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A detailed theoretical study of the interaction of thiourea with *cis*-diaqua(ethylenediamine) platinum(II)

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ABSTRACT

Density functional theory (DFT), Hartree–Fock (HF) and Möller–Plesset second order perturbation (MP2) calculations were applied to study the mechanism of the two-step substitution reaction of *cis*-$[Pt(en)(H_2O)_2]^{2+}$ (en = ethylenediamine) and thiourea. Pentacoordinated platinum transition state (TS) geometries for both steps of the title S_N2 reaction were fully optimized at HF, B3LYP and MPW1PW91 levels of calculations. Distorted trigonal-bipyramidal TS's with rather small entering ligand to metal to leaving ligand angles ($\approx 80^0$) and with prolonged bonds to the leaving and entering ligands ($R_{Pt\text{—}O} \approx 2.4$ Å and $R_{Pt\text{—}S} \approx 2.85$ Å) were investigated in this paper. Natural bond orbital (NBO) analysis method was performed for the investigation of major stabilizing orbital interactions. The self-consistent reaction field (SCRF) methods were used to study the reaction in liquid phase. Both steps of the reaction are exothermic and the computed activation enthalpy ($\Delta H^\ddagger$) and entropy ($\Delta S^\ddagger$) in the rate-determining steps (RI → T-S → PI) are in good agreement with the experimental results. Thorough study of the reaction for improved values of energies and activation parameters was carried out at PCM/MP2 and PCM/B3LYP levels using 6-311+(d,p) and 6-311++(2d,2p) basis sets. The structural and activation parameters of the reaction suggest an associative interchange (I_a) substitution mechanism.

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1. Introduction

Since the accidental discovery of biological activity of *cis*-diamminedichloroplatinum commonly known as cisplatin in 1965 by Rosenberg [1], the experimental and theoretical investigation of substitution reactions of platinum(II) complexes by bioactive ligands has become a topic of current interest [2]. The hydrolysis of cisplatin and some of its analogs is believed to be the key activation step before the drug reaches its intracellular target DNA. The hydrolyzed diaqua product is believed to be the reactive species [3]. Quantum mechanical studies of the hydrolysis of cisplatin and its derivative dichloro(ethylenediamine) platinum(II) have been carried out [4,5]. However, in spite of the impressive antitumor activity, the major drawbacks of cisplatin therapy are its side effects [6] namely, gastrointestinal, nephro- and ototoxicity. Owing to high affinity of sulfur to platinum, nucleophilic sulfur containing compounds may act as protective agents against cisplatin toxicity. Thus, sodium thiosulfate, thiourea, glutathione, penicillamine, *N*-acetyl-L-cysteine, 1,3-dimethyl-2-thiourea and methionine have been applied as rescue or protective agents, in order to reduce the toxicity of platinum antitumor complexes [7–12].

It has been reported that thiourea (Tu) can block the action of *cis*-Pt(II) complexes on mouse leukemia cells [9]. Tu is one of the best known nucleophiles [13,14] for Pt(II) complexes and is commonly used in the investigation of ligand substitution reactions in coordination chemistry. Recently detailed study of platinum and Tu complex has been demonstrated by Schiessl et al. [15]. Thiourea is an interesting strong nucleophile as it combines the ligand properties of thioethers (σ-donor, π-acceptor) and thiolates (π-donor). For this reason it is necessary to investigate the ligand substitution reactions of Pt complexes with Tu. In the present work the following two-step reaction has been investigated theoretically:

$$[Pt^{II}(en)(H_2O)_2]^{2+} + Tu \rightarrow [Pt^{II}(en)(H_2O)(Tu)]^{2+} + H_2O \qquad (1)$$

$$[Pt^{II}(en)(H_2O)(Tu)]^{2+} + Tu \rightarrow [Pt^{II}(en)(Tu)_2]^{2+} + H_2O \qquad (2)$$

Experimental data for this reaction were reported earlier by some groups [16–18] independently. However, both steps of the reaction are supposed to pass through a pentacoordinated trigonal-bipyramidal (TB) transition state (TS) whose geometry may bring a new insight into the reaction dynamics of square planar Pt complex where the entering and leaving ligands are not

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identical. Because the binding of Pt to DNA is kinetically controlled, a better understanding of this process requires the use of quantum chemical methods for probing transition states. To know the exact TS structure ab initio or DFT method is required since other (empirical or semi-empirical) parametric approach employs experimental data to determine values for the relevant adjustable parameters and these data are not available for TS's. In the present work structural, thermodynamic and kinetic parameters of the above reactions have been computed theoretically and compared with the available experimental data. The effect of solvent on the energetic properties has been analyzed employing SCRF models. It is expected that the theoretical analysis reported here will provide valuable information regarding the role of Tu as a protective agent. The study has been carried out in neutral aqueous medium since it has been recently reported that in the pH range 0–7, Tu remains unprotonated [19].

2. Computational methods

All geometries and energies presented in the present work are computed at the Hartree–Fock (HF) and two density functional methods: (i) the gradient-corrected DFT level using the three-parameter fit of exchange and correlation functionals of Becke (B3LYP) [20] which includes the correlation functional of Lee, Yang, and Parr (LYP) [21] and (ii) MPW1PW91[22,23] which utilizes a modification of the gradient corrected Perdew–Wang exchange functional, PW91, combined with the non-local Perdew–Wang correlation functional. The relativistic effective core potential (ECP) and associated valence double ζ basis set of Hay and Wadt [24,25] (LANL2DZ) were employed for Pt. This includes electrons in the 6s, 6p, and 5d orbitals. The standard split valence basis set 6-31G(d) [26,27] was applied for other atoms. All stationary points located on the PES were characterized as minima (all positive frequencies) or first order transition state (one imaginary frequency) through harmonic frequency calculations. For every TS the corresponding structures of the intermediates were confirmed by the intrinsic reaction coordinate (IRC) method [28,29]. Thermal contribution of the energetic properties was also considered at the standard state, namely, at 298.15 K and 1 atm.

The rate constants (k) were calculated within the transition state theory according to the Eyring equation [30].

$$k(T) = \frac{k_B T}{h} e^{-\frac{\Delta G^\ddagger}{RT}} \tag{3}$$

where k_B is the Boltzmann constant, T the absolute temperature and h the Planck constant. $\Delta G^\ddagger$ is the activation free energy for each step. The standard concentration ($c^0 = 1$ mol/dm^3) was considered. All the quantum mechanical calculations have been carried out with the GAUSSIAN 03 Revision D.01 program [31].

To evaluate the role of solvent, geometry optimization and single point energy calculations for stationary points in aqueous medium were performed by self-consistent reaction field (SCRF) technique. Two models, namely, Onsager reaction field model [32] and polarized continuum-model (PCM) were attempted. In the SCRF model the solvent is taken as a polarizable continuum of uniform dielectric constant. In the Onsager model, the solute is placed in a spherical cavity of radius a_0 within the solvent field. The cavity size, a_0 for each solvated species was computed from a tight molecular volume calculation on the fully optimized gas-phase stationary states. In the PCM, the solute is placed in the solvent reaction field cavity created by a series of overlapping spheres initially devised by Tomasi et al. [33,34] and implemented by Barone et al. [35–38] and also by Tomasi, Mennucci and co-workers [39,40]. Improved PCM single point energy calculation were performed at B3LYP level using the same ECP and valance basis set for Pt but the larger basis sets 6-311++(2d,2p) for the other atoms and also by the Möller–Plesset second order perturbation (MP2) method using the same ECP and valance basis set for Pt and 6-311+(d,p) basis sets for the other atoms. B3LYP/LANL2DZ/6-31G(d) level 'gas phase' thermal corrections were used in these calculations. All the PCM calculations were carried out at 298.15 K using an average tesserea area of 0.2 Å^2. The United Atom Topological model (UATM) was used for building the cavity in PCM model. Stabilities of all the wave functions under the perturbations were checked and verified.

Natural bond orbital (NBO) analysis [41] at B3LYP/LANL2DZ/6-31G(d) level was carried out to understand the orbital interactions and charge delocalization during the course of the reaction. In the NBO analysis, NBOs are first defined for each covalent bond, lone pair, and anti-bonding orbital by using the molecular orbitals obtained by quantum chemical calculations, and the orbital interaction energies are subsequently calculated for all possible interactions between electron-donor Lewis-type NBO (i) and acceptor non-Lewis NBO (j). For each electron-donor NBO (i) and acceptor NBO (j), the stabilization energy E_{ij} associated with delocalization $i \rightarrow j$ is estimated as

$$E_{ij} = q_i \frac{F(i,j)^2}{\varepsilon_j - \varepsilon_i} \tag{4}$$

where q_i is the donor orbital occupancy, ε_i,ε_j are orbital energies and $F(i,j)$ is the off-diagonal NBO Fock matrix element [42,43].

3. Results and disscussion

3.1. Conformational space searching

The title reaction was characterized by an exchange of two ligands Tu and H_2O. It belongs to the class of second order nucleophilic substitution (S_N2). In a general S_N2 reaction path, five stationary states e.g., reactant (R), reactant intermediate (RI), TS, product intermediate (PI) and product (P) are found [44]. Geometries of all the stationary states found on the potential energy surface (PES) from detailed conformational space searching were optimized at HF, B3LYP and MPW1PW91 levels of theory using LANL2DZ/6-31G(d) basis set combination and those obtained at B3LYP level are shown in Figs. 1 and 2. The reactant complex $[Pt^{II}(en)(H_2O)_2]^{2+}$ (R1) shows almost a square planar geometry around the central Pt(II) with an out-of-plane distortion caused by the en group with dihedral angle (∠N—C—C—N) around 51^0. Pt—N, Pt—O and O—H bond lengths are 2.05 Å, 2.14 Å and 0.98 Å, respectively, at B3LYP level of theory. The calculated bond angles ∠O—Pt—O, ∠O—Pt—N and ∠N—Pt—N are 95.5^0, 90.4^0 and 83.6^0, respectively. No crystal structure was found for $[Pt^{II}(en)(H_2O)_2]^{2+}$ in literature for comparison. The calculated Pt—N bond length and ∠N-Pt-N angle are in conformity with available crystallographic data [45] for the stable product, and also close to those obtained theoretically by Summa et al. [17] calculated at B3LYP/LANL2DZp level of theory. All the intermediate structures found in this reaction are stabilized only through H-bonds since the interaction with Pt(II) atom is negligible (Pt—S distances being above 3.8 Å) as previously investigated by Chval and Sip [46] for the two steps hydrolysis reaction of cisplatin. Three reactant intermediates (RI1, RI1′ and RI1″) and two product intermediate (PI1 and PI1′) are found in the first step. The proposed reaction mechanism is presented in Scheme 1. The intermediate RI1 and PI1 are connected via TS1 by an IRC run (Fig. S1(a), Supplementary data). All these RI's differ mainly in the position of H-bonded entering Tu molecule and PI's differ in the position of H-bonded leaving H_2O molecule. The absolute minimum structure RI1″ is 5.7 kJ/mol and 27.2 kJ/mol more stable than the local minimum structure RI1′

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