Nanotechnology-Based Approaches for Targeting and Delivery of Drugs via Hexakis (m-PE) Macrocycles

Samaneh Pasban¹ and Heidar Raissi^{2*}

¹Department of Chemistry, University of Birjand, Birjand, Iran
Tel: +985632502064, Email: samaneh_pasban@birjand.ac.ir
²Department of Chemistry, University of Birjand, Birjand, Iran
Tel: +985632502064, Email: hraeisi@birjand.ac.ir

* Corresponding E-mail: <u>hraeisi@birjand.ac.ir</u>



Hexakis (m-phenylene ethynylene) macrocycles

Figure S1 – Molecular structures of doxorubicin (DOX) anticancer drug and hexakis (m-PE) monomer.



Outside complex

Inside complex

Figure S2 – The molecular graph of the outside and inside complexes obtained from the DFT calculation.



Figure S3 – The calculated electronic density of states for free DOX drug, hexakis dimer carrier, and their complexe.

Table. S1 – The calculated average distance between the N and O atoms and average H-bond length (Å) in water and chloroform for each monomer^a and hexakis dimer.

| Hexakis dimer | Adsorption site | Distance Å |
|---------------|-----------------|--------------|
| Chloroform | O115-H109 | 1.986 |
| Water | | 2.025 |
| | O132-H105 | 1.987 |
| | | 2.007 |
| | O149-H101 | 1.991 |
| | | 2.020 |
| | O137-H97 | 1.988 |
| | | 2.020 |
| | O127-H125 | 1.979 |
| | | 1.999 |
| | O119-H113 | 1.989 |
| | | 2.012 |
| | N····O | 2.941 |
| | | 2.947 |
| | N–H | 1.338(1.328) |
| | | 1.345(1.331) |
| | C=O | 1.012(1.00) |
| | | 1.023(1.011) |

^aValues in parentheses refer to calculation for each monomer

Table S2. Computed equilibrium bond lengths (unites in Å) at the binding sites of DOX/hexakis dimer complexes in chloroform and water solvents. Atom labels are defined in Fig.2.

| Model | Adsorption site | Distance |
|-------------------|------------------------------------|------------|
| Inside complexes | O ₂₃₇ -H ₂₁₆ | 2.68 |
| | | 2.72^* |
| | O ₂₃₈ -H ₂₁₀ | 2.21 |
| | | 2.24^{*} |
| | O234-H196 | 2.27 |
| | | 2.29^{*} |
| | O ₂₃₇ -H ₂₉₆ | 2.39 |
| | | 2.42^{*} |
| | O ₂₃₃ -H ₂₀₆ | 2.28 |
| | | 2.31^{*} |
| | O ₂₂₉ -H ₂₈₈ | 2.05 |
| | | 2.1^{*} |
| Outside complexes | O ₃₉ -H ₁₈₅ | 3.6 |
| | | 3.91* |
| | O33-H284 | 2.2 |
| | | 2.34^{*} |
| | O ₃₇ -H ₂₇₇ | 2.9 |
| | | 3.2^{*} |
| | N34-H283 | 3.9 |
| | | 4.2^{*} |

* In water solvent.

Table S3. The selected topological parameters of the investigated complexes, the density of the total energy of electrons (H_{BCP}), the kinetic (G_{BCP}) and potential (V_{BCP}) electron energy densities (all in a.u.), - G_{BCP}/V_{BCP} ratio and the hydrogen bond energy (E_{HB} , in kJ/mol) for the intermolecular interactions between DOX drug and hexakis dimer in chloroform and water solution.

| Site | ρвср | ∇²рвср | GBCP | VBCP | HBCP | -GBCP/VBCP | Ehb |
|------------------------------------|---|---|--|---|---|---|---|
| adsorption | | | | | | | |
| O ₂₃₉ -H ₂₁₆ | 0.01661 | 0.0505 | 0.01160 | -0.0105 | 0.00101 | 1.0960 | -13.901 |
| | 0.01658 | 0.0502 | 0.01154 | -0.0105 | 0.00100 | 1.0950 | -13.843* |
| O ₂₃₈ -H ₂₁₀ | 0.01634 | 0.0574 | 0.01267 | -0.0109 | 0.00167 | 1.1526 | -14.431 |
| | 0.00817 | 0.0294 | 0.00588 | -0.0044 | 0.00146 | 1.3323 | -5.795* |
| O ₂₃₄ -H ₁₉₆ | 0.0138 | 0.0457 | 0.00996 | -0.0085 | 0.00146 | 1.1720 | -11.158 |
| | 0.00649 | 0.0265 | 0.00508 | -0.0035 | 0.00153 | 1.4332 | -4.659* |
| O ₂₃₇ -H ₂₉₆ | 0.0118 | 0.0453 | 0.00935 | -0.0073 | 0.00196 | 1.2659 | -9.7046 |
| | 0.00101 | 0.0156 | 0.00263 | -0.0013 | 0.00126 | 1.9326 | -1.786^{*} |
| O ₂₃₃ -H ₂₀₆ | 0.01307 | 0.0463 | 0.0098 | -0.0081 | 0.00171 | 1.2105 | -10.692 |
| | 0.00583 | 0.0202 | 0.00392 | -0.0028 | 0.00112 | 1.3999 | -3.683* |
| O229-H288 | 0.01939 | 0.0691 | 0.01564 | -0.0140 | 0.00163 | 1.1165 | -18.39 |
| | 0.01921 | 0.0614 | 0.01429 | -0.0132 | 0.00105 | 1.0796 | -17.381 [*] |
| | | | | | | | |
| O ₃₉ -H ₁₈₅ | 0.0201 | 0.0809 | 0.01786 | -0.0155 | 0.00236 | 1.1524 | -20.347 |
| | 0.02239 | 0.0702 | 0.01693 | -0.0163 | 0.00061 | 1.0374 | -21.431* |
| O33-H284 | 0.0204 | 0.0813 | 0.01803 | -0.0157 | 0.00228 | 1.1451 | -20.677 |
| | 0.02142 | 0.0698 | 0.0165 | -0.0155 | 0.0009 | 1.0610 | -20.413* |
| O37-H277 | 0.02389 | 0.0989 | 0.02231 | -0.0199 | 0.00240 | 1.1209 | -26.134 |
| | 0.02251 | 0.0711 | 0.01713 | -0.0164 | 0.0006 | 1.0388 | -21.652* |
| N ₃₄ -H ₂₈₃ | 0.0508 | 0.01646 | 0.02315 | -0.0421 | -0.0190 | 0.5487 | -55.382 |
| | 0.0501 | 0.0121 | 0.02196 | -0.0409 | -0.0189 | 0.5369 | -53.685* |
| | Site adsorption O239-H216 O238-H210 O238-H210 O234-H196 O237-H296 O237-H296 O229-H288 O39-H185 O39-H185 O33-H284 O33-H284 O37-H277 N34-H283 | Site adsorptionρBCPadsorption0.01651O239-H2160.01658O238-H2100.01634O238-H2100.00817O234-H1960.00381O237-H2960.0118O237-H2960.0101O233-H2060.01307O229-H2880.01939O29-H1850.0201O39-H1850.0201O33-H2840.0204O37-H2770.02389O37-H2770.02251N34-H2830.0508 | Site adsorption ρ BCP $\nabla^2 \rho$ BCPadsorption0.016510.0505 O_{239} -H ₂₁₆ 0.016580.0502 O_{238} -H ₂₁₀ 0.016340.0574 O_{238} -H ₂₁₀ 0.008170.0294 O_{234} -H ₁₉₆ 0.01380.0457 O_{237} -H ₂₉₆ 0.01180.0453 O_{237} -H ₂₉₆ 0.01180.0453 O_{233} -H ₂₀₆ 0.013070.0463 O_{229} -H ₂₈₈ 0.019390.0691 O_{39} -H ₁₈₅ 0.02010.0809 O_{33} -H ₂₈₄ 0.02040.0813 O_{37} -H ₂₇₇ 0.023890.0989 O_{37} -H ₂₇₇ 0.023890.01646 N_{34} -H ₂₈₃ 0.05080.0121 | Site adsorption ρ_{BCP} $\nabla^2 \rho_{BCP}$ GBCPadsorption0.016610.05050.01160 O_{239} -H ₂₁₆ 0.016610.05020.01154 O_{238} -H ₂₁₀ 0.016340.05740.01267 O_{238} -H ₁₉₆ 0.008170.02940.00588 O_{234} -H ₁₉₆ 0.01380.04570.00996 O_{237} -H ₂₉₆ 0.01180.04530.00935 O_{237} -H ₂₉₆ 0.01180.04630.0098 O_{233} -H ₂₀₆ 0.013070.04630.0098 O_{233} -H ₂₀₆ 0.013070.04630.0098 O_{229} -H ₂₈₈ 0.019390.06910.01564 O_{39} -H ₁₈₅ 0.02010.08090.01786 O_{33} -H ₂₈₄ 0.02040.08130.01803 O_{37} -H ₂₇₇ 0.023890.09890.02231 O_{37} -H ₂₇₇ 0.023890.09890.02231 N_{34} -H ₂₈₃ 0.05080.016460.02315 O_{00501} 0.01210.02196 | Site adsorption ρ BCP $\nabla^2 \rho$ BCPGBCPVBCPadsorption O_{239} -H2160.016610.05050.01160-0.0105 O_{238} -H2100.016340.05740.01267-0.0109 O_{238} -H2100.016340.02940.00588-0.0044 O_{234} -H1960.01380.04570.00996-0.00857 O_{234} -H1960.01180.04570.00996-0.0085 O_{237} -H2960.01180.04530.00935-0.0073 O_{237} -H2960.013070.04630.0098-0.0081 O_{233} -H2060.013070.04630.0098-0.0081 O_{239} -H2880.019390.06910.01564-0.0140 O_{239} -H2880.019390.06910.01564-0.0132 O_{239} -H2880.019390.06910.01564-0.0132 O_{239} -H2880.02010.08090.01786-0.0155 O_{39} -H1850.02010.08090.01786-0.0155 O_{33} -H2840.02040.08130.01803-0.0157 O_{37} -H2770.023890.09890.02231-0.0199 O_{34} -H2830.05080.016460.02315-0.0421 N_{34} -H2830.05080.016460.02315-0.0421 O_{30} -H2770.05010.01210.02196-0.0409 | Site adsorption ρ BCP $\nabla^2 \rho$ BCPGBCPWBCPHBCPadsorption0.016610.05050.01160-0.01050.00101 O_{239} -H_{216}0.016610.05020.01154-0.01050.00100 O_{238} -H_2100.016340.05740.01267-0.01090.00167 O_{238} -H_1960.01380.04570.00996-0.00850.00146 O_{234} -H_1960.01380.04570.00996-0.00850.00146 O_{237} -H_2960.01180.04530.00935-0.00730.00196 O_{237} -H_2960.013070.04630.0098-0.00810.00171 O_{233} -H_2060.013070.04630.0098-0.00810.00171 O_{229} -H_2880.019390.06910.01564-0.01400.00163 O_{39} -H ₁₈₅ 0.02010.08090.01786-0.01550.00236 O_{33} -H_2840.02040.08130.01803-0.01550.00238 O_{37} -H_2770.023890.09890.02231-0.01990.00240 O_{37} -H_2770.023890.09890.02231-0.01990.00240 N_{34} -H_{2830.05080.016460.02315-0.0409-0.0189 | Site adsorption ρ_{BCP} $\nabla^2 \rho_{BCP}$ GBCPVBCPHBCP-GBCP/VBCP O_{239} -H2160.016610.05050.01160-0.01050.001011.0960 O_{238} -H2100.016340.05740.01267-0.01090.001671.1526 O_{238} -H2100.016340.02940.00588-0.00440.001461.3323 O_{234} -H1960.01380.04570.00996-0.00850.001461.1720 O_{237} -H2960.01180.04530.00935-0.00730.001961.2659 O_{237} -H2960.01180.04530.00935-0.00130.01261.9326 O_{233} -H2060.013070.04630.0098-0.00810.001711.2105 O_{229} -H2880.019390.06910.01564-0.01400.001631.1165 O_{39} -H1850.02010.08090.01786-0.01550.002361.0796 O_{39} -H1850.02010.08090.01786-0.01550.002361.1524 O_{39} -H1850.02040.08130.01803-0.01570.002281.1451 O_{37} -H2770.023890.09890.02231-0.01990.02401.1209 O_{37} -H2770.023890.09890.02231-0.01400.00641.0388 N_{34} -H2830.05080.016460.02315-0.0421-0.01900.5487 O_{35} -H2740.05080.016460.02315-0.0409-0.01890.5369 |

* In water solvent.

Table S4. The DOX optimized structural geometries in vacuum phase and experimental data²².Lengths are in angstrom (Å)

| | EXP ²² | DFT/6-31G** | %SD |
|----------------|-------------------|-------------|---------|
| <i>C2-C3</i> | 1.32 ^c | 1.35 | 1.5151 |
| C2-C1 | 1.39° | 1.36 | -1.1582 |
| <i>C1-C16</i> | 1.40 ^c | 1.39 | -0.7142 |
| <i>C15-C16</i> | 1.36 ^c | 1.37 | 0.7352 |
| C4-C15 | 1.42 ^c | 1.40 | -1.4084 |
| СЗ-НЗ | 0.98 ^c | 1.00 | 2.0408 |
| <i>C4-C3</i> | 1.41 ^c | 1.40 | -0.7092 |
| С2-Н2 | 1.01° | 1.02 | -0.9803 |
| <i>C4-04</i> | 1.34 ° | 1.34 | 0 |
| <i>04-C23</i> | 1.46 ° | 1.44 | -1.3698 |
| C5-F5 | 1.34 ^c | 1.33 | -0.7462 |
| С23-Н23 | 1.16° | 1.13 | -2.5862 |
| C5-C15 | 1.50 ° | 1.47 | -1.9087 |
| <i>C17-C18</i> | 1.37 ° | 1.39 | 0.01459 |
| <i>C18-C12</i> | 1.46 ° | 1.47 | 0.6849 |
| <i>C12-C16</i> | 1.50° | 1.49 | -0.6666 |
| <i>C12-012</i> | 1.25 ° | 1.20 | -4.00 |
| <i>C5-05</i> | 1.24 ° | 1.24 | 0 |
| <i>C6-C17</i> | 1.40 ° | 1.38 | -0.7142 |
| <i>C19-C20</i> | 1.36° | 1.37 | 0.7352 |
| <i>C9-09</i> | 1.44 ° | 1.43 | -0.6944 |
| 09-H9 | 1.09 ° | 1.05 | -3.66 |
| С10-Н10 | 1.01 ° | 1.04 | 2.4798 |
| <i>C13-013</i> | 1.20 ° | 1.21 | 0.8349 |
| C14-H14 | 0.99 ° | 1.01 | 2.02 |
| <i>C13-C14</i> | 1.50° | 1.49 | -0.6666 |
| N22-H22 | 1.00 ° | 0.99 | 1 |

c X-ray data (average for four molecules

Table S5. ¹H NMR chemical shifts (δ , in ppm) obtained from the DFT calculation, ¹H shifts relative to monomer and dimer of hexakis.

| Type of H Description of Proton | | Hexakis dimer | Hexakis monomer |
|---------------------------------|------------------------------------|-------------------------|-----------------|
| | | δ (ppm) | б (ррт) |
| Ar-H | aromatic (H is on phenyl ring) | 7.1 | 7.9 |
| R CO NHR | amide | 8.2 | 9.08 |
| R_2N-CH_3 | a to nitrogen (C is attached to N) | 1.2 | 1.5 |