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A DFT study on the hydrolysis mechanism of the potential antitumor Ru(III) complex TzNAMI

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ABSTRACT

The hydrolysis process of Ru(III) complex [TzH][*trans*-$RuCl_4$(DMSO)(Tz)]·(DMSO) (TzNAMI), a potential antitumor complex similar to the well-known antitumor agent NAMI-A, has been investigated by using density functional theory (DFT) method, and the solution effect was also considered and calculated by conductor-like polarizable calculation model (CPCM). The structural characteristics and the detailed energy profiles for the hydrolysis processes of this complex have been obtained. The analysis of thermodynamic and kinetic characteristics of hydrolysis reaction suggests the following: for the 1st hydrolysis step, the complex TzNAMI with thiazole ligand has slightly lower hydrolysis rate than NAMI-A with imidazole ligands, and such a calculated result is in good agreement with experimental one and reasonably explained in theory. For the 2nd hydrolysis step, the formation of *cis*-diaqua species is thermodynamically preferred to that of *trans* isomer. In addition, based on the analysis of electronic characteristics of species in the hydrolysis process, the trend in nucleophilic attack abilities (*A*) of hydrolysis products by pertinent biomolecules is revealed.

1. Introduction

In the past few years, Ru(III) compounds as peculiar antitumor agents, have attracted large attention due to their generally less toxic side effects than platinum-based drugs and their activities against cisplatin-resistant cells [1,2]. Among all ruthenium-based anticancer complexes, the most promising antimetastatic agent, [ImH][*trans*-$RuCl_4$(DMSO)(Im)] (NAMI-A) [3], is the first ruthenium anticancer complex that has entered clinical testing and recently has finished in the clinical trials of the first phase as an antimetastatic drug [4,5]. In preclinical development, NAMI-A shows marked efficacy against metastases [6–9].

In the search for novel Ru(III) complexes with better pharmacological profile, Mura et al. recently showed that the thiazole analogue of NAMI-A, i.e., [TzH][*trans*-$RuCl_4$(DMSO)(Tz)]·(DMSO) (TzNAMI) (Fig. 1), manifests some interesting pharmacological properties compared to NAMI-A [10]. In addition, TzNAMI has many similar characteristics compared to NAMI-A [10], for instance, they all exhibit higher reactivity toward serum albumin than toward calf thymus DNA, higher stability in organic solvent and fast hydrolysis when the compounds are dissolved within a physiological buffer at pH 7.4 and noncytotoxic in vitro test. Although the cytotoxicity experiments in vitro revealed that TzNAMI is virtually noncytotoxic even at the highest tested concentrations, the lack of cytotoxicity does not represent a clear drawback for the pharmaceutical applications of this NAMI-A-type of compound [10]. It is well known that the favorable pharmacological properties of NAMI-A are unrelated to cytotoxicity [3,6–8], that is, NAMI-A itself represents a typical example of a promising antitumor drug that lacks cytotoxicity in vitro. Since TzNAMI with thiazole ligand has the similar structure and properties to NAMI-A, this compound maybe become a new promising member of NAMI-A kind of antimetastatic agent.

Despite ruthenium complexes have been regarded as a peculiar family of antitumor agents with selective antimetastatic properties and low systemic toxicity, so far the action mechanism has not been elucidated yet. Moreover, no clear structure–activity relationship (SAR) has been established. For the parental complex NAMI-A, many experimental results show that in physiological conditions, the complex is relatively labile and undergoes stepwise hydrolysis for two chlorides in two steps [1,11] and transforms into the corresponding more reactive aquated species [12,13]. The resulting bis-aquated species may bind to various biomolecular targets and thus it is very likely responsible for NAMI-A's selective antimetastatic activity in vivo [14–16]. Hence, hydrolysis appears to play an important role in the compounds' mode of action. Since TzNAMI has similar structure and characteristics to NAMI-A, the hydrolysis

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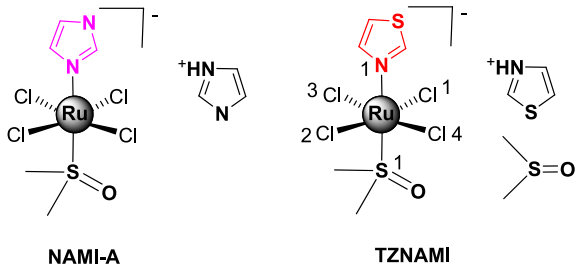


Fig. 1. Structural diagrams of Ru(III) complexes, (ImH)[*trans*-$RuCl_4$(DMSO)(Im)] (NAMI-A) and (TzH)[*trans*-$RuCl_4$(DMSO)(Tz)]·(DMSO) (TzNAMI).

process should be also the key activation step before the potential drug reaches its intracellular target.

In order to understand the mode of action of ruthenium(III)-based drugs at the molecular level, the theoretical studies on the hydrolysis mechanism of the well-known anticancer agents NAMI-A and [ImH][*trans*-$RuCl_4Im_2$](ICR) were reported by the current authors [17,18]. More recently, deeper insight into the aquation of these two complexes were further investigated and supplemented by Bešker et al. and Vargiu et al. using DFT-PB methods [19,20], respectively. However, TzNAMI with thiazole ligand possesses own structural characteristics different from the reported antitumor drugs NAMI-A and ICR. These structural characteristics closely relate to the aquation and bioactivity of this compound. Therefore, the theoretical studies on the hydrolytic properties of TzNAMI at the molecular level are still very significant for understanding action mechanism and revealing SAR of this kind of compound.

In this paper, the hydrolysis process of potential antitumor Ru(III) complex [TzH][*trans*-$RuCl_4$(DMSO)(Tz)]·(DMSO) (TzNAMI) (Scheme 1), a new member of NAMI-A-type complexes, was investigated by using density functional theory (DFT) method, and the solvent effect was also considered and calculated by conductor-like polarizable calculation model (CPCM) [21–23]. The related structural characteristics (including the geometrical structure and electronic structure), thermodynamic properties, and energy profiles of this complex were calculated, discussed and compared with those of NAMI-A. On the basis of the calculated results, the trend of hydrolysis was obtained, and some experimental observations were explained and further confirmed. We expect these theoretical results help to understanding the action mechanism and SAR of NAMI-A-type Ru(III) antitumor complexes.

2. Computational methods

All geometry optimizations in vacuo for each structure in its low ($S = 1/2$) spin state were carried out using UB3LYP exchange-correlation functional [24,25] at the level of LanL2DZ+6-31G(d), in which the LanL2DZ [26,27] basis set was used for Ru atom only and 6-31G(d) basis set was employed for other atoms. Frequency calculations were performed at the same level of theory to verify the correct nature of the stationary points, and to estimate zero-point vibrational energies and thermal and entropy corrections at room temperature. In order to obtain an improved value of the internal energy, single-point energies were further calculated in gas phase and in solution (adopting the CPCM continuum solvation method) using a larger basis set on optimized structures, that is, 6-311++G(3df, 2pd) on the nonmetal atoms, and LanL2DZ(f) ($\zeta_f = 1.235$) [28] on Ru atom. Each transition state was further confirmed by intrinsic reaction coordinate (IRC) [29,30] calculations. The natural orbital population analysis (NPA) [31,32] was carried out to obtain more electronic information for these hydrolysis reactions. All calculations were performed by using Gaussian 03 program package [33] running on the High Performance Computing Clusters (HPCCs).

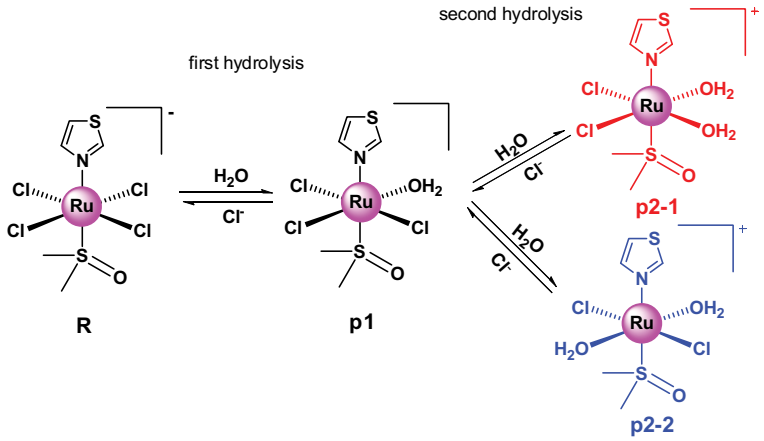
The rate constants (k) were calculated according to the transition state theory [34] proposed by Eyring, as can be seen in Eq. (1), where k_B is the Boltzmann constant, T is the absolute temperature, and h is the Planck constant. $\Delta G^{\ddagger}$ is the activation free energy for each step. The standard concentration ($c^{\circ} = 1$ mol/L) was considered. This equation generally used to evaluate the approximate rate constant for the aquation of ruthenium and platinum-based complexes [19,35–37].

$$k(T) = \frac{k_B T}{h} e^{-\Delta G^{\ddagger}/RT}. \quad (1)$$

3. Results and discussion

3.1. Structural characteristics

The title complex was modeled considering the [*trans*-$RuCl_4$(DMSO)(Tz)]$^-$ anion. The fully optimized structures for the species involved in the first step of hydrolysis of TzNAMI are shown in Fig. 2, and those in the second step of the hydrolysis process are depicted in Fig. 3. The selected structural parameters for the optimized stationary points are listed in Tables 1 and 2 for the first and second steps of hydrolysis, respectively, including separated reactants, intermediates, transition states, and separated



Scheme 1. Proposed hydrolysis process of (TzH)[*trans*-$RuCl_4$(DMSO)(Tz)]·(DMSO) (TzNAMI) in physiological conditions (pH = 7.4).