Interaction between threonine and cadmium cation in $[Cd(Thr)_n]^{2+}$ (n = 1—3) complexes: density functional calculations

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Structures corresponding to energy minima and the binding of cadmium cation to threonine (Thr) in model systems $[Cd(Thr)_n]^{2+}$ (n = 1—3) were studied theoretically. Quantum chemical computations were performed within the framework of the density functional theory using the B3LYP, BLYP, and P functionals. In the optimized structures of the complexes $[CdThr]^{2+}$ and $[Cd(Thr)_2]^{2+}$, threonine acts as a bidentate ligand and cadmium binds to oxygen atoms of carbonyl and hydroxyl groups with the formation of one and two six-membered rings, respectively. In the complex $[Cd(Thr)_3]^{2+}$, cadmium binds to three nitrogen atoms and three oxygen atoms of carbonyl groups in three Thr molecules to form three five-membered rings.

Key words: cadmium, threonine, cation, quantum chemical calculations, density functional theory.

Complexes of amino acids with metal cations play an important role in biological processes. They have been studied both experimentally and theoretically.[1—8] The main metabolic feature of cadmium is an exceptionally long biological half-life resulting in a virtually irreversible accumulation of the metal in the body throughout life. In blood, more than 90% of cadmium is found in cells. Cadmium is a relatively rare element (abundance in the Earth crust is estimated to be 0.2 mg kg^{-1}) and is not found in the pure state in nature.[9,10] The average amount of cadmium inhaled daily by humans in rural, urban, and industrialized areas should not exceed 0.01, 0.2, and 0.4 μg, respectively.[3] In food, the concentration of cadmium is in the range 1—50 μg kg^{-1} in meat, fish, and fruits and 10—300 μg kg^{-1} in stable foods such as wheat, rice, and potatoes. The highest cadmium levels (100—1000 μg kg^{-1}) are found in the internal organs (kidney and liver) of mammals and in species of mussels, scallops, and oysters. The average amount of cadmium absorbed *via* food can thus be estimated at about 1 μg kg^{-1}.[11—13] Cadmium is first transported to the liver through the blood and binds there to proteins to form complexes that are subsequently transported to the kidneys. Cadmium accumulates in kidneys, where it damages filtering mechanisms. This causes the excretion of essential proteins (in particular, threonine) and sugars from the body and further kidney damage. It takes a very long time before cadmium that has accumulated in kidneys is excreted from a human body.

The main goal of the present work was to use the density functional theory calculations to study the interaction of threonine with cadmium cation (Cd^{2+}) and the formation of threonine complexes with cadmium Cd^{2+}—$(Thr)_n$ (n = 1—3).

Calculation Procedure

In this work, calculations of the model systems $[Cd(Thr)_n]^{2+}$ (n = 1—3) were carried out within the framework of the density functional theory with the B3LYP, BLYP, and P functionals (hereafter, the B3LYP, BLYP, and P methods, respectively) using the GAUSSIAN-98 program package.[14] The $[Cd(Thr)_n]^{2+}$ fragment was considered as a doublet molecule, with partitioning of the basis set. For systems containing C, H, N, and O atoms, the 6-31G* basis set was used; for cadmium, the LANL2DZ basis set was used. Threonine is a tetradentate ligand; therefore, we studied the interactions of cadmium with oxygen atoms of carbonyl, hydroxyl, and acidic OH groups as well as the nitrogen site and the formation of isomeric structures of the complex $[CdThr]^{2+}$. To identify the most stable isomer, calculations were performed without any symmetry constraints. Test calculations on the most stable isomers of the complexes $[Cd(Thr)_2]^{2+}$ and $[Cd(Thr)_3]^{2+}$ were carried out by the B3LYP, BLYP, and P methods with full geometry optimization.

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Results and Discussion

Complex $[CdThr]^{2+}$. In this case, cadmium was allowed to coordinate to the nitrogen and different oxygen sites. Therefore, we considered six isomeric structures (**1**—**6**) corresponding to energy minima (Fig. 1). The lowest energies of the isomers were obtained by the BLYP method (Fig. 2).

The relative energies of structures **1**—**6** are collected in Table 1. The most stable is structure **6**. It contains cadmium coordinated to oxygen atoms of carbonyl and hydroxyl groups and a six-membered ring, which is more stable than four- or five-membered rings because of a much lower angular strain compared to other structures.

Selected geometric parameters of structure **6** are listed in Table 2.

Complex $[Cd(Thr)_2]^{2+}$. Prior to geometry optimization, we assumed that in the complex $[Cd(Thr)_2]^{2+}$ two threonine ligands are coordinated at nitrogen sites and oxygen atoms of carbonyl groups to form two five membered-rings.

According to calculations, in the optimized structure of the complex $[Cd(Thr)_2]^{2+}$ cadmium is coordinated with oxygen atoms of carbonyl and alcohol hydroxyl groups in the main chain of the amino acid molecule. It should be noted that the optimized structure contains two six-membered rings (Fig. 3) having a lower angular strain compared to five-membered rings. The energies and selected geometric parameters of the optimized structure of complex $[Cd(Thr)_2]^{2+}$ (see Fig. 3) are listed in Tables 3 and 4, respectively. The lowest energy of the complex $[Cd(Thr)_2]^{2+}$ was obtained by the B3LYP method.

Complex $[Cd(Thr)_3]^{2+}$. Initially, we assumed that in the complex $[Cd(Thr)_3]^{2+}$ each of the three threonine ligands is coordinated at the oxygen atom of carbonyl group and the nitrogen atom to form a structure with three five-membered rings. Indeed, geometry optimization showed that cadmium is coordinated to all oxygen atoms of carbonyl groups and all nitrogen atoms and the optimized structure contains three five-membered rings (Fig. 4) unlike the trend shown in the structures of the complexes $[Cd(Thr)_2]^{2+}$ and $[Cd(Thr)]^{2+}$. The results

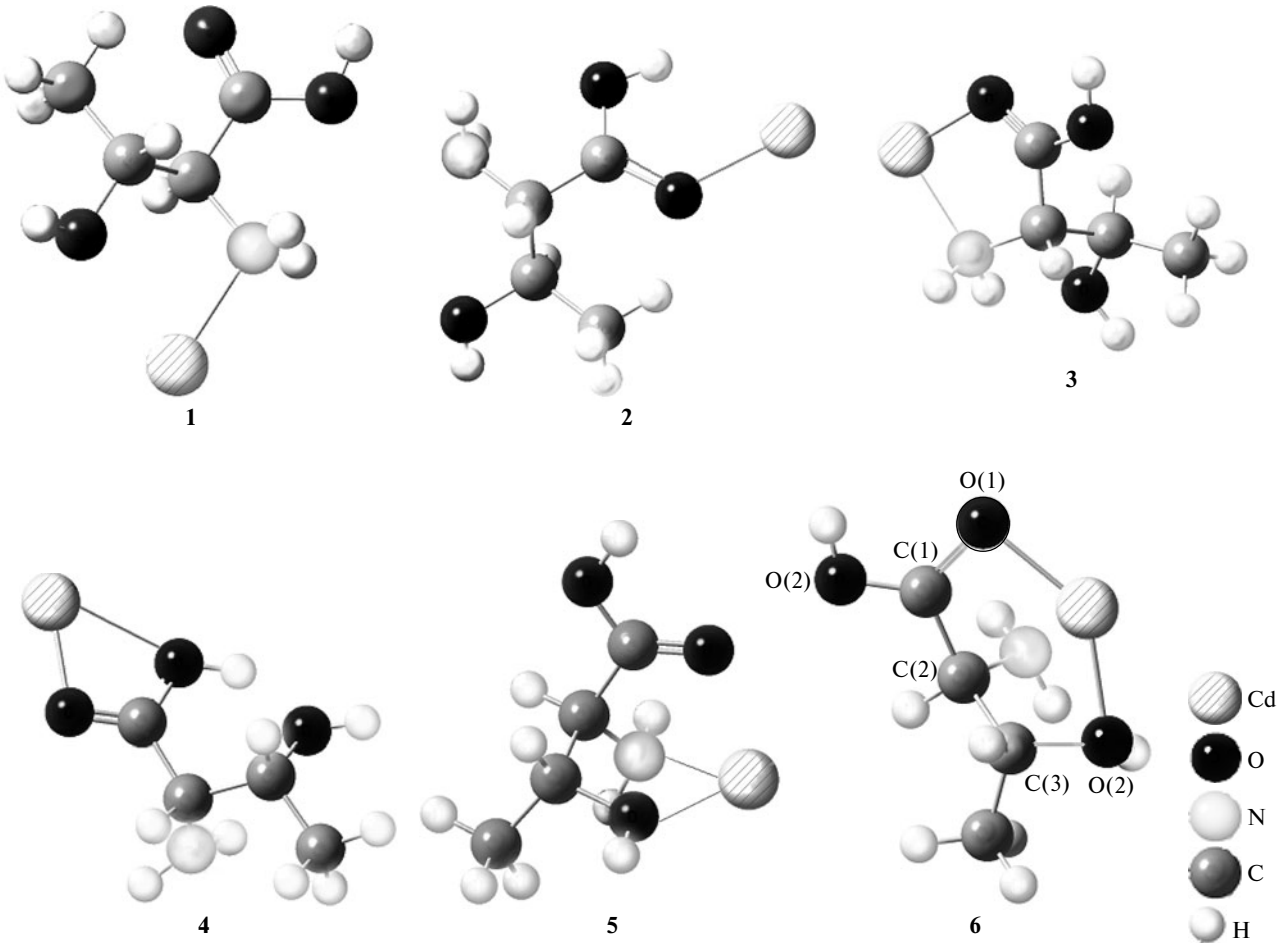

Fig. 1. Isomeric structures **1**—**6** of complex $[CdThr]^{2+}$ corresponding to energy minima.

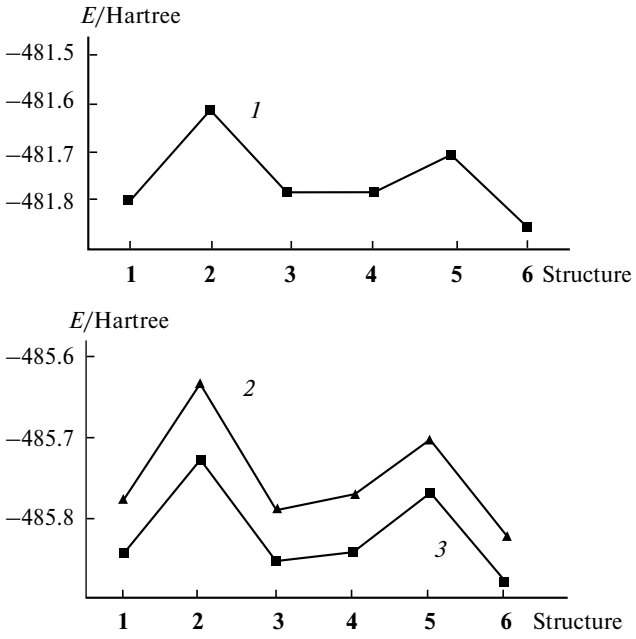

Fig. 2. Energies (E) of structures **1**—**6** of the complex $[Cd(Thr)]^{2+}$ obtained from P (*1*), B3LYP (*2*), and BLYP (*3*) calculations.

Table 1. Relative energies (ΔE) of structures **1**—**6** of the complex $[Cd(Thr)]^{2+}$ calculated by different methods

Isomer	ΔE/kcal mol^{-1}		
	P	BLYP	B3LYP
1	31.38	17.26	25.10
2	156.88	96.40	119.23
3	43.92	23.01	25.15
4	50.20	23.53	37.65
5	94.12	69.56	75.30
6	0	0	0

Table 2. Selected bond lengths (d) and bond angles (ω) in the optimized structure **6** of the complex $[CdThr]^{2+}$

Bond	d/Å	Angle	ω/deg
Cd—O(1)	2.26	O(1)—Cd—O(2)	84.96
C(2)—C(3)	1.56	C(2)—C(3)—O(2)	105.34
C(1)—C(2)	1.55	C(1)—C(2)—C(3)	109.99
Cd—O(3)	2.28	C(1)—O(1)—Cd	107.72
C(1)—O(1)	1.26	C(3)—O(2)—Cd	114.63
C(3)—O(2)	1.50	O(1)—C(1)—C(2)	122.84

obtained are due to the influence of steric effects which are more pronounced than in other cases because of the addition of three amino acid molecules. Thus, in the complex $[Cd(Thr)_3]^{2+}$ the five-membered rings are more stable than the six-membered rings. The energies and selected

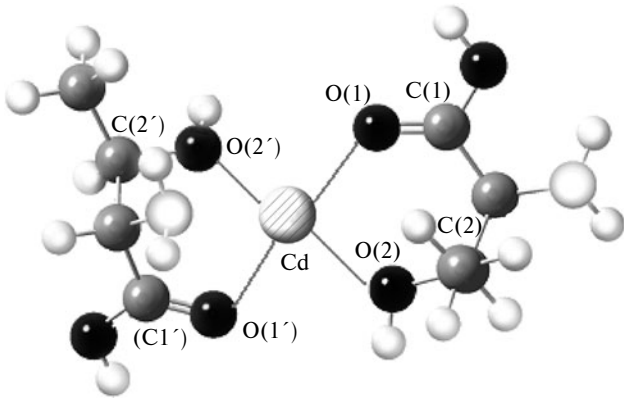

Fig. 3. Optimized structure of the complex $[Cd(Thr)_2]^{2+}$.

Table 3. Energies (E) of the complexes $[Cd(Thr)_2]^{2+}$ and $[Cd(Thr)_3]^{2+}$ calculated by different methods

Complex	−E/Hartree		
	B3LYP	BLYP	P
$[Cd(Thr)_2]^{2+}$	924.12	924.03	917.65
$[Cd(Thr)_3]^{2+}$	1362.43	1362.17	1353.46

Table 4. Selected bond lengths (d) and bond angles (ω) in the complex $[Cd(Thr)_2]^{2+}$ calculated by the B3LYP method

Bond	d/Å	Angle	ω/deg
Cd—O(1)	2.34	O(1)—Cd—O(2)	79.95
Cd—O(2)	2.34	O(1′)—Cd—O(2′)	82.15
Cd—O(1′)	2.22	C(1)—O(1)—Cd	109.76
C(1)—O(1)	1.23	C(2)—O(2)—Cd	116.73
C(1′)—O(1′)	1.25	C(2′)—O(2′)—Cd	125.26
Cd—O(2′)	2.25	C(1′)—O(1′)—Cd	132.34

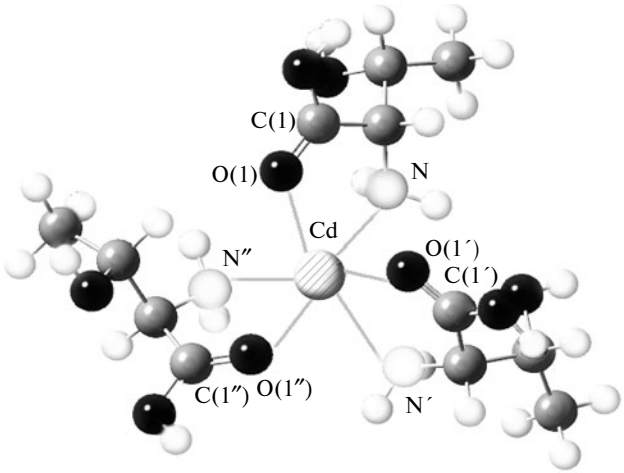

Fig. 4. Optimized structure of the complex $[Cd(Thr)_3]^{2+}$.

Table 5. Selected bond lengths (d) and bond angles (ω) in the complex $[Cd(Thr)_3]^{2+}$ calculated by the B3LYP method

Bond	d/Å	Angle	ω/deg
Cd—O(1′)	2.41	O(1)—Cd—N	69.31
Cd—O(1)	2.50	O(1)—Cd—N	69.51
Cd—N	2.47	O(1)—Cd—N	70.30
C(1′)—O(1′)	1.21	C—N—Cd	109.33
C(1′′) —O(1′′)	1.20	C—N—Cd	112.15
C(1)—O(1)	1.20	C—N—Cd	113.88
Cd—O(1′)	2.48	C(1)—O(1)—Cd	119.16
Cd—N′′	2.43	C(1′′)—O(1′′)—Cd	120.39
Cd—N′	2.45	C(1)—O(1)—Cd	122.79

geometric parameters of the optimized structure of this complex are listed in Tables 3 and 5, respectively. The lowest energy of the complex $[Cd(Thr)_3]^{2+}$ was obtained from the B3LYP calculations.

The most important results presented above can be summarized as follows. We have shown that in the optimized structures of the complexes $[Cd(Thr)]^{2+}$ and $[Cd(Thr)_2]^{2+}$ cadmium is coordinated to oxygen atoms of carbonyl and hydroxyl groups and the structures contain one and two six-membered rings, respectively. According to calculations, six-membered rings are more stable than the four- or five-membered rings because of much lower angular strain. Unlike the complexes $[Cd(Thr)_2]^{2+}$ and $[CdThr]^{2+}$, in the optimized structure of the complex $[Cd(Thr)_3]^{2+}$ cadmium is coordinated to oxygen atoms of three carbonyl groups and three nitrogen atoms in such a fashion that three five-membered rings are formed. This is due to steric effects. The lowest energies were obtained using the BLYP (for the complex $[CdThr]^{2+}$) and B3LYP (for the complexes $[Cd(Thr)_2]^{2+}$ and $[Cd(Thr)_3]^{2+}$) functionals. It is noteworthy that the Cd—O bonds in the complex $[CdThr]^{2+}$ are shorter than in the complexes $[Cd(Thr)_2]^{2+}$ and $[Cd(Thr)_3]^{2+}$ for which steric effects are more pronounced because of the addition of several amino acid molecules.

References

1. L. M. Mallis, D. H. Russel, *Anal. Chem.*, 1985, **58**, 1076.
2. R. P. Grese, R. L. Cerny, M. L. Gross, *J. Am. Chem. Soc.*, 1989, **111**, 2835.
3. F. Jensen, *J. Am. Chem. Soc.*, 1992, **114**, 9533.
4. S. Bouchonnet, Y. Hoppilliard, *Org. Mass Spectrom.*, 1992, **27**, 71.
5. D. Yu, A. Rauk, D. A. Armstrong, *J. Am. Chem. Soc.*, 1995, **117**, 1789.
6. M. Benzakour, A. Cartier, M. Mcharfi, A. Daoudi, *J. Mol. Struct.*, 2004, **681**, 99.
7. S. Hoyau, K. Norrman, T. B. McMahon, G. Ohanessian, *J. Am. Chem. Soc.*, 1999, **121**, 8864.
8. M. M. Kish, G. Ohanessian, C. Wesdemiotis, *Int. J. Mass Spectrom.*, 2003, **227**, 509.
9. L. Friberg, E. Tal, *Cadmium and Health: a Toxicological and Epidemiological Appraisal. Vol. 1. Exposure, Dose and Metabolism*, CRC Press, Boca Raton, 1986.
10. *Beryllium, Cadmium, Mercury, and Exposure in the Glass Manufacturing Industry*, International Agency for Research on Cancer (Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans), Lyon, 1993, **58**.
11. *Cadmium*, Geneva, World Health Organization, 1992 (Environmental Health Criteria, No. 134).
12. A. Bernard, R. Lauwerys, *Effects of Cadmium Exposure in Man. Handbook of Experimental Pharmacology*, Berlin, Springer-Verlag, 1980, **80**, 135.
13. R. Lauwerys, *Cadmium and its Compounds*, in *Occupational Medicine*, Eds C. Zenz, O. B. Dickinson, E. P. Horvath, Mosby, St. Louis, 1994, 481.
14. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, J. A. Pople, *GAUSSIAN-98, Revision A.6*. Gaussian, Inc., Pittsburgh (PA), 1998.

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