Regular Article

PHYSICAL CHEMISTRY RESEARCH
Published by the
Iranian Chemical Society
www.physchemres.org
info@physchemres.org

***Phys. Chem. Res.**, Vol. 2, No. 2, 131-136, December 2014.*
DOI: 10.22036/pcr.2014.4583

A Thermodynamic Study of the Interactions between Acetamide Derivatives and PCA-PEG-PCA Copolymers: ONIOM Calculations

M. Oftadeh* and N. Madadi Mahani

Chemistry Department, Payame Noor University, 19395-4697 Tehran, I. R. of Iran

(Received 30 October 2013, Accepted 28 January 2014)

To improve drug selectivity toward target cells, one interesting approach for drug delivery is to use polymer nanoparticles. A two-layered ONIOM Becke3-LYP: UFF calculation was carried out to study the structural and thermodynamic properties of the interaction between acetamide derivatives and the PCA-PEG-PCA copolymers. The Interaction enthalpies and the Gibbs free energies between acetamide derivatives as anti-HIV and polymeric nanoparticles in the gas and solution phases were calculated. The structure as well as the thermodynamics of optimized complexes was discussed from the biological point of view. In the gas phase, substitutes of phenyl, flurophenyl, 4-acetyl-2-bromophenyl, and 3-methyl-acetate-thiophen-2-yl had the highest energies, and in the water phase, the enthalpies and Gibbs free energies of the interaction for most compounds were almost identical. In the both phases the interaction is relatively weak and copolymers can be used for drug delivery.

Keywords: ONIOM2, Copolymer, Anti-HIV drug, Enthalpy, Gibbs free energy, Drug Delivery

INTRODUCTION

Nowadays, non-nucleoside reverse transcriptase-inhibitors (NNRTIs) represent very potent and most promising anti-AIDS agents that specifically target the HIV-1 reverse transcriptase (RT). However, the effectiveness of NNRTI drugs can be hampered by the rapid emergence of drug-resistant viruses and severe side effects upon long-term use. Therefore, there is an urgent need to develop novel, highly potent NNRTIs with broad spectrum antiviral activity and improved pharmacokinetic properties, and more efficient strategies [1]. Recently, a series of 2-(4-(naphthalen-2-yl)-1,2,3-thiadiazol-5-ylthio) acetamide (TTA) derivatives as novel non-nucleoside HIV-1reverse transcriptase inhibitors have been synthesized by Zhan and coworkers [2]. To improve drug selectivity toward target cells, one interesting approach for drug delivery is to use polymer and peptide based transporters [3]. Currently, the potential of polymeric nanoparticles for targeted drug delivery is being investigated for several life threatening disorders, including cancer and HIV [4].

The well-defined structure, compact globular shape, size mono disparity and controllable 'surface' functionalities of dendrimers make them excellent candidates for evaluation as drug carriers [5]. Based on their molecular self-assembly, linear-dendritic of poly (citric acid) (PCA) and poly(ethylene glycol) (PEG) as PCA-PEG-PCA copolymers are promising nanomaterials to be used in nanomedicine [6]. Theoretical study on interactions between constituents of biological systems is very important to design new medicines. Hence, quantum study of interactions between anti-HIV drug and polymeric nanoparticles PCA-PEG-PCA is considerably important. The interaction between drugs (benzoates, diltiazem, cyanocobalamin, dextrans) and poly(*N*-isopropylacrylamide) polymers by quantum method has already been investigated by Coughlan and coworkers [7].

The thermodynamic study of the interaction between acetamide derivatives and PCA-PEG-PCA copolymer will be really important for understanding the biological impact

*Corresponding author. E-mail: m_oftadeh@pnu.ac.ir

of drug.

Hybrid QM/MM methods were developed and applied to study the reaction mechanisms in biological systems. The ONIOM (our own n-layered integrated molecular orbital and molecular mechanics) approach is a hybrid QM/MM method which has been proved efficient over the year. In the ONIOM approach, a small part of a system is treated at a high level of calculation whereas the larger surroundings are modeled using a lower level of calculation [8]. In the two-layered ONIOM method, the total energy of the system is obtained from three independent calculations as shown in Eq. (1):

$$E_{(\mathrm{ONIOM2})} = E_{(\mathrm{High,\ Model})} + E_{(\mathrm{Low,\ Real})} - E_{(\mathrm{Low,\ Model})} = E_{(\mathrm{High,\ Model})} + \Delta E_{(\mathrm{Low,\ Real} \leftarrow \mathrm{Model})} \quad (1)$$

where 'Real' denotes the full system treated at the 'Low' level, while 'Model' denotes that part of the system at which the energy is calculated at both 'High' and 'Low' levels.

Applicability of the ONIOM2 and ONIOM3 methods to the NNRTIs and the HIV-1 reverse transcriptase binding site has been under study. In this respect, the HIV-1 RT binding site and nevirapine [9], TIBO [10] and efavirenz [11] have been investigated through ONIOM calculations. Also, the interaction between different ligands and the proteins responsible for the human immunodeficiency virus type 1 (HIV-1) cycle replication has been studied using QM/MM methods by Swiderek *et al.* [12].

The density functional theory (DFT) using Becke3LYP functional and the two-layered ONIOM Becke3-LYP:MNDO calculations was carried out to investigate the structural and thermodynamic properties of angiotensin-converting enzyme inhibitors [13]. Two-layer ONIOM method (B3LYP/6-31+G(d):UFF) for the study of the interaction between N-substituted piperazinylfluoro-quinolones and ds-DNA as well as the calculation of thermodynamic properties of this interaction was applied by Ahmadi *et al.* [14].

Since the direct experimental determination of structural and thermodynamic parameters of drug-polymer systems is very complicated, the methods of computational chemistry are good alternatives [15,16].

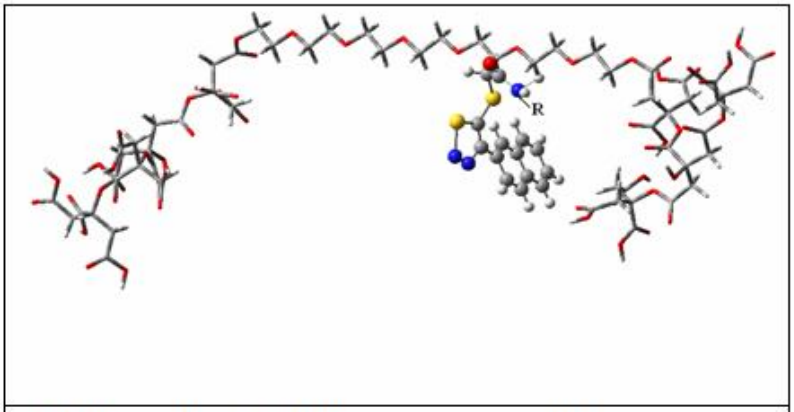
In the previous works [17-19], the binding energies of the anti-HIV drugs (TTAs derivatives) and the polymeric nanoparticle were investigated by the ONIOM2 (B3LYP/6-31G:UFF) method. Results show that the interactions are weak indicating the fact that these nanocarriers can be utilized to improve the biological and anti-HIV activity of TTAs. To confirm the previous results, thermodynamic quantities of interaction were calculated using the two-layered ONIOM Becke3LYP:UFF method.

Method

The optimized molecular geometries of 2-(4-(2,4-dichlorophenyl)-1,2,3-thiadiazol-5-ylthio)-N-acetamide (TTA)/PCA-PEG-PCA systems are depicted in Fig. 1. They have been optimized in the gas phase using Gaussian 09 program [20] by ONIOM2 method [21]. The ONIOM2-PCM method [22] was also used in water phase, which combines the ONIOM method with the polarizable continuum model (PCM). The model system as well as the real molecule were modeled for the two-layer ONIOM calculations. This level of calculation will hereafter be called (B3LYP/6-31G:UFF). The interaction between the drugs and the polymeric nanoparticles has been thermodynamically investigated. The model system and the real molecule applied in ONIOM2 calculations are shown in Fig. 1. The QM region was treated at the level of gradient-corrected DFT [23,24] using a three-parameter fit of the exchange-correlation potential suggested by Becke, B3, in conjunction with the functional correlation suggested by Lee, Yang and Parr, LYP [25,26]. The MM region was treated using the UFF force field.

RESULTS AND DISCUSSION

One of the methods for developing new drug compounds is to improve their pharmacological effects. Study of the thermodynamic properties of the interaction between acetamide derivatives as anti-HIV and polymeric nanoparticles is biologically important for the prediction of pharmacological properties of acetamide derivatives as well as the use of polymer as drug carriers. According to the multi-layered approach (ONIOM) developed by morokuma [21], the following relationships can be suggested for the enthalpy and Gibbs free energy of ONIOM2 (QM/MM):



System	R	System	R
1	H	7	$PhNO_2$
2	Ph	8	2-bromo-4-methylphenyl
3	PhF	9	4-acetyl-2-bromophenyl
4	PhCl	10	2-choloropyridine-3-yl
5	PhBr	11	O-tolyl
6	PhOH	12	5-methylacetate-thiophen-2-yl

Fig. 1. TTA derivatives and $(PCA)_3$-$(PEG)_{10}$-$(PCA)_3$ copolymer (ONIOM2).

$$G_{ONIOM} = G_{QM(Model)} + G_{MM(Real)} - G_{MM(Model)} \quad (3)$$

$$H_{ONIOM} = H_{QM(Model)} + H_{MM(Real)} - H_{MM(Model)} \quad (4)$$

Hence, the enthalpy and the Gibbs free energy of interaction QM/MM between drug and polymer can be obtained as follows:

$$\Delta G_{int} = G_{ONIOM} - G_{QM,drug} - G_{MM,polymer} \quad (5)$$

$$\Delta H_{int} = H_{ONIOM} - H_{QM,drug} - H_{MM,polymer} \quad (6)$$

The constituent values of the enthalpy and the Gibbs free energy of acetamide derivatives as anti-HIV drugs and polymeric nanoparticles as polymer drug carriers evaluated from the ONOIM2 output results are listed in Tables 1 and 2 in the gas phase and the water phase, respectively. The enthalpy and the Gibbs free energy of entitled polymer calculated constituently by UFF method in the gas phase are 2.5105 and 2.3269 and in the water phase are 2.0282 and 1.7497 Hartree, respectively. The calculated values of thermodynamic quantities for the interaction between drugs and polymer through the application of the ONIOM2 approach, based on Eqs. (3)-(6) in the gas and water phases, are summarized in Table 3. The relative values of the thermodynamic quantities with respect to system 1 are also given in Table 4.

In both phases, the calculated enthalpies and Gibbs free energies of the interaction values were negative and relatively low indicating that this interaction is spontaneous but weak. In the gas phase, among the TTA derivatives, substitutes of H by Ph, PhF, 4-acetyl-2-bromophenyl and 3-Methylacetate-thiophen-2-yl (systems 2, 3, 9 and 12, respectively) lead to the highest energies, whereas the other substitutes had lower values. Through the data analysis of

Table 1. Enthalpy and Gibbs Free Energy Values of Drug and Polymer (in Hartree) in the Gas Phase

	Drug (UFF)		Drug-Polymer (UFF)		Drug (B3lyp/6-31G)	
R	H	G	H	G	H	G
1	2.3550	2.0374	4.8568	4.3549	-1575.3525	-1575.4955
2	0.8468	0.7690	3.3498	3.0881	-1802.5446	-1802.6029
3	0.8379	0.7587	3.341	3.0780	-1897.3447	-1897.3989
4	1.2298	1.1518	3.7370	3.4745	-2260.6387	-2260.6975
5	1.1879	1.1094	3.6949	3.4320	-4372.2102	-4372.2687
6	0.4618	0.3866	2.9686	2.7091	-1881.5116	-1881.5758
7	1.2593	1.1809	3.7659	3.5032	-2010.5540	-2010.6202
8	0.5053	0.4215	3.0118	2.7438	-4415.6943	-4415.7585
9	2.8487	2.7667	5.3545	5.0888	-4526.8961	-4526.9621
10	0.4317	0.3548	2.9392	2.6784	-2281.5089	-2281.5803
11	0.8685	0.7919	3.3758	3.1151	-1844.3853	-4411.7902
12	0.4779	0.3980	2.9839	2.7199	-2353.5466	-2353.6089

Table 2. Enthalpy and Gibbs Free Energy Values of Drug and Polymer (in Hartree) in the Water Phase

	Drug (UFF)		Drug-Polymer (UFF)		Drug (B3lyp/6-31G)	
R	H	G	H	G	H	G
1	1.4527	1.2683	3.4688	3.0055	-1575.3714	-1575.4472
2	0.7533	0.7045	2.7714	2.4438	-1805.2662	-1805.3234
3	1.2845	1.2185	3.3035	2.9588	-1903.1176	-1903.1758
4	0.9362	0.8271	2.9562	2.5685	-2263.4524	-2263.5115
5	1.0091	1.0035	3.0292	2.7449	-4372.2556	-4372.3147
6	0.4769	0.4015	2.4964	2.1422	-1881.5603	-1881.6229
7	0.9817	0.7020	3.0017	2.4429	-2010.5942	-2010.66358
8	0.5941	0.4139	2.6136	2.1543	-4415.7489	-4415.8148
9	2.2125	1.7298	4.2311	3.4696	-4526.8961	-4526.9621
10	0.4449	0.3691	2.4652	2.1106	-2281.5603	-2281.6310
11	0.5607	0.5251	2.5809	2.2666	-1844.4252	-1844.4973
12	0.4814	0.3881	2.4998	2.1278	-2353.5999	-2353.6619

Table 3. Enthalpies, Relative Enthalpies, Gibbs Free Energies andR Gibbs Free Energies (in kcal mol^{-1}) of Iinteraction Drug and Polymer with ONIOM2 (B3LYP/6-31G:UFF) Method in the Gas and Water Phases

	Gas				Water			
R	ΔH_{int}	$\Delta H_{Relative}$	ΔG_{int}	$\Delta G_{Relative}$	ΔH_{int}	$\Delta H_{Relative}$	ΔG_{int}	$\Delta G_{Relative}$
1	-5.47	0	-5.96	0	-7.58	0	-7.88	0
2	-4.72	0.75	-4.87	1.09	-6.40	1.18	-6.53	1.35
3	-4.66	0.81	-4.79	1.17	-5.79	1.80	-5.92	1.96
4	-2.02	3.45	-2.62	3.34	-5.12	2.46	-5.24	2.63
5	-2.21	3.26	-2.73	3.23	-5.11	2.47	-5.28	2.60
6	-2.37	3.10	-2.78	3.18	-5.48	2.11	-5.68	2.20
7	-2.49	2.98	-2.83	3.13	-5.15	2.44	-5.57	2.31
8	-2.46	3.01	-2.93	3.03	-5.50	2.09	-5.84	2.04
9	-2.97	2.50	-3.07	2.89	-6.08	1.50	-6.26	1.62
10	-1.90	3.57	-2.09	3.86	-4.98	2.60	-5.15	2.73
11	-2.01	3.46	-2.30	3.66	-5.05	2.54	-5.20	2.69
12	-2.85	2.62	-3.09	2.87	-6.16	1.42	-6.35	1.53

the relative enthalpies and Gibbs free energies in the gas phase it was found that the interaction between systems 4, 5, 6, 10 and 11 are weaker than system 1. In the water phase, the enthalpies and Gibbs free energies of the interaction for most systems are almost identical and the substituents have little effect on the thermodynamic properties. Moreover, the calculated relative enthalpies and the Gibbs free energies in the water phase show that the TTA derivatives have the same interactions in the presence of water molecules. The interaction of substituted TTA by Ph and PhF with polymeric nanoparticles is more exothermic whereas the other substitutions make the interaction enthalpy less exothermic. Maybe Ph and PhF substitutions can slightly increase relative polarity and so the interaction enthalpies more exothermic. The results show that the most stable complex of the drug-polymer is unsubstituted TTA-polymer, No. 1. Finally, the substitutions of PhCl, PhBr, 2-choloropyridine-3-yl and o-tolyl lead to form less stable complexes in both phases which have 3.34, 3.23, 3.86 and 3.66 kcal mol^{-1} (in the gas phase) and 2.63, 2.60, 2.73 and 2.69 kcal mol^{-1} (in the water solvent) Gibbs free energy higher than those of TTA, respectively. These results suggest that the interaction between the drug and copolymer is weak. In addition, PCA-PEG-PCA copolymeric nanoparticles can be used as a drug carrier for drug delivery process in the AIDS patients.

CONCLUSIONS

The present research was carried out to investigate the

interaction enthalpies and the Gibbs free energies between acetamide derivatives as the anti-HIV and the polymeric nanoparticles. The calculated interaction enthalpies and the Gibbs free energies with ONIOM2 have negative and low values indicating the relatively weak and spontaneous interaction. Therefore, these systems have relatively low level of stability and the PCA-PEG-PCA copolymers can be used for drug delivery. The calculated results showed that the interaction is spontaneous ($\Delta G < 0$) and exothermic ($\Delta H < 0$) in both gas phase and water solvent.

REFERENCES

[1] P. Zhan, X. Chen, D. Li, Z. Fang, E.D. Clercq, X. Liu, Med. Res. Rev. 1 (2011) 72.

[2] P. Zhan, X. Liu, Z. Fang, Z. Li, C. Pannecouque, E.D. Clercq, Eur. J. Med. Chem. 44 (2009) 4648.

[3] M. Adeli, R. Haag, J. Polym. Sci. A Pol. Chem. 44 (2006) 5740.

[4] T. Akagi, M. Baba, M. Akashi, J. Pharm. Soc. Jpn. 127 (2007) 307.

[5] A.D. Costache, L. Sheihet, K. Zaveri, D.D. Knight, J. Mol. Pharmaceut. 127 (2009) 1620.

[6] A. Tavakoli Naeini, M. Adeli, M. Vossoughi, Nanomed-Nanotechnol. 6 (2010) 556.

[7] D.C. Coughlan, O.I. Corrigan, Int. J. Pharm. 313 (2006) 163.

[8] T. Matsubara, S. Sieber, K. Morokuma, Int. J. Quant. Chem. 60 (1996) 110.

[9] M. Kuno, S. Hannongbua, K. Morokuma, Chem. Phys. Letts. 380 (2003) 456.

[10] S. Saen-oon, M. Kuno, S. Hannongbua, Proteins 61 (2005) 859.

[11] P. Nunrium, M. Kuno, S. Saen-oon, S. Hannongbua, Chem. Phys. Letts. 405 (2005) 102.

[12] K. Swiderek, S. Marti, V. Moliner, Phys. Chem. Chem. Phys. 14 (2012) 12614.

[13] M. Sramko, V. Garaj, M. Remko, J. Mol. Struc-THEOCHEM 869 (2008) 19.

[14] F. Ahmadi, S. Jahangard-Yekta, A. Heidari-Moghadam, A.R. Aliabadi, Comput. Theor. Chem. 1006 (2013) 9.

[15] A. Adamescu, I.P. Hamilton, H.A. Al-Abadleh, Environ. Sci. Technol. 45 (2011) 10438.

[16] D.A. McQuarrie, J.D. Simon, Molecular Thermodynamics, Sausalito, Calif., University Science Books, 2010.

[17] M. Oftadeh, N. Madadi Mahani, M. Hamadanian, Res. Pharmaceut. Sci. 8 (2013) 285.

[18] M. Oftadeh, N. Madadi Mahani, J. Pharmaceut. Invest. 45 (2013) 323.

[19] M. Oftadeh, N. Madadi Mahani, R. Bahjatmanesh Ardakani, J. Nanostruct. 2 (2013) 485.

[20] 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, O. Farkas, J.B. Foresman, J.V. Ortiz, J. Cioslowski, D.J. Fox, Gaussian, Inc., Wallingford CT, 2009.

[21] T. Vreven, B. Mennucci, C.O. Silva, K. Morokuma, J. Tomasi, J. Chem. Phys. 115 (2001) 62.

[22] K. Morokuma, Bull. Korean Chem. Soc. 24 (2003) 797.

[23] R.G. Parr, W. Yang, Density Functional Theory of Atoms and Molecules, Oxford University Press, Oxford, 1989.

[24] D.C. Yang, Computatinal Chemistry: A Practical Guide for Applying Techniques to Real-World Problems, A JOHN WILEY & SONS, Inc., 2001.

[25] A.D. Becke, J. Chem. Phys. 98 (1993) 5648.

[26] C. Lee, W. Yang, R.G. Parr, Phys. Rev. B 37 (1988) 785.