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Host-Guest Interactions Between Cyclophane and Arginine-Methyl Ester: A Theoretical Study

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With the goal of understanding the supramolecular interactions between cyclophane and nitrogen-rich amino-acid with guanidinium group, we performed theoretical calculations in vacuum with neutral molecules. Since our future plans are to compare our theoretical results with the experiments, we designed a system composed of cyclophane with four pendant hexyl chains, which can dissolve in a non-aqueous media and arginine methyl ester, which has guanidinium group that can play an important role in the stabilization of the system. The conformational search and geometry optimizations were performed with the density functional theory functional B3LYP in conjunction with the 6-31G* basis set. The results show that when the guanidinium group of the arginine methyl ester participates with a hydrogen bond or supramolecular interaction with the cycle, the dissociation energies tend to be lower than in the cases in which guanidinium group does not participate in the formation of the complex.

Keywords: Guanidinium group, Arginine-methyl ester, Cyclophane.

INTRODUCTION

One of the most important processes in biochemical systems is molecular recognition. Natural receptors are generally linear molecules that fold into three-dimensional structures through intramolecular interactions that have specific active sites involved in very efficient recognition processes [1]. However, they offer some disadvantages for molecular recognition, such as high molecular weight, high sensibility to temperature and specific pH range [2]. Therefore, it has been interesting to search for novel structures that mimic the same recognition without the limitations of proteic receptors. A promising tactic is to design relatively small cyclic units with different functional groups attached to form potential binding sites. It has been reported that cyclophanes have been designed for the molecular recognition of amino acid derivatives [3]. A wide variety of experiments are realized in aqueous media [4-6]. In a previous work, Inoue and coworkers [2] performed an experimental study of the molecular recognition of compounds of biochemical interest with amino groups by two similar cyclophane hosts in aqueous media. According to their results, the cyclophanes formed stable complexes due to the polar interactions with the amino groups of dopamine, tyramine and phenethylamine as guests.

Anyhow, other important interactions like hydrogen bonds are not clearly appreciated in water due to the competition between the interactions guest-water and host-water. To accomplish this, it is important to study the role of this kind of interactions in organic solvents with a less dielectric constant than water [7,8]. Thus, we need first to esterify the carboxylic group of the hosts in order to solubilize them in organic media. According with our future experimental plans, we carried out a theoretical study of a cyclophane reported by Inoue and coworkers [2] but modified it with four pendant hexyl chains (cyc) and selected a nitrogen rich amino acid derivative with a guanidinium group, arginine methyl ester (argMe) as a guest (Fig. 1).

COMPUTATIONAL METHODS

Quantum mechanical calculations were computed with the Gaussian 09 software [9]. Due to the relatively large size of the systems, geometry optimizations were performed with the density functional theory (DFT)-B3LYP [10] method coupled to the 6-31G* [11] basis set. Tight convergence criteria were applied to make sure that the energies obtained were accurate enough within the realm of the methods employed.

In this work we calculated dissociation energies (ΔE) for the structures in order to determine their relative stability with respect to the cyclophane-arginine methyl ester interactions:

$$\Delta E = E_{cyc-argme} - (E_{cyc} + E_{argme})$$

where cyc-argMe stands for the structure composed of hexyl chains and arginine methyl ester. In this work, we performed a conformational search and found several energy minima structures. All of the configurations discussed in this manuscript were obtained from a conformational search and only list the most stable. We selected the most stable structures, with the most negative dissociation energy values. In order to compare these values, we calculated the relative dissociation energies. Thus, the most stable geometry has a relative dissociation energy and the rest of the systems have positive values, where the highest value is the least stable system.

The results in the present work were compared to other DFT methods (PW91 [12], PBE [13], HCTH [14]) as well as local density approximation (LDA) methods (*i.e.* VWN [15,16]) and we have observed similar trends in the geometries and energies of the structures. It is our belief that the strength of the dispersion forces for simple van der Waals complexes has been shown to be adequately computed by the B3LYP method. Since we are trying to observe general trends in the observed behaviour we have limited the basis set to 6-31G* for computational feasibility.

RESULTS AND DISCUSSION

The structures studied were obtained from the system composed of a cyclophane with four pendant hexyl groups (which we refer to as cyc) as a receptor shown schematically in Fig. 1 with arginine as a guest. We have organized the structures from lowest to highest dissociation energies in Table-1 and Figs. 2 and 3. Table-1 displays dissociation energies (ΔE) in kcal/mol and HOMO/LUMO gaps (GAP) in eV of the structures. Figs. 2 and 3 show energy minima configurations of the system. In these figures we only depict the longest and shortest dimensions of the cavities without considering the hydrogens.

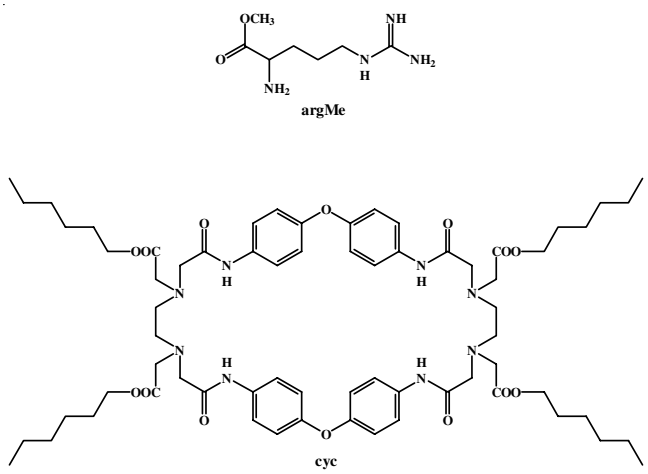

Fig. 1. Illustration of the species cyc and argMe

Structural energy discussion: The first and most stable geometry has a cavity with dimensions of 5.50 and 15.56 Å. In this structure, it is evident that the guanidinium group participates in the stabilization of the system. This can be confirmed by the fact that most of the hydrogen bonds formed are with the guanidinium group. Five hydrogen bonds are

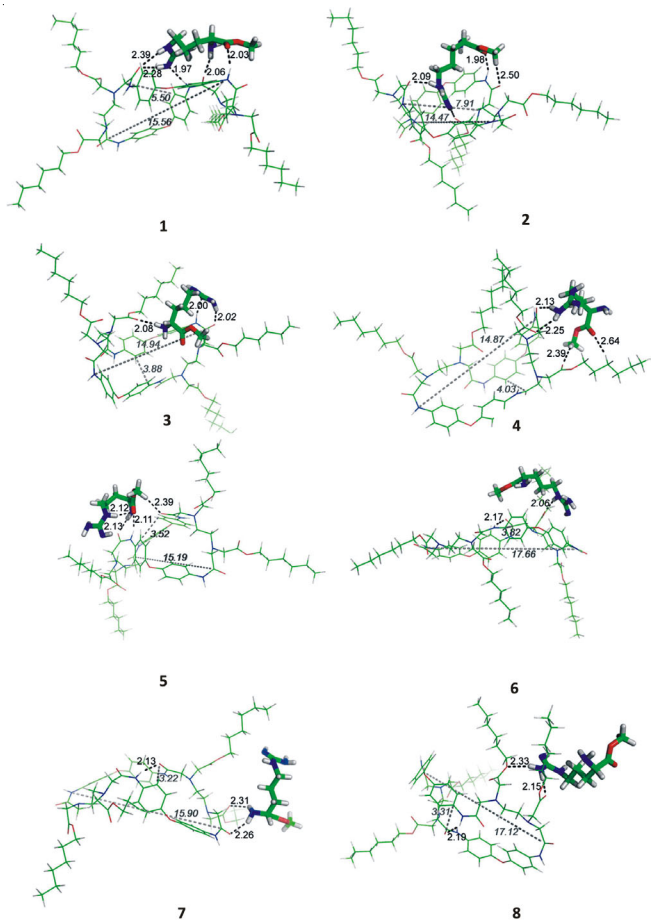

Fig. 2. Selected geometrical parameters of structures 1-8 formed by cyc and argMe whereby the distances are in Å

TABLE-1
RELATIVE DISSOCIATION ENERGIES (ΔE_{rel}, kcal/mol) AND HOMO/LUMO GAPS (eV) ARE LISTED UNDER GAP CALCULATED AT THE B3LYP/6-31G* LEVEL FOR THE STRUCTURES STUDIED

Structure	ΔE_{rel}	GAP	Structure	ΔE_{rel}	GAP
1	0.000	4.608	9	8.229	4.715
2	3.545	4.678	10	8.323	4.672
3	4.286	4.774	11	8.532	4.908
4	5.434	4.584	12	9.141	4.545
5	5.593	4.955	13	10.106	4.415
6	6.785	4.892	14	10.327	4.780
7	7.175	4.883	15	10.460	4.932
8	8.167	4.867	16	12.859	4.650

formed with distances of 2.39, 2.28, 1.97, 2.06 and 2.03 Å. The first three are formed with the guanidinium group. The arginine methyl ester is practically linear, extended on top of the cycle only on one side of it and does not interact with any of the pendant hexyl groups. Structure 2 forms three hydrogen bonds of 2.09, 2.39 and 1.98 Å and a CH---O interaction of 2.50 Å, with a cavity of 7.91 and 14.47 Å. Its relative dissociation energy is higher, with a value of 3.54 kcal/mol. This could be due to a the fact that it has two less hydrogen bonds and to the steric hindrance caused by the partial inclusion of the guanidinium group of the arginine methyl ester.

Structure 3 has a cavity of 14.94 Å by 3.88 Å. It forms three hydrogen bonds of 2.08, 2.00 and 2.02 Å. However, one of them forms with an oxygen of the ester group (2.08 Å) of a

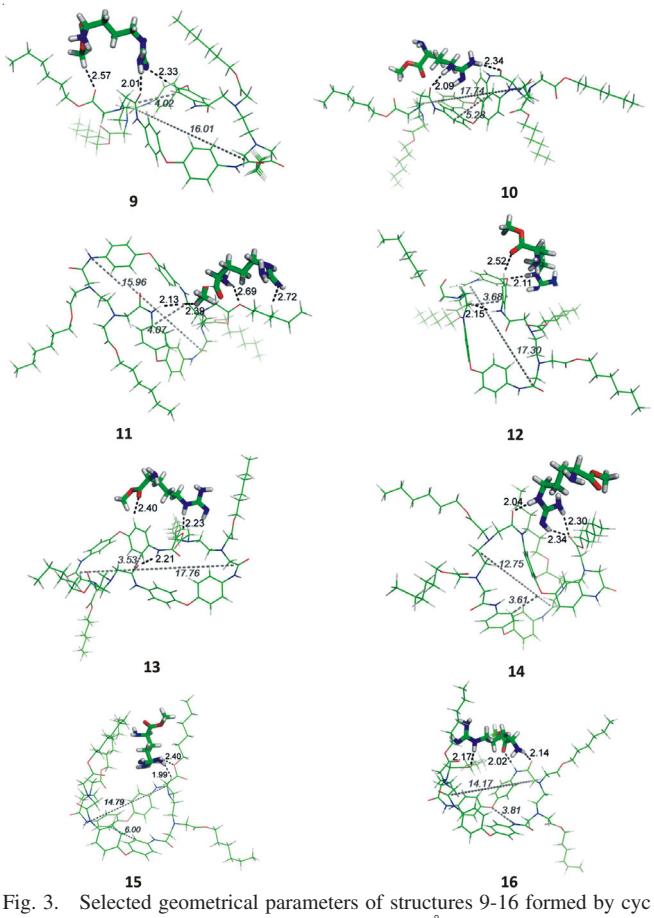

Fig. 3. Selected geometrical parameters of structures 9-16 formed by cyc and argMe whereby the distances are in Å

pendant hexyl group, which has more degrees of freedom than the macrocyclic structure. Therefore, it is less stable than the previous geometries, with a relative dissociation energy of 4.28 kcal/mol. Similarly to structure 3, in structure 4 the shortest dimension of the cavity decreases and the longest dimension increases, yielding values of 4.03 and 14.87 Å, respectively. It forms two hydrogen bonds of 2.13 and 2.25 Å with the guanidinium group. Furthermore, it forms two CH---O interactions of 2.39 and 2.64 Å with one of the pendant hexyl groups. This contributes to its rise in relative dissociation energy to a value of 5.43 kcal/mol. The dimensions of cyc in structure 5 are of 15.19 and 3.52 Å and. It forms two hydrogen bonds with the macrocyclic structure of 2.11 and 2.13 Å and one CH---O interaction of 2.39 Å. In contrast to the last geometries, in this case, the guanidinium group does not form hydrogen bonds. It has been reported that in many cases, when the guanidinium group is involved, more than one hydrogen bonds are favoured thanks to its abundance of nitrogen [16]. In this scenario, an intramolecular hydrogen bond involving a nitrogen in the guanidinium group in the arginine methyl ester is present. Therefore, it could influence the lack of interactions between the guanidinium group and the macrocycle. Instead, one of the hydrogen bonds is formed with the alpha amine group (2.13 Å) which is more available. Thus, this reduces mildly the relative dissociation energy, rising it to 5.59 kcal/mol.

In structure 6 the cavity dimensions are of 17.66 and 3.82 Å. There is only one hydrogen bond of 2.06 Å is formed between the guanidinium group in the arginine methyl ester and one of the oxygens of the ester group of a pendant hexyl group. This could cause the energy to rise to 6.78 kcal/mol. In structure 7, the cavity dimensions are of 15.90 Å and 3.22 Å. An intramolecular hydrogen bond is formed in the macrocycle, which could enable a rise in relative dissociation energy. Two hydrogen bonds are formed between the hydrogens of the α-amino group and an amide oxygen of the cycle and an ester group oxygen of the cycle. This is less stable than structure 6 most likely due to the fact that in structure 6 the arginine methyl ester lies parallel above the cycle, while in structure 7, it is perpendicular to the cycle and only interacts with a tip, modifying the shape of the cyclophane. Therefore, the relative dissociation energy elevates to 7.17 kcal/mol.

Structure 8 has a cavity of 17.12 and 3.31 Å. It also forms an intramolecular bond in the macrocycle of 2.13 Å, which could cause tension and destabilize the system. Furthermore, two hydrogen bonds are formed between the arginine methyl ester and the cyclophane, with values of 2.33 Å and 2.15 Å. These two interactions are formed with only one nitrogen of the guanidinium group with two of the pendant hexyl groups. This forces the chains to be in proximity, yielding a less favourable relative dissociation energy of 8.17 kcal/mol. Structure 9 has a similar relative dissociation energy of 8.23 kcal/mol. Its cavity dimensions are of 16.01 Å and 4.02 Å. This configuration forms only one half of the hydrogen bonds in structure 8. The only hydrogen bond is of 2.01 Å, formed between one nitrogen of the guanidinium group and cyc. However, there are CH---O and CH---N interactions with values of 2.57 and 2.33 Å, respectively. This could compensate for the extra hydrogen bond in structure 8, causing the relative dissociation energy of structure 9 to be almost the same. The cavity dimensions of structure 10 are of 5.28 and 17.74 Å. This geometry forms two hydrogen bonds with two nitrogens of the guanidinium group and the cycle. Nevertheless, they are too far apart. This draws near the interaction groups and causes tension in a similar fashion as in structure 8. This tension is stronger in the cycle frame than in the pendant hexyl groups. Consequently, the relative dissociation energy is slightly higher for structure 10, with a value of 8.32 Å. Structure 11 has a cavity with dimensions of 15.96 and 4.07 Å. It forms only one hydrogen bond of 2.69 Å. It also forms CH---N and CH---O interactions, with values of 2.72 and 2.39 Å, respectively. Although these interactions favour the stability of the system, the macrocycle forms a intramolecular hydrogen bond of 2.13 Å which could affect its relative dissociation energy, yielding a value of 8.53 kcal/mol.

Structure 12 has cavity dimensions of 17.30 and 3.68 Å and forms an intramolecular hydrogen bond of 2.15 Å. This geometry has a hydrogen bond of 2.11 Å and forms a CH---O interaction of 2.52 Å. Even so, the hydrogen bond formed with an ether group of the cyc. This group has the lowest polarizability compared to the rest of the functional groups containing electronegative atoms. Hence, the relative dissociation energy is higher than in the last cases, with a value of 9.14 kcal/mol. Structure 13 has a cavity with dimensions of 17.76 Å and 3.53 and also forms an intramolecular hydrogen bond of 2.21 Å. It forms a hydrogen bond of 2.23 Å and a CH---O interaction of 2.40 Å. The rise in relative dissociation

energy could be due to the fact that the hydrogen bond formed with a pendant hexyl group, instead of the cycle. Since a pendant hexyl group has more degrees of freedom than the cycle, the interactions with it can be less stable. As a result, the relative dissociation energy of structure 13 is of 10.11 kcal/mol.

Structure 14 has a cavity with dimensions of 12.75 and 3.61 Å. It forms three hydrogen bonds of 2.04, 2.34 and 2.30 Å. Although this geometry forms several hydrogen bonds, they are distant. This forces both the arginine methyl ester and cyc to adopt a spatial arrangement that is not stable. This is portrayed in the dimensions of the cycle. The shortest dimension remains almost unchanged compared to structure 13, but the longest dimension is considerably reduced to 12.75 Å. The conformational change could increase tension and the repulsion between neighboring atoms, causing a destabilization. The relative dissociation energy for this case has a value of 10.33 kcal/mol. Structure 15 forms two hydrogen bonds of 1.99 and 2.40 Å with the hydrogens attached to the same nitrogen in the guanidinium group, yet the rest of the arginine methyl ester does not interact with the macrocycle. In addition, the cyc has a concave shape. This could cause tension and rise the relative dissociation energy to a value of 10.46 kcal/mol. Finally, structure 16 has a cavity with dimensions of 14.17 and 3.81 Å. It forms three hydrogen bonds of 2.17, 2.02 and 2.14 Å. Eventhough these interactions reduce the dissociation energy, the cavity presents a concave shape which elevates the relative dissociation energy to 12.86 kcal/mol.

The HOMO/LUMO gaps of the configurations are listed in Table-1. They have similar values to the isolated cyclophane (4.51 eV). Their values do not fully explain the contribution of HOMO and LUMO orbitals to the stability of each species. Therefore, HOMO and LUMO electronic density plots (at a contour level of 0.022 a.u.) are shown in Fig. 4. The plots have been drawn for the arginine methyl ester, the cyclophane and cases 1and 16. This has been used to represent the bonding character in the remainder of the structures under consideration for the interest of space.

HOMO and LUMO plots: It can be noted that the HOMO plot of the arginine methyl ester is centered over the guanidinium group and slightly over the α-amino-group. This was expected, since the guanidinium group donates electrons to form hydrogen bonds with the cyclophane, contributing to the complex stability. On the other hand, the LUMO plot is placed over the methyl ester and mildly over the α-amino-group. In the case of the cyclophane, its HOMO and LUMO plots placed along the longest arcs of the cyc (from one hexyl chain to another). The most stable system is structure 1. In this configuration, the arginine methyl ester is placed over the HOMO and LUMO orbitals. The guanidinium group forms hydrogen bonds donating electrons from its HOMO to the LUMO of the cycle, forming a more stable orbital. Thus, the guanidinium group lies on top of the LUMO of the system. The methyl ester also interacts with the cyc and is placed over the HOMO of the system. This behaviour also is observed in the most stable systems. However, as the stability of the systems decreases, the arginine methyl ester does not lie over both, HOMO and LUMO orbitals. This can be portrayed in the least stable structure, configuration 16. Its HOMO remains almost unchanged compared to the

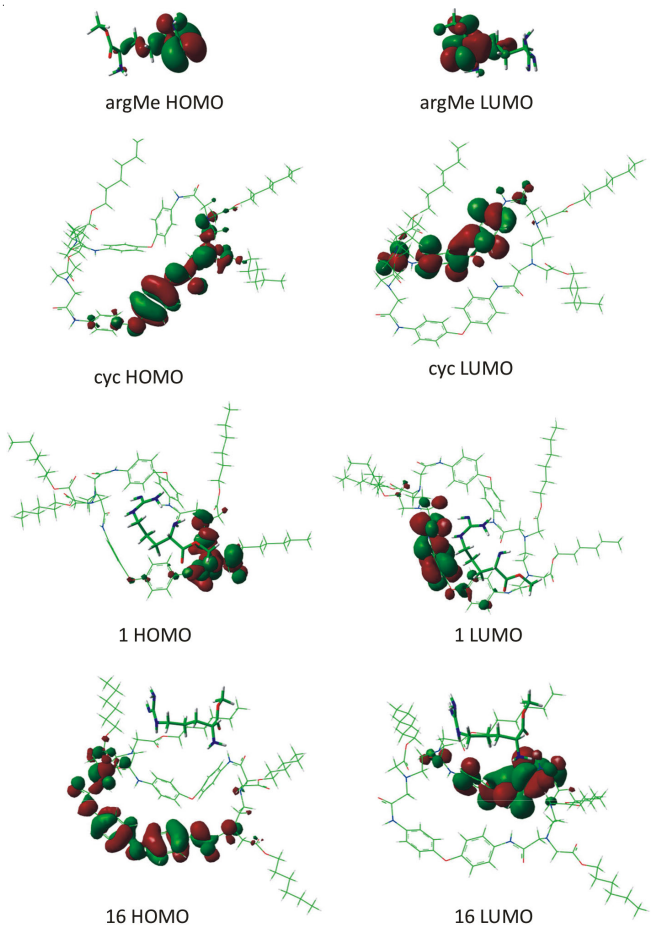

Fig. 4. HOMO and LUMO isosurfaces (at 0.02 a.u. contour level) for the isolated cyc, the isolated argMe and structures 1 and 16

isolated cyclophane. The LUMO is beneath the α-amino and ester groups of the arginine methyl ester. Thus, the host-guest interactions are not maximized causing the stability of the system to decrease.

Conclusion

In this study we performed quantum mechanical calculations of a cyclophane with four pendant hexyl chains as a receptor of arginine methyl ester. The complex between the two species formed in all the cases through supramolecular interactions such as hydrogen bonds and CH---O and CH---N interactions. Structure 1 is the most stable and the one that formed the most supramolecular interactions. Structure 16 is the least stable and had a relative dissociation energy of 12.86 kcal/mol.

The results showed that the strongest configurations interact with the macrocycle frame and not with the pendant hexyl chains. This could be due to their degrees of freedom which increase the relative dissociation energy, affecting its stability. It is interesting to note that the guanidinium group plays an important role in the stability of the systems. This is corroborated by the fact that all the structures except 5 and 7 formed complexes involving the guanidinium group. The importance of this group can also be confirmed by the LUMO plot. The α-amino group also formed hydrogen bonds with the cycle, although its contribution to the stability of the structures was not as noteworthy as for the guanidinium group. The HOMO

and LUMO plots also reveal that in the most stable systems the arginine methyl ester is placed above both HOMO and LUMO orbitals. On the other hand, the least stable systems lie only above one of these orbitals.

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REFERENCES

1. W. Verboom, D.M. Rudkevich and D.N. Reinhoudt, *Pure Appl. Chem.*, **66**, 679 (1994).
2. M.B. Inoue, E.F. Velazquez, M. Inoue and Q. Fernando, *J. Chem. Soc., Perkin Trans. II*, 2113 (1997).
3. J.-S. You, X.-Q. Yu, Q.-X. Xiang, J.-B. Lan, R.-G. Xie and G.-L. Zhang, *Chem. Commun.*, 1816 (2001).
4. M. Rekharsky and Y. Yoshihisa, Solvation Effects in Supramolecular Recognition, In: Supramolecular Chemistry: From Molecules to Nanomaterials, John Wiley & Sons (2012).
5. N. Ahmed, B. Shirinfar, I. Geronimo and K.S. Kim, *Org. Lett.*, **13**, 5476 (2011).
6. O. Hayashida, N. Ogawa and M. Uchiyama, *J. Am. Chem. Soc.*, **129**, 13698 (2007).
7. M. Mazik and C. Geffert, *Org. Biomol. Chem.*, **9**, 2319 (2011).
8. M. Mazik and H. Cavga, *J. Org. Chem.*, **71**, 2957 (2006).
9. M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J.L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J.A. Montgomery, Jr., J.E. Peralta, F. Ogliaro, M. Bearpark, J.J. Heyd, E. Brothers, K.N. Kudin, V.N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J.M. Millam, M. Klene, J.E. Knox, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, R.L. Martin, K. Morokuma, V.G. Zakrzewski, G.A. Voth, P. Salvador, J.J. Dannenberg, S. Dapprich, A.D. Daniels, Ö. Farkas, J.B. Foresman, J.V. Ortiz, J. Cioslowski and D.J. Fox, Gaussian 09, Gaussian, Inc., Wallingford CT (2009).
10. A.D. Becke, *J. Chem. Phys.*, **98**, 5648 (1993).
11. G.A. Petersson, A. Bennett, T.G. Tensfeldt, M.A. Al-Laham, W.A. Shirley and J. Mantzaris, *J. Chem. Phys.*, **89**, 2193 (1988).
12. J.P. Perdew, in ed.: Ed. P. Ziesche and H. Eschrig, Electronic Structure of Solids, Akademie Verlag, Berlin (1991).
13. J.P. Perdew, K. Burke and M. Ernzerhof, *Phys. Rev. Lett.*, **77**, 3865 (1996).
14. F.A. Hamprecht, A. Cohen, D.J. Tozer and N.C. Handy, *J. Chem. Phys.*, **109**, 6264 (1998).
15. S.H. Vosko, L. Wilk and M. Nusair, *Can. J. Phys.*, **58**, 1200 (1980).
16. S. Balakrishnan, M.J. Scheuermann and N.J. Zondlo, *ChemBioChem*, **13**, 259 (2012).