled Boron Clusters to the Diagnosis and Treatment of Cancer," Chemical Reviews, vol. 99, pp. 3421-3434, 1999.

[19] D. S. Wilbur, M-K. Chyan, D. K. Hamlin, R. L. Vessella, T. J. Wedge, and M. F. Hawthorne, "Reagents for Astatination of Biomolecules. 2. Conjugation of Anionic Boron Cage Pendant Groups to a Protein Provides a Method for Direct Labeling that is Stable to in Vivo Deastatination," Bioconjugate Chemistry, vol. 18, pp. 1226-1240, 2007.

[20] R. L. Julius, and M. F. Hawthorne, "Amyloid disease prevention by transthyretin native state complexation with carborane derivatives lacking cyclooxygenase inhibition," Drug News and Perspectives, vol. 21, pp. 258, 2008.

[21] P. Hunter, "Not boring at all. Boron is the new carbon in the quest for novel drug candidates," European Molecular Biology Organization reports, vol. 10, pp. 125-128, 2009.

[22] A. D. Zdetsis, "The boron connection: a parallel description of aromatic, bonding, and structural characteristics of hydrogenated silicon-carbon clusters and isovalent carboranes," Inorganic Chemistry, vol. 47, pp. 8823, 2008.

[23] A. D. Zdetsis, "A new class of silicon-carbon clusters: A full study of the hydrogenated $Si_nC_2H_2$, n=3,4,5, clusters in comparison with their

isoelectronic carboranes $C_2B_nH_{n+2}$,", The Journal of Chemical Physics, vol. 128, pp. 184305, 2008.
[24] A. D. Zdetsis, "Success and pitfalls of the Sin-2 C2H2–C2Bn−2Hn isolobal analogy: Depth and breadth of the boron connection", The Journal of Chemical Physics, vol. 130, pp. 064303, 2009.
[25] E. N. Koukaras, and A. D. Zdetsis, "Multidecker Sandwiches of Silicon-Carbon Clusters," Organometallics, vol. 28, pp. 4308–4315, 2009.
[26] A. D. Zdetsis. "From "structural democracy" to "boron connection"," AIP Conference Proceedings, vol. 1108, pp. 231-241, 2009.
[27] A. D. Zdetsis, "Similarities and Differences Between Silicon and Carbon Nanostructures: Theoretical Predictions," AIP Conference Proceedings, vol. 963, pp. 474, 2007.
[28] E. N. Koukaras, A. D. Zdetsis, and G. E. Froudakis, "Theoretical Study of Amino Acid Interaction with Metal Organic Frameworks," The Journal of Physical Chemistry Letters, vol. 2, pp. 272–275, 2011.
[29] C. Adamo, and V. Barone, "Toward Reliable Density Functional Methods Without Adjustable Parameters: The PBE0 model," The Journal of Chemical Physics, vol. 110, pp. 6158-69, 1999.
[30] M. J. Frisch, G.W. Trucks, H. B. Schlegel, G. E. Scuseria, et al., Gaussian 09, Revision C.01, Gaussian, Inc., Wallingford CT, 2009.