EAST EUROPEAN JOURNAL OF PHYSICS. 1. 507-519 (2026)
DOI:10.26565/2312-4334-2026-1-58 ISSN 2312-4334

QUANTUM-CHEMICAL CALCULATIONS OF TECHNETIUM RADIOPHARMACEUTICALS

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Received January 5, 2026, revised February 15, 2026; accepted February 19, 2026

The synthesis of radiopharmaceuticals is a major task of nuclear medicine, and Technetium-99m (^{99m}Tc) has ideal nuclear properties for non-invasive nuclear medical diagnostics by single-photon emission computed tomography (SPECT) – a cheaper method than CT, MRI, and PET, suitable for developing countries. Of particular relevance today is the design of various covalently labelled ^{99m}Tc radiopharmaceuticals for the diagnosis and theranostics of oncological diseases. However, the correct selection of ligands and the development of high-quality ^{99m}Tc-based imaging agents that will not disrupt the functions of biologically active molecules requires a good understanding of the coordination chemistry of group 7 transition metals. In this work, the quantum-chemical characteristics of ten ^{99m}Tc radiopharmaceuticals were calculated using *ab initio* (a combined basis set: SBKJC on the Tc atom and 6-31G (d,p)/DFT – on other atoms, Gamess) and semi-empirical (PM6, MOPAC) methods. Negative (for Tc-Exametazime, Tc-ECD) and positive (for other ^{99m}Tc complexes) values of the E_{LUMO} parameter indicated the electrophilic and nucleophilic properties of the radiopharmaceuticals, respectively. Analysis of the absolute hardness values of the complexes revealed that the studied radiopharmaceuticals are soft reagents, with Pertechnetate having the lowest reactivity, which is consistent with the literature data. Dipole moments of most of the ^{99m}Tc radiopharmaceuticals were similar or up to one order of magnitude greater as compared to that of a water molecule. Finally, a strong correlation was established between the ground state dipole moments, lipophilicity and the percentage of nonspecific binding of five radiopharmaceuticals (Tc-Exametazime, Tc-MAG3, Tc-MDP, Tc(III)-DMSA, Tc-DTPA) to plasma proteins (Pearson's correlation coefficients were *ca.* -0.719 and 0.611, respectively). The obtained results could be employed for the design of new ^{99m}Tc-based theranostic agents suitable for cancer treatment, in particular those with high nonspecific binding to plasma proteins.
Keywords: *^{99m}Tc radiopharmaceuticals; Quantum-chemical calculations; Nonspecific protein binding; Dipole moment; Lipophilicity*
PACS: 87.14.C++c, 87.16.Dg

Development of the current nuclear medicine is associated with the design of new radiolabeled agents, and technetium-99m (^{99m}Tc) is a component of more than 80% of radiopharmaceuticals employed for the imaging of function and physiological/ pathological changes in organs by the non-invasive single-photon emission computed tomography (SPECT) [1, 2]. Broad application of ^{99m}Tc in nuclear medicine is explained by its ideal characteristics, i.e.: i) low production cost [3, 4]; ii) high specificity, rapid elimination from the blood and low toxicity [5]; iii) the half-life of ^{99m}Tc is 6.01 h and the gamma photon energy is about 140 keV, allowing the synthesis and transportation of the radionuclide over long distances, a reduction in the internal radiation hazard compared to other radioisotopes, as well as the study of tissues at any depth from the body surface [1, 6, 7]. Moreover, ^{99m}Tc plays an important role in molecular imaging, since SPECT has similar spatial resolution with positron emission tomography (PET) [7]. The first radiopharmaceutical of ^{99m}Tc, Pertechnetate (TcO_4^-), is widely employed for brain and thyroid gland imaging, because it distributes within the body to a similar extent as iodine [8, 9]. Pertechnetate is obtained by the beta decay of molybdenum (^{99}Mo), although chemical reduction of the ^{99m}Tc oxidation state +7 is required to allow formation of stable complexes of ^{99m}Tc radiopharmaceuticals with organic ligands or biomolecules [1]. Thus, in the last decades synthesis of ^{99m}Tc coordination complexes has been accompanied by binding of the radionuclide to the so-called "core", allowing the incorporation of ^{99m}Tc into bioactive molecules without affecting their bioactivity [7]. The physicochemical properties, concentration of the reducing agent and the coordinating ligand, pH, etc. significantly affect the stability of the resulting ^{99m}Tc radiopharmaceuticals in the bloodstream [10]. There is an urgent need to design theranostic agents based on ^{99m}Tc radiopharmaceuticals for cancer early diagnosis and treatment, real time monitoring of the therapy progress, which would improve treatment outcomes and life quality of patients [10 − 14]. For example, Tc(V)-DMSA, typically used for medullary thyroid cancer diagnostics, was proved to be efficient in lung cancer detection [15], and the myocardial perfusion SPECT radiotracer, Tc-Sestamibi, appeared to be suitable for breast cancer imaging [10, 16]. Notably, new theranostic agents based on ^{99m}Tc radiopharmaceuticals should be characterized by high affinity for blood plasma proteins, which would increase their biological half-life and thus prolong the therapeutic effect. Good understanding of the coordination chemistry of transition metals with an oxidation state of +7, as well as deep investigating the influence of various coordinating ligands on the physicochemical properties of the resulting complexes, are required for successful development of new ^{99m}Tc radiopharmaceuticals [7]. Quantum-chemical calculations are believed to facilitate the search for coordinating ligands suitable for synthesizing new, more thermodynamically stable ^{99m}Tc radiopharmaceuticals, characterized by certain molecular interactions and biological

Cite as: K. Vus, V. Trusova, V. Romashyna, U. Malovytsia, O. Zhytniakivska, G. Gorbenko, East Eur. J. Phys. 1, 507 (2026), https://doi.org/10.26565/2312-4334-2026-1-58

activity. The density functional theory (DFT) method is largely used to study the influence of various ligands on the spectroscopic properties, NMR chemical shifts, stability and electronic structure of ^{99m}Tc complexes [17, 18]. In view of the above, this work was aimed at investigating the quantum-chemical characteristics of ten ^{99m}Tc radiopharmaceuticals: Tc-MAG3, Tc-Medronate, Tc(III)-DMSA, Tc-DTPA, Tc-Exametazime, Tc-DISIDA, Tc-ECD, Pertechnetate, Tc-Sestamibi and Tc-Mebrofenin. To achieve this goal, the following tasks were performed: i) *ab initio* and semi-empirical quantum-chemical calculations of the ^{99m}Tc radiopharmaceuticals using the combined basis set: SBKJC on the Tc atom and 6-31G (d,p)/DFT – on other atoms (Gamess), and the PM6 method (MOPAC), respectively; ii) characterizing HOMO and LUMO orbitals, the electron density distribution, solvation energy and the lowest singlet excited state energy of the optimized structures of the ^{99m}Tc complexes; iii) accession of the reliability of the obtained results by comparing them with available literature data; iv) establishing the correlation between the calculated quantum-chemical descriptors of the geometric and electronic structure, electronic and thermodynamic properties of the ^{99m}Tc complexes [19] and the nonspecific binding of radiopharmaceuticals to plasma proteins.

MATERIALS AND METHODS

Nine largely used radiopharmaceuticals for nuclear medicine containing coordinating ligands for the ^{99m}Tc atom combined with the core of the complex (Tc-MAG3 (^{99m}Tc-Mercaptoacetyltriglycine), Tc-Medronate, Tc(III)-DMSA, Tc-DTPA, Tc-Exametazime, Tc-DISIDA (Tc-Disofenin), Tc-ECD (Tc-Ethylene cysteine dimer), Tc-Sestamibi and Tc-Mebrofenin), as well as Pertechnetate (which does not contain any coordination ligand) [7], were employed in the present study.

Tc-MAG3 is a tetradentate monooxocomplex of Tc(V) and mercaptoacetyltriglycine, which is used for the diagnosis of renal failure and urinary tract obstruction, as well as for assessing kidney function in a donor before transplantation [20, 21]. This radiopharmaceutical has low affinity for plasma proteins and thus is rapidly excreted from the body of a healthy person by glomerular filtration through the kidneys, but provides quantitative characterization of impaired renal function in sick patients [20, 21]. Tc-ECD, a five-coordinate square pyramidal complex of the Tc(V) atom with N,N′-1,2-ethenediylbis-L-cysteine diethylester, acts in a similar way to Tc-MAG3, and therefore is used as an imaging agent for renal function and brain perfusion (notably, high lipophilicity allows Tc-ECD to pass through the blood-brain barrier) [7, 9]. Radioactive half-life of Tc-ECD is about 50 minutes in patients with normal renal function, but may be prolonged in renal failure [7, 9]. Tc-Exametazime is a five-coordinate square pyramidal complex of Tc(V) with a hexamethyl-functionalized derivative of propylene amine oxime, employed for radioactive labeling of leukocytes [9], as well as a brain perfusion imaging agent (due to its high lipophilicity and affinity for blood plasma proteins) [22]. Tc-DTPA is a six-coordinate complex of the Tc(IV) atom with three N atoms and three O atoms for coordination [9, 23]. After intravenous administration it is rapidly eliminated from the bloodstream by glomerular filtration and is used to assess the glomerular filtration rate of the kidneys [9, 23]. Tc(IV)-Medronate, like Tc(IV)-DTPA, is formed by reduction of Pertechnetate with tin chloride in the presence of a coordinating ligand [9]. Tc-Medronate contains medronic acid and thus, is highly bound to albumin, transporting the radiopharmaceutical to the liver and then localizing it in the bones (due to high affinity of Tc-Medronate for hydroxyapatite crystals in the bones), thereby making Tc-Medronate suitable for visualization of areas of altered osteogenesis [9]. Tc(III)-DMSA is a dimeric complex that forms at low pH, and after intravenous administration slowly accumulates in the renal cortex (due to its high affinity for plasma proteins), binding the proximal convoluted tubule cells. Tc(III)-DMSA is used to assess renal parenchymal diseases [9].

Tc-DISIDA and Tc-Mebrofenin are analogues of Tc-Iminodiacetic acid (IDA), hexacoordination complexes of Tc(III), stabilized by two N atoms and four O atoms of two IDA ligands, which are employed to assess hepatobiliary function in acute and chronic cholecystitis [9] due to their high affinity for plasma proteins [24 – 27]. After intravenous administration, these radiopharmaceuticals are rapidly extracted from the blood into the bile by active transport through the anionic site on the hepatocyte membrane, which is the same site for bilirubin transport [9].

Tc-Sestamibi is an octahedral, cationic Tc(I) complex containing six isonitrile ligands, characterized by low affinity for plasma proteins [28– 30] and used for visualization of myocardial perfusion, cardiac ischemia and necrosis, as well as breast cancer [31 – 33].

The main physicochemical properties of the ^{99m}Tc radiopharmaceuticals studied in this work are summarized in Table 1.

The three-dimensional structures of the ^{99m}Tc radiopharmaceuticals were drawn in MarvinSketch (version 24.1.2) [34], followed by modification of the total charge of each complex to reach that shown in Table 1, pre-optimization and generation input files for Gamess in Avogadro (version 1.97.0).

Quantum-chemical calculations of the ground state S_0 free energy (E_g), the ground state dipole moment (μ_g) and its projections on the X, Y and Z axes (μ_{gx}, μ_{gy} and μ_{gz}, respectively), the partial charge on the Tc atom in the ground state (q_g) were performed in the gas phase using the Gamess software package (version 30 SEPT 2017 (R2)). Free energy in water (E_{H2O}) and the solvation energy (E_{solv}) of the radiopharmaceuticals were also estimated. For all *ab initio* calculations, the combined basis set: SBKJC on the Tc atom [35] and 6-31G (d,p) – on other atoms [36], as well as density functional theory (DFT) and B3LYP functional [35, 37], were used. The SBKJC basis set (unlike 6-31G (d,p)) can be employed in Gamess for heavy elements: it takes into account only the valence electrons of the atom, and

replaces the inner electrons with the effective nuclear potential [37, 38]. To estimate the energy characteristics of the ^{99m}Tc complexes in water, we used the optimized geometry in the gas phase, the PCM theory, and the covalent radius of Tc – 1.47 Å [39]. All other quantum-chemical descriptors of the ^{99m}Tc radiopharmaceuticals (except for E_{H2O} and E_{solv}) were calculated in the gas phase. To estimate the free energy (E_e), the partial charge on the Tc atom (q_e) and dipole moment (μ_e) of the non-relaxed excited state S_1 (the lowest singlet excited state formed immediately after photon absorption), the excited state energy (ΔE_e) and oscillator strength (f) of the $S_0 \rightarrow S_1$ electronic transition, we used the optimized ground state geometry in the gas phase, density functional theory (TDDFT=EXCITE) and B3LYP functional [35, 37]. The calculation of the absorption wavelength (λ_{abs}) of the ^{99m}Tc radiopharmaceuticals in the excited state was also performed using the ΔE_e values.

The ALOGPS 2.1 online server (http://www.vcclab.org/) was used to calculate the lipophilicity of the ^{99m}Tc complexes (*CLogP*), their molecular weight (*Mol. wt.*), and water solubility (*LogS*).

To estimate the geometric parameters of the ^{99m}Tc radiopharmaceuticals (length, width, thickness, molecular volume, solvent-accessible surface area (*SASA*), as well as the *heat of formation*, semi-empirical PM6 method and the MOPAC program (version 23.1.2 Linux) were used, although the accuracy of semi-empirical calculations for transition metal complexes is low [40]. The number of hydrogen bond donors (*No. of H-bond donors*) and acceptors (*No. of H-bond acceptors*), as well as the number *of rotatable bonds* were calculated using the SwissADME online server: http://www.swissadme.ch/ .

Table 1. Physico-chemical properties of ^{99m}Tc radiopharmaceuticals

№	Name	*Charge of the complex*	*Core of the complex*	^{99m}Tc oxidation state	Stability	References
1	Tc-MAG3 (^{99m}Tc-Mercaptoacetyltriglycine, ^{99m}Tc-Mertiatide)	-1	Tc=O3+	+5	Stable in water	9
2	Tc-Medronate (or Tc-MDP)	-2	Tc4+	+4	Stable	9
3	Tc(III)-DMSA (or Tc(III)-Succimer)	-3	Tc3+	+3	Has a lability to oxidation	9
4	Tc-DTPA (or Tc-pentetate)	-2	Tc4+	+4	Stable	9, 32
5	Tc-Exametazime (or Tc-HMPAO)	0	Tc=O3+	+5	Lipophilic, unstable in water	9
6	Tc-DISIDA (Tc-Disofenin)	-1	Tc3+	+3	Kinetically inert	9
7	Tc-ECD (Tc-Ethylene cysteine dimer)	0	Tc=O3+	+5	Lipophilic	7, 9
8	Pertechnetate	-1	[Tc+7O4] –	+7	Stable in water	9
9	Tc-Sestamibi	+1	Tc+	+1	Lipophilic	9
10	Tc-Mebrofenin (Tc-BRIDA)	-1	Tc3+	+3	Kinetically inert	9

To visualize the obtained results (geometry of the ^{99m}Tc complexes, their electron density distribution, HOMO and LUMO orbitals), the wxMacMolPlt program (version 7.7.2) [41] was employed.

Absolute hardness (η) of the ^{99m}Tc radiopharmaceuticals was calculated using the formula [42, 43]:

$$\eta = ½ (E_{nvmo} - E_{vzmo}) \quad (1),$$

where E_{HOMO} and E_{LUMO} are the energies of the lowest unoccupied and highest occupied molecular orbitals in the gas phase, respectively.

According to Koopmans' theorem, the following parameters were estimated: *the ionization potential* is the E_{HOMO} parameter, taken with the opposite sign, and the electron *affinity* is equivalent to the E_{LUMO} parameter [42,43].

20 quantum-chemical descriptors and five ^{99m}Tc complexes (Tc-Exametazime, Tc-MAG3, Tc-MDP, Tc(III)-DMSA, Tc-DTPA) were selected for correlation analysis in order to establish the correspondence between theoretical calculations and the percentage of nonspecific binding of the ^{99m}Tc radiopharmaceuticals to plasma proteins. By fitting the quantum-chemical descriptor value dependence on percentage of protein binding, estimation of the Pearson's correlation (*Pearson's r*) and determination (*Adj.* R^2) coefficients were carried out in the OriginPro software (version 9.1).

RESULTS AND DISCUSSION

In the first stage of our study the quantum-chemical characteristics of ten ^{99m}Tc radiopharmaceuticals were evaluated. Fig. 1 shows the optimized structures of the ^{99m}Tc radiopharmaceuticals. It is worth noting that after geometry optimization of Tc-Sestamibi, atoms of the Tc-C-N chain, linked by a coordination (Tc-C) and a covalent C≡N bonds of the complex, lay on one straight line (Fig. 1I), which is consistent with the literature data [9].

Tables 2 and 3 comprise the results of quantum-chemical calculations of the ^{99m}Tc radiopharmaceuticals in Gamess and MOPAC, respectively. Interestingly, the Mulliken charge on the Tc atom (q_g) in all the ^{99m}Tc complexes ranged from -0.67 (in Tc-Sestamibi) to 1.38 (in Pertechnetate), although the supposed values of the partial charges on the Tc atom are +1 and -1 for the above two radiopharmaceuticals, respectively (*Core of the complex*, Table 1). Furthermore, other eight ^{99m}Tc complexes most likely would have partial charge values close to +3 – +4 because these

are the charges of their cores (*Core of the complex*, Table 1). Unfortunately, Gamess, unlike Gaussian, has low accuracy in calculating partial charges on atoms, so the obtained charges on the Tc atom were far from the correct ones [9]. However, the Tc partial charge values (Table 2) increased in a similar manner to those taken from other sources (*Pearson's* $r = 0.828$, *Adj.* $R^2 = 0.646$), highlighting the possibility of comparing the relative values for different ^{99m}Tc complexes calculated using the combined basis set (SBKJC on the Tc atom and 6-31G (d,p) – on other atoms). Furthermore, the total charges of the complexes obtained from quantum-chemical calculations matched the literature data (*Charge of the complex*, Table 1).

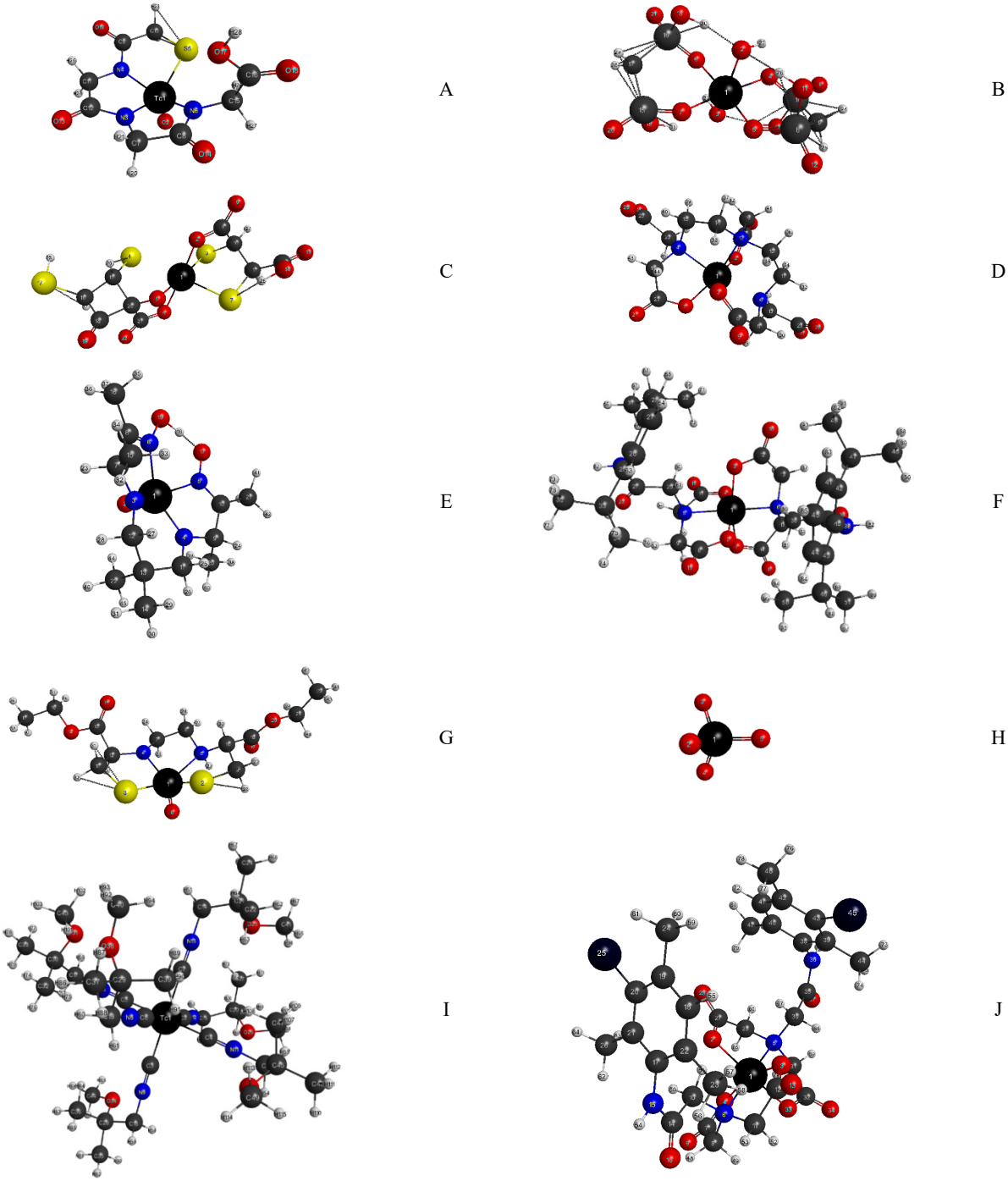

Figure 1. Optimized structures of Tc-MAG3 (A), Tc-Medronate (B), Tc(III)-DMSA (C), Tc-DTPA (D), Tc-Exametazime (E), Tc-DISIDA (F), Tc-ECD (G), Pertechnetate (H), Tc-Sestamibi (I), Tc-Mebrofenin (J) in the gas phase.

As seen in Figs. 2 and 3, the HOMO orbitals of Tc-MAG3, Tc(III)-DMSA, Tc-DTPA, Tc-DISIDA, Tc-Mebrofenin and Tc-Sestamibi are localized on the Tc atom, and that for Tc-MAG3 – additionally on the O and N atoms. In contrast, the LUMO orbitals are localized mainly on the Tc atom for Tc-MAG3, Tc(III)-DMSA, Tc-DISIDA, Tc-Mebrofenin and Tc-DTPA (in Tc-DTPA additionally – on four O atoms of the two carboxyl groups), and in Tc-Sestamibi – only on C and N forming coordinate bonds with the Tc atom.

Table 2. Quantum-chemical characteristics of ^{99m}Tc radiopharmaceuticals calculated in Gamess (using combined basis set: SBKJC on the Tc atom and 6-31G (d,p) – on other atoms)

Parameter, units	Tc-MAG3	Tc-Medronate	Tc(III)-DMSA	Tc-DTPA	Tc-Exametazime	Tc-DISIDA	Tc-ECD	Pertechnetate	Tc-Sestamibi	Tc-Mebrofenin
E_g, Hartree	-1404	-2581	-2621	-1541	-1035	-2451	-1832	-381	-2270	-7362
E_g, kcal/mol	-38211	-1619640	-1644620	-966799	-649494	-1538254	-1149522	-239315.85	-61779	-4619689
E_e, Hartree	-1404	-2581	nd	-1541	-1035	-2451	-1832	-38	-2270	-7362
ΔE_e, eV	2.717	0.276	nd	0.516	2.606	0.252	2.106	3.862	4.305	0.273
E_{H2O}, kcal/mol	-881234	-1619791	-1644938	-966954	-649504	-1538310	-1149536	-239371.18	-1424711	-4619748
λ_{abs}, nm	456	4492	nd	2403	476	4920	589	321	288	4542
f	0.0033	0.000	nd	0.0003	0.0004	0.0000	0.0012	0.0000	0.0002	0.0000
E_{solv}, kcal/mol	-48.47	-153.43	-324.82	-161.15	-12.83	-60.98	-17.24	-55.137	-33.90	-63.82
E_{HOMO}, Hartree	-0.0976	0.0429	0.1976	0.0255	-0.2048	-0.0621	-0.2053	-0.1038	-0.2645	-0.0627
E_{LUMO}, Hartree	0.0546	0.0842	0.2702	0.1091	-0.0599	0.0233	-0.0764	0.0950	-0.0671	0.0224
η, eV	2.07	0.56	0.99	1.14	1.97	0.60	1.75	2.71	2.69	1.16
Ionization potential, eV	2.66	-1.17	-5.38	-0.69	5.57	1.69	5.59	2.82	7.2	1.71
Electron affinity, eV	1.49	2.29	7.35	2.97	-1.63	0.63	-2.08	2.59	-1.83	0.61
μ_{gx}, D	1.55	0.322	-2.45	3.11	1.05	-13.18	5.77	0.003	0.65	0.38
μ_{gy}, D	0.67	0.70	-1.02	5.80	-1.77	2.23	-2.70	-0.003	0.87	12.06
μ_{gz}, D	-0.80	0.34	-0.84	7.88	4.73	-3.69	2.64	0.002	1.83	12.13
μ_g, D	1.87	0.84	2.78	10.26	5.16	13.87	6.90	0.004	2.13	17.11
μ_e, D	1.78	0.95	nd	10.30	5.67	13.91	6.97	0.13	2.14	17.00
q_g, a.u.	0.90	0.92	0.36	0.91	1.07	0.79	0.55	1.38	-0.67	0.78
q_e, a.u.	0.98	0.95	nd	0.93	1.16	0.91	0.59	1.26	-0.62	0.88

nd — not determined

Table 3. Quantum-chemical characteristics of ^{99m}Tc radiopharmaceuticals calculated in MOPAC (PM6) and by the ALOGPS 2.1 online server

Parameter, units	Tc-MAG3	Tc-Medronate	Tc(III)-DMSA	Tc-DTPA	Tc-Exametazime	Tc-DISIDA	Tc-ECD	Pertechnetate	Tc-Sestamibi	Tc-Mebrofenin
CLogP	-1.35	0.17	1.07	-1.17	1.71	2.53	0.97	-0.59	1.32	2.11
LogS	-0.67	-1.57	-2.86	-2.71	-1.43	-6.33	-2.00	0.51	-4.89	-6.03
Mol. wt., Da	418.2	480.9	469.3	487.2	384.3	795.7	436.3	162.9	776.0	869.3
Length, Å	8.6	9.2	11.6	10.6	9.7	14.0	15.3	2.9	15.2	12.6
Width, Å	7.4	5.5	6.1	7.7	8.7	12.5	6.2	2.9	14.7	11.0
Thickness, Å	4.7	4.9	4.9	6.8	4.8	9.9	4.6	2.0	14.0	8.6
SASA, Å^2	264	291	313	336	312	598	353	105	699	572
Volume, Å^3	305	339	382	432	383	878	408	93	1046	824
Heat of formation, kcal/mol	-289	-789	-227	-424	-22	-427	-189	-167	-88	-416
No. of H-bond donors	2	6	1	0	4	2	1	0	6	2
No. of H-bond acceptors	7	14	8	10	9	10	8	4	12	10
No. of rotatable bonds	3	0	1	4	1	12	7	0	30	8

The LUMO orbitals of Pertechnetate and Tc-Medronate are localized mainly on the Tc atom, and the HOMO orbitals – on the O atoms (belonging to two OH groups in the case of Tc-Medronate). The LUMO orbital of Tc-Exametazime is localized mainly on the Tc atom, on one of the N atoms and on the O atom of the Tc=O3+ core, and the HOMO orbital is localized on the Tc and O atoms of the Tc=O3+ core. The LUMO orbital of Tc-ECD is localized mainly on the Tc atom and on one of the S atoms, and the HOMO orbital is localized on the Tc atom and on the O atoms of the Tc=O3+ core. Thus, orbitals of the Tc and sometimes N, O, S atoms (forming covalent/ coordinate bonds with Tc) participate in the formation of the HOMO and LUMO orbitals of the ^{99m}Tc complexes. Negative (for Tc-Exametazime, Tc-ECD) and positive (for all other studied ^{99m}Tc radiopharmaceuticals) values of the E_{LUMO} parameter determine the electrophilic (with a negative sign of *the electron affinity* value, because according to Koopmans' theorem, the electron affinity energy is equal to the LUMO energy) and nucleophilic properties of the ^{99m}Tc complexes, respectively (Table 2) [42, 43].

As seen in Table 2, the absolute rigidity (η) of radiopharmaceuticals fall in the range of 0.56 eV (Tc-Medronate) to 2.71 eV (Pertechnetate), indicating that they will react with soft reagents, e.g. aromatic chemical compounds and alkaline amino acids. At the same time, Tc-Medronate and Tc-DISIDA, possessing the highest reactivity and high affinity for blood plasma proteins [24 – 26], showed the lowest value of the η parameter. In turn, Pertechnetate and Tc-Sestamibi, possessing the lowest reactivity (Pertechnetate) [1] and the lowest ability to associate with proteins and lipid bilayers (Tc-Sestamibi) [28 – 30], showed the highest value of the η parameter. The obtained results indicate the reliability of using the selected combined basis set for calculating the HOMO and LUMO energies of the ^{99m}Tc radiopharmaceuticals.

Fig. 4 shows the electron density distribution of the ^{99m}Tc complexes. The electrostatic charge +1 of Tc-Sestamibi is uniformly distributed between the atoms of the complex, while the charge -1 of Tc-MAG3 is concentrated on the O and S atoms, so the second complex should have better solubility in water, which is consistent with the literature data [44, 45]. Pertechnetate has a positive/ negative partial charge on the Tc/ O atom, which is consistent with the results of other authors [9]. Tc-Medronate, Tc(III)-DMSA and Tc-DTPA, possessing the highest absolute charge (-2 for Tc-Medronate, Tc-DTPA, and -3 for Tc(III)-DMSA), also had the most irregular electron density distribution than other complexes (Table 2). Also, high net charge values and irregular charge distribution of the above three ^{99m}Tc complexes should induce their high solubility in water, which is confirmed by the literature data (Table 1), but is not confirmed by semi-empirical calculations (Tc(III)-DMSA, Tc-DTPA have the lowest *LogS* values, lower than those of lipophilic Tc-Exametazime and Tc-ECD, Table 3), emphasizing the inaccuracy of semi-empirical calculations for the ^{99m}Tc radiopharmaceuticals [7, 9, 33]. The most negative partial charge of Tc-Medronate, Tc(III)-DMSA and Tc-DTPA is

localized on the O atoms (these atoms are most abundant in these three complexes compared to others), while the Tc atom has a positive partial charge (Figure 4). Tc-Mebrofenin and Tc-DISIDA have a net charge of -1 and a similar distribution of electron density: a positive charge on the Tc atom and negative charges on the O atoms (Figure 4). The charges of Tc-Exametazime and Tc-ECD are distributed uniformly (Figure 4), which is probably due to zero net charge of these radiopharmaceuticals (Table 1).

The dipole moment (μ_g) of Pertechnetate was close to zero, in Tc-Medronate (Tc-MAG3 and Tc-Sestamibi) – less than (close to) that of a water molecule, in other radiopharmaceuticals – 1.5–9 times higher than the μ_g of water (Table 2). Furthermore, no significant changes in the dipole moments (μ_e) of the ^{99m}Tc radiopharmaceuticals were observed in the excited state as compared to the ground state (Table 2). It should be noted that the estimated dipole moment values are not very precise, since e.g., for neutral Tc-Exametazime and Tc-ECD they were several times higher than those for the charged ^{99m}Tc complexes, while the lowest μ_g value was obtained for Tc-Medronate possessing a charge of -2 (Table 2).

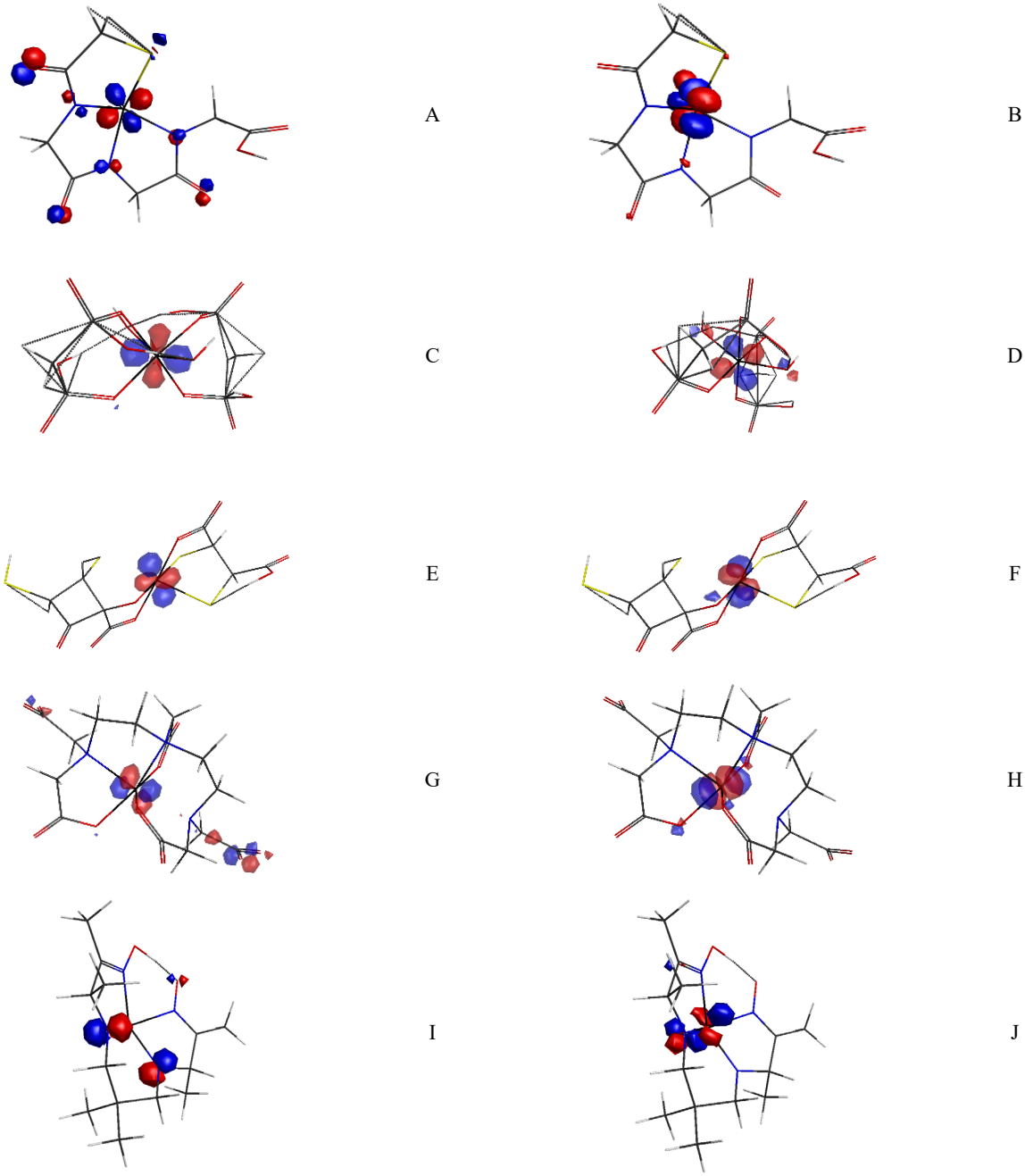

Figure 2. HOMO (A – 79, C – 106, E – 103, G – 110, I – 85) and LUMO (B – 80, D – 107, F – 104, H – 111, J – 86) orbitals of the optimized structures of Tc-MAG3 (A, B), Tc-Medronate (C, D), Tc(III)-DMSA (E, F), Tc-DTPA (G, H), Tc-Exametazime (I, J) in the gas phase.

The solvation energy (E_{solv}) of the ^{99m}Tc radiopharmaceuticals ranged between -12.8 kcal/ mol (Tc-Exametazime) and -324.8 kcal/ mol (Tc(III)-DMSA), with the highest values of this parameter obtained for neutral Tc-Exametazime and Tc-ECD, and the lowest – for the most charged complexes (Tc(III)-DMSA, Tc-DTPA, Tc-Medronate), which is consistent with the high water solubility of the latter complexes (Table 2) [7, 9, 33]. Interestingly, the E_{solv} value of Tc-MAG3 was lower than that of Tc-Sestamibi, which is consistent with higher water solubility of Tc-MAG3 [44 , 45].

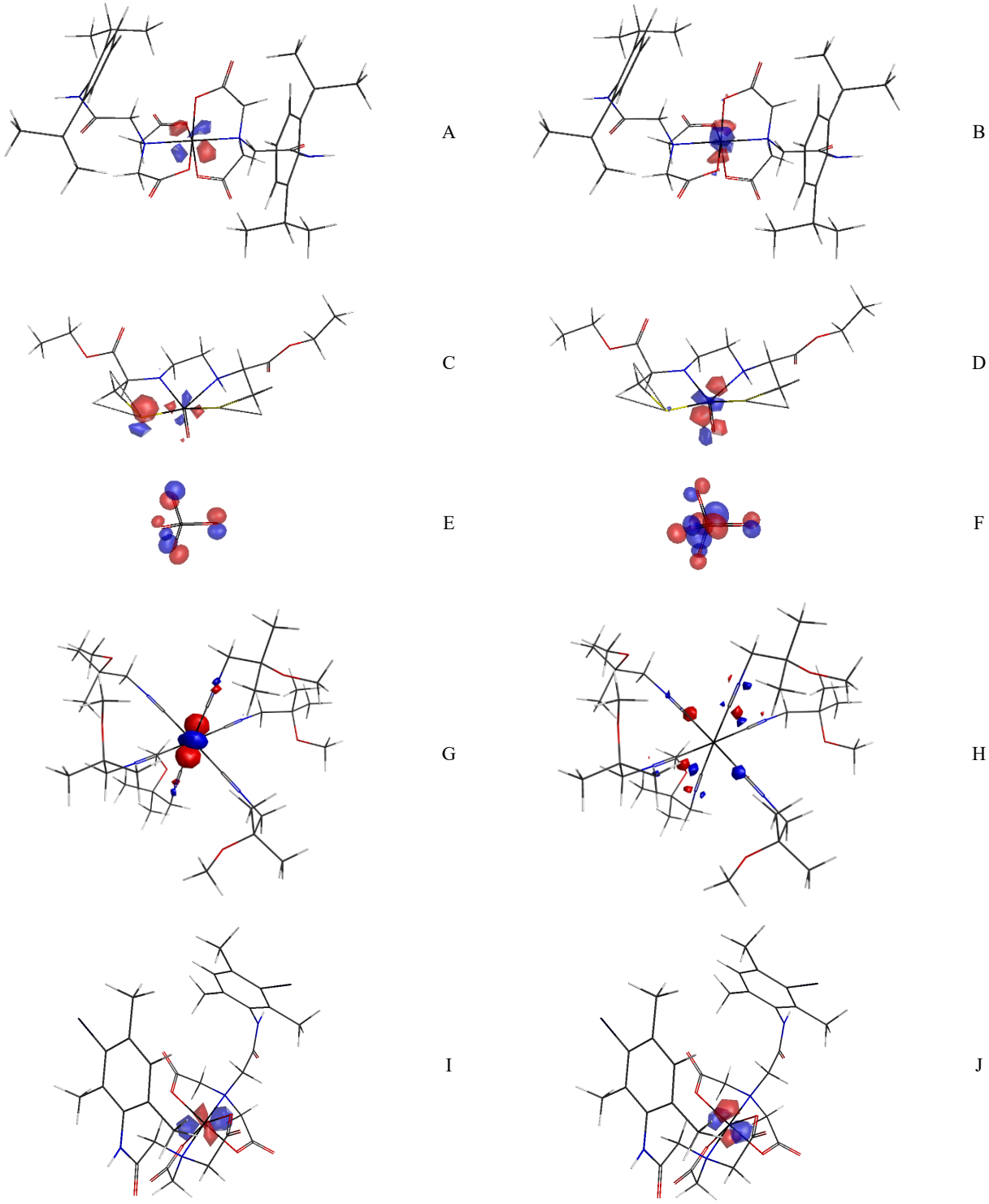

Figure 3. HOMO (A – 194, C – 97, E – 24, G – 193, I – 204) and LUMO (B – 195, D – 98, F – 25, H – 194, J – 205) orbitals of the optimized structures of Tc-DISIDA (A, B), Tc-ECD (C, D), Pertechnetate (E, F), Tc-Sestamibi (G, H), Tc-Mebrofenin (I, J) in the gas phase.

The oscillator strength *f* (that is proportional to the fluorescence quantum yield, Table 2) for all the ^{99m}Tc complexes was about zero (the highest value was 0.0012, indicating a weak fluorescence of Tc-ECD, followed by light

absorption at 589 nm). Notably, Tc-Sestamibi, Pertechnetate, Tc-MAG3, Tc-Exametazime and Tc-ECD had absorption wavelengths (λ_{abs}) in the ultraviolet and visible (288 nm, 321 nm, 456 nm, 476 nm and 589 nm, respectively), Tc-Medronate, Tc-DISIDA and Tc-Mebrofenin – in the far-infrared (4500 – 5000 nm), and Tc-DTPA – in the mid-infrared (2500 nm) regions of the electromagnetic spectrum. Interestingly, λ_{abs} of Tc-Sestamibi in the gas phase was in the ultraviolet region, similar to that of its MIBI ligand in water (Table 2) [33]. For Tc-MAG3, the predicted value of λ_{abs} was 456 nm, which is consistent with the data on the high light sensitivity of the TechnescanMAG3 kit used for the preparation of Tc-MAG3 [21, 46]. The above results indicate the reliability of calculation of the physicochemical characteristics of the ^{99m}Tc radiopharmaceuticals in the excited state using the combined basic set. It is worth noting that Tc-ECD, a renal imaging agent, possessing low protein binding and low liver activity [47, 48], may, according to our data, have a slight absorption of visible light in the same region as the hemoglobin molecule [49]. Interestingly, after excitation of the ^{99m}Tc radiopharmaceuticals (except Pertechnetate), the charge q_e on the Tc atom slightly increased compared to its value in the ground state (q_g, Table 2).

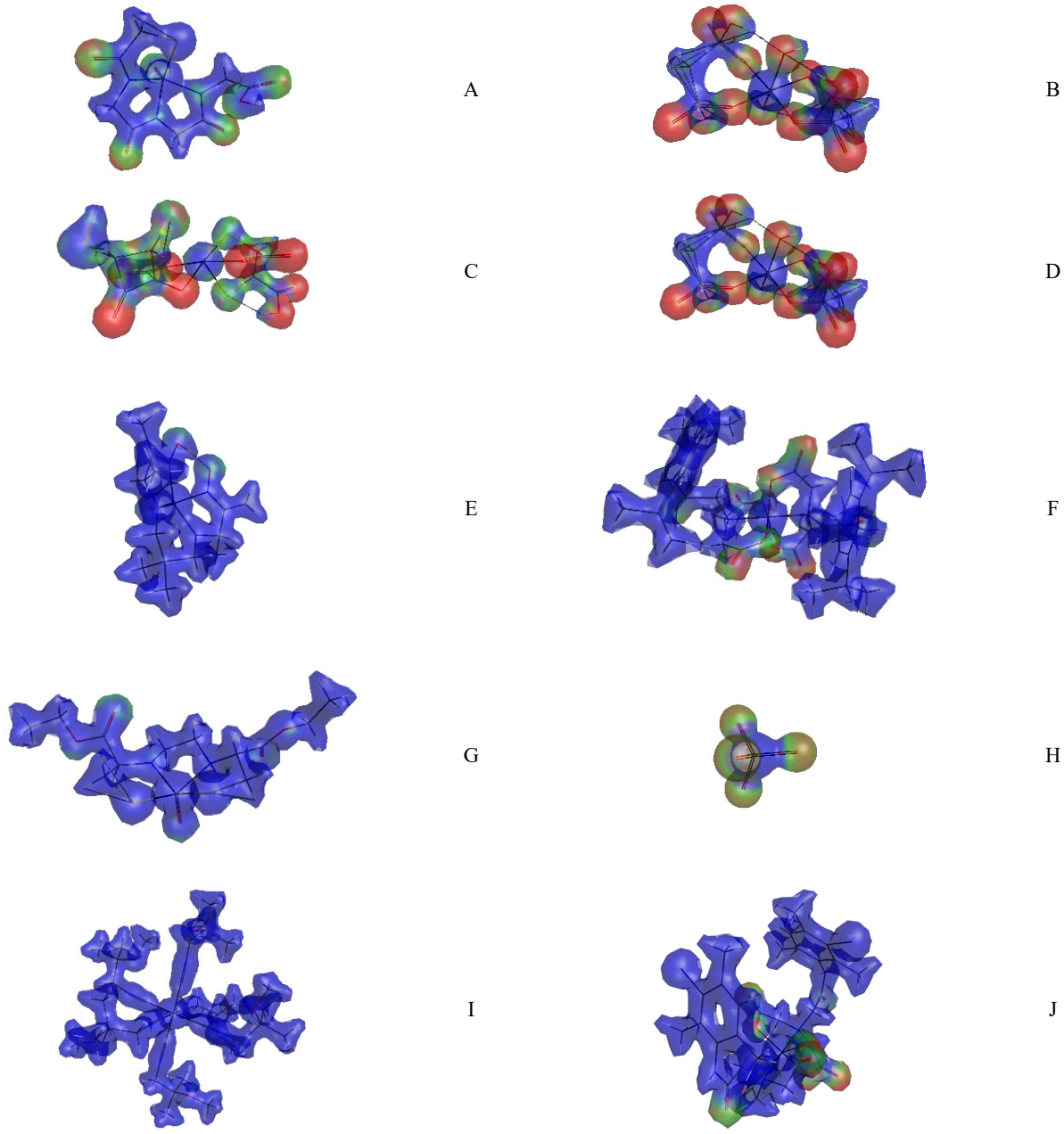

Figure 4. Electron density distribution of Tc-MAG3 (A), Tc-Medronate (B), Tc(III)-DMSA (C), Tc-DTPA (D), Tc-Exametazime (E), Tc-DISIDA (F), Tc-ECD (G), Pertechnetate (H), Tc-Sestamibi (I), Tc-Mebrofenin (J) in the gas phase. Positive and negative values of the electron density are colored in blue and red, respectively.

ALOGPS 2.1 online server revealed negative *CLogP* values of Tc-MAG3, Tc-DTPA and Pertechnetate (Table 3), suggesting high hydrophilicity of these radiopharmaceuticals [9, 33]. For other ^{99m}Tc complexes *CLogP* values ranged

from 0.17 (Tc-Medronate) to 2.53 (Tc-DISIDA), and were the highest for the lipophilic Tc-DISIDA, Tc-Mebrofenin and Tc-Exametazime, possessing high affinity for plasma proteins [25, 26, 50].

The *heat of formation* value (Table 3) of Tc-MAG3 was 3.3 times lower than that of Tc-Sestamibi, showing a greater thermodynamic stability of the first complex [51]. Similarly, the *heat of formation* values of Tc-Medronate, Tc-DISIDA, Tc-DTPA and Tc-Mebrofenin were 1.4–35 times lower than those of Tc-MAG3, Tc(III)-DMSA, Tc-ECD, Pertechnetate, Tc-Sestamibi and Tc-Exametazime, showing a greater thermodynamic stability of the first four complexes [51]. Notably, according to *ab initio* calculations, Tc-Exametazime and Tc-Medronate had one of the largest and lowest values of η (i.e. one of the smallest and largest reactivity), respectively (Table 2). However, the *heat of formation* values revealed that Tc-Exametazime was the least and Tc-Medronate was the most thermodynamically stable, presumably due to low accuracy of the PM6 method.

In the next step of our study, the compliance of the quantum-chemical characteristics of the studied radiopharmaceuticals with Lipinski's "rule of five" was assessed, which would allow prediction of passive intestinal absorption, side effects and pharmacokinetics of the new ^{99m}Tc complexes [52]. For drug-like substances, the following conditions should be met: i) ≤ 5 *hydrogen bond donors* (OH- and NH- bonds) in the molecular structure; b) ≤ 5 *hydrogen bond acceptors* (O and N atoms) in the molecular structure; c) *molecular weight* < 500 Da; d) octanol-water partition coefficient (*CLogP*) ≤ 5; e) number of *rotatable bonds* ≤ 5 – 10. The results obtained (Table 4) showed that the best/ worst compliance with Lipinski's "rule of five" was observed for Pertechnetate, Tc-MAG3, Tc(III)-DMSA, Tc-DTPA, Tc-Exametazime, Tc-ECD/ Tc-Sestamibi, Tc-Medronate, Tc-DISIDA, Tc-Mebrofenin. Indeed, Pertechnetate has been used in the diagnosis of a wide range of diseases by SPECT [8], while e.g., Ts-Sestamibi and Tc-Medronate are nuclear myocardial perfusion and bone imaging agents, respectively [20, 28]. Furthermore, Tc-DISIDA and Tc-Mebrofenin are typically employed to measure the function of liver and gallbladder (they do not need to penetrate the blood-brain barrier, so they are "allowed" to have high *Mol. wt.* values) [24, 25]. Notably, all ^{99m}Tc complexes, except Pertechnetate, possessed *No. of H-bond acceptors* higher than 5.

Table 4. Complience of ^{99m}Tc radiopharmaceuticals with Lipinski's "rule of 5"

Criterion	Tc-MAG3	Tc-Medronate	Tc(III)-DMSA	Tc-DTPA	Tc-Exametazime	Tc-DISIDA	Tc-ECD	Pertechnetate	Tc-Sestamibi	Tc-Mebrofenin
No. of H-bond donors ≤ 5	+	–	+	+	+	+	+	+	–	+
No. of H-bond acceptors ≤ 5	–	–	–	–	–	–	–	+	–	–
Mol. wt. < 500	+	+	+	+	+	–	+	+	–	–
CLogP ≤ 5	+	+	+	+	+	+	+	+	+	+
No. of rotatable bonds ≤ 5 – 10	+	+	+	+	+	–	+	+	–	+

In the last step of our study the correlation between the nonspecific binding of the ^{99m}Tc radiopharmaceuticals to plasma proteins and quantum-chemical descriptors was estimated (Table 5). There is poor data regarding the affinity of ^{99m}Tc radiopharmaceuticals for protein molecules [53 – 55]. For example, the equilibrium dialysis carried out by Vanlić-Razumenić et al. showed the percentage of plasma proteins bound at 4 °C to 5 radiopharmaceuticals: Tc(III)-DMSA (82.7%), Tc-Exametazime (54.7%), Tc-MAG3 (52.7%), Tc-MDP (45.0%), and Tc-DTPA (5.7%) [20]. The above ^{99m}Tc complexes were selected for a correlation analysis. As seen in Table 5, the strongest positive correlation (i.e. the largest value of the Pearson's correlation coefficient, *Pearson's r* = -0.719) of nonspecific protein binding was revealed for the dipole moment (μ_g, a parameter obtained using *ab initio* quantum-chemical calculations) of the ^{99m}Tc radiopharmaceuticals, although this relationship was observed for slightly less than half of the studied complexes (*Adj.* R^2 = 0.355). It should be noted that high values of Pearson's correlation coefficients for the parameters *CLogP* and *Thickness* were also obtained, although semi-empirical calculations for the ^{99m}Tc complexes were less reliable than *ab initio* calculations [40]. Additionally, among the above three descriptors, μ_g and *Thickness* showed a strong cross-correlation (*Pearson's r* = 0.888), so it can be concluded that two quantum-chemical characteristics – μ_g and *CLogP*, determine the degree of the nonspecific binding of the ^{99m}Tc radiopharmaceuticals to plasma proteins (Table 5). Interestingly, the lipophilicity of a small organic molecule typically increases with a decrease in its dipole moment (overall polarity) [56].

Thus, a decrease in the dipole moment and an increase in lipophilicity induced higher nonspecific binding of the ^{99m}Tc radiopharmaceuticals to plasma proteins. This result is consistent with the previous data reported for Tc-Mebrofenin, Tc-DISIDA and their derivatives: the higher was the lipophilicity value, the better was binding to proteins [24 – 26]. Interestingly, despite the fact that our correlation analysis was carried out for hydrophilic ^{99m}Tc

radiopharmaceuticals (except Tc-Exametazime), the result was the same as that obtained previously for lipophilic radiopharmaceuticals (Tc-Mebrofenin, Tc-DISIDA) [24 – 26].

Table 5. Pearson's correlation coefficitnts (*Pearson's r*) and Adj. R^2 coefficients (*Adj. R^2*), showing the relationship between amount of protein binding (%) and quantum-chemical descriptors of the group of 5 complexes: Tc(III)-DMSA, Tc-Exametazime, Tc-MAG3, Tc-MDP and Tc-DTPA

	E_g	E_{H2O}	E_{solv}	E_{HOMO}	E_{LUMO}	η	μ_g	q_g	*CLogP*	*LogS*
Pearson's r	-0.197	-0.373	-0.311	0.223	0.326	0.090	-0.719	-0.330	0.611	0.086
Adj. R^2	-0.281	-0.148	-0.205	-0.265	-0.192	-0.322	0.355	-0.188	0.164	-0.324
	Mol. wt.	*Length*	*Width*	*Thickness*	*SASA*	*Volume*	*Heat of formation*	*No. of H-bond donors*	*No. of H-bond acceptors*	*No. of rotatable bonds*
Pearson's r	-0.321	0.181	-0.307	-0.851	-0.368	-0.430	0.359	0.187	-0.345	-0.629
Adj. R^2	-0.196	-0.290	-0.208	0.633	-0.153	-0.087	-0.161	-0.287	-0.175	0.195

CONCLUSIONS

To summarise, quantum-chemical geometry optimization, calculation of HOMO, LUMO and solvation energies, as well as energies of the $S_0 \rightarrow S_1$ electronic transition for ten commonly used ^{99m}Tc radiopharmaceuticals in the combined basis set (SBKJC on the Tc atom and 6-31G (d,p)/DFT – on other atoms) revealed the results consistent with the available experimental data. The estimated partial charge values on the Tc atom were unfaithful, although it was possible to draw trustworthy conclusions by comparing the obtained electron density distribution in the ^{99m}Tc complexes. Semi-empirical quantum-chemical calculations of the ^{99m}Tc radiopharmaceuticals by the PM6 method gave less reliable results than *ab initio* calculations.

Pertechnetate, Tc-MAG3, Tc(III)-DMSA, Tc-DTPA, Tc-Exametazime, Tc-ECD showed the best, and Tc-Sestamibi, Tc-Medronate, Tc-DISIDA, and Tc-Mebrofenin had worst compliance with Lipinski's "rule of five", and all the ^{99m}Tc coordinate complexes had a number of hydrogen bond acceptors higher than 5. Therefore, the search for new coordinating ligands would be valuable for the development of improved ^{99m}Tc radiopharmaceuticals.

Finally, the percentage of nonspecific binding of five ^{99m}Tc complexes (Tc-Exametazime, Tc-MAG3, Tc-MDP, Tc(III)-DMSA, Tc-DTPA) to blood plasma proteins increased with increasing lipophilicity and decreasing ground state dipole moment (Pearson's correlation coefficients were 0.611 and -0.719, respectively). The above correspondence between the quantum-chemical descriptors and the experimental data can be employed in designing new ^{99m}Tc radiopharmaceuticals for cancer theranostics, which would possess high nonspecific binding to plasma proteins.

Acknowledgements

This work was supported by the Ministry of Education and Science of Ukraine (the Young Scientist projects № 0125U000840 "Nanocomposite materials based on metal-organic frameworks for environmental remediation, ecological screening, and medical diagnostics" and № 0124U000968 "Development of economically affordable nanosystems for rapid identification and purification of water from heavy metal ions based on carbon nanoallotropes and amyloids from organic waste").

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КВАНТОВО-ХІМІЧНІ РОЗРАХУНКИ РАДІОФАРМПРЕПАРАТІВ ТЕХНЕЦІЮ

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Синтез радіофармпрепаратів є головним завданням ядерної медицини, причому Технецій-99m (^{99m}Tc) має ідеальні ядерні властивості для неінвазивної ядерної медичної діагностики методом однофотонної емісійної комп'ютерної томографії (SPECT) – дешевшим методом, ніж КТ, МРТ і ПЕТ, що підходить для країн, які розвиваються. Особливо актуальним у наш час є дизайн різноманітних ковалентно мічених радіофармпрепаратів ^{99m}Tc для діагностики і тераностики онкологічних захворювань. Однак для правильного підбору лігандів і розробки якісних візуалізуючих агентів на основі ^{99m}Tc, що не будуть порушувати функції біологічно активних молекул, науковці повинні добре розбиратися у координаційній хімії перехідних металів групи 7. У даній роботі методами *ab initio* (комбінований базис: SBKJC на атомі Tc та 6-31G (d,p)/DFT – на інших атомах, Gamess) та напівемпіричними (PM6, MOPAC) розраховано квантово-хімічні характеристики десяти радіофармпрепаратів ^{99m}Tc. Негативне (Tc-Exametazime, Tc-ECD) і позитивне (всі інші) значення параметра E_{LUMO} зумовлюють електрофільні та нуклеофільні властивості радіофармпрепаратів, відповідно. Аналізуючи значення абсолютної жорсткості комплексів виявлено, що досліджені радіофармпрепарати – це м’які реагенти, причому пертехнетат має найнижчу реактивну здатність, що узгоджується з літературними даними. Для більшості радіофармпрепаратів ^{99m}Tc дипольні моменти були подібними або до 10 разів вищими у порівнянні з дипольним моментом молекули води. Нарешті, виявлено сильну кореляцію між значеннями дипольних моментів основного стану, ліпофільністю п’яти радіофармпрепаратів (Tc-Exametazime, Tc-MAG3, Tc-MDP, Tc(III)-DMSA, Tc-DTPA) та відсотком їх неспецифічного зв'язування з білками плазми крові (коефіцієнти кореляції Пірсона складали -0.719 та 0.611, відповідно). Отриманні результати є корисними для дизайну нових тераностичних протиракових агентів на основі ^{99m}Tc, що мають високий ступінь зв'язування з білками плазми крові.

Ключові слова: *радіофармпрепарати ^{99m}Tc; квантово-хімічні розрахунки; неспецифічне зв'язування з білками; дипольний момент; ліпофільність*