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Journal of Molecular Structure: THEOCHEM 801 (2006) 21–28

THEO CHEM

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An ab initio study of the S_N2 reaction of 1- and 3-methyltriazene with halide ions

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Received 1 August 2006; received in revised form 29 August 2006; accepted 29 August 2006
Available online 7 September 2006

Abstract

Methyltriazenes are believed to be the active metabolite of triazene containing anti-neoplastic agents, such as Dacarbazine and Temozolomide. It has been proposed that these agents methylate the O6-oxygen of guanine. Methylguanine formation is believed to be responsible for their observed cytotoxic properties. To facilitate a better understanding of this proposed mechanism, a series of ab initio calculations of the bimolecular nucleophilic substitution (S_N2) reaction between 1- and 3-methyltriazene and the halide ions were undertaken, the results of which are presented here.

Keywords: Triazene; Methyltriazene; Dacarbazine; Temozolomide; Bimolecular nucleophilic substitution reaction

1. Introduction

It has been well established that 5-(3,3-dimethyl-1-triazenyl)imidazole-4-carboxamide (Dacarbazine, DTIC®, NSC-45388) (Fig. 1) is the single most active agent for the treatment of malignant melanoma [1–3]. In addition to Dacarbazine other dimethyltriazenes have been shown to demonstrate anti-tumor properties [1,4]. It has been proposed that the method of action of these anti-neoplastic dimethyltriazenes involves the demethylation of the terminal nitrogen through an oxidative process carried out via hepatic cytochrome P450 enzymes [5]. The hepatic oxidative demethylation yields a methyltriazene (Scheme 1), which are known DNA and RNA alkylating agents [6,7]. It has been proposed that the methylation of DNA is responsible for the observed properties of these anti-neoplastic triazene compounds [1,3,6,8]. Methyltriazenes have been proposed to methylate the O6-oxygen of guanine through a bimolecular nucleophilic substitution reaction (S_N2) at the methyl carbon resulting in the formation of an aryl amine (RNH_2), molecular nitrogen (N_2) and methylated DNA ($NuCH_3$) (Scheme 2) [1,6,7].

Carbon centered S_N2 reactions have been widely studied [9,10]. Various methods have been employed; for instance, kinetic experiments [11–20], ab initio quantum mechanical and semi-classical dynamical methods and trajectory simulations [21–27], statistical mechanical studies [28–35], ab initio and density functional structural analyses [36–48] and electron-transfer investigations [49–55].

The current study is focused on investigating the S_N2 reaction that is proposed to occur between monomethyltriazene and the O6-oxygen of guanine as the mechanism of action for triazene containing anti-neoplastic agents, such as Dacarbazine (Fig. 1) and Temozolomide (Fig. 2). This study will examine a model S_N2 reaction that simulates the proposed reaction by which methyltriazenes methylate DNA (Scheme 1). The proposed method of action will be simulated by replacing the DNA base guanine with various halide ions; fluoride, chloride, bromide and iodide. The halide ions were chosen to give a variety of nucleophilicities without introducing too many geometric degrees of freedom or an extremely basic ion. The methyltriazene will be modeled with 1- and 3-methyltriazene. The S_N2 reaction

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doi:10.1016/j.theochem.2006.08.059

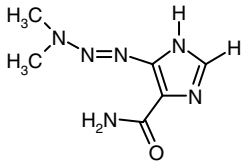


Fig. 1. The chemical structure of 5-(3,3-dimethyl-1-triazenyl)imidazole-4-carboxamide (Dacarbazine, DTIC®).

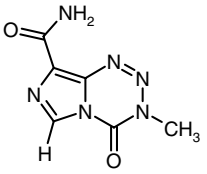
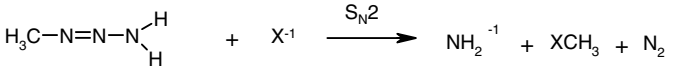


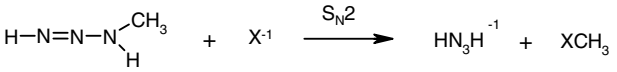
Fig. 2. The chemical structure of Temozolomide (3,4-dihydro-3-methyl-4-oxoimidazo-[5,1,d]-1,2,3,5-tetrazine-8-carboxamide, Temodal®).

that occurs between 1-methyltriazene and a halide ion results in a halomethane, molecular nitrogen and NH_2^- (Scheme 3), whereas the S_N2 reaction that occurs with 3-methyltriazene results in a halomethane and HN_3H^- (Scheme 4). The model S_N2 reaction, involving 1-methyltriazene best represents the proposed mechanism of action that triazene containing anti-neoplastic agents utilize.

It is intended that these studies of monomethyltriazene will facilitate a better understanding of the mechanism of action of triazene containing anti-neoplastic agents that are known DNA alkylating agents. It should be noted that this ab initio study is part of a series of studies, investigating triazene based anti-neoplastic agents. Previous studies have included an ab initio study of triazene and its mono-, di- and trimethyl derivatives [56]. Future studies will focus on the S_N2 reactions of dimethyltriazene and trimethyltriazene with various halide ions. These studies will provide the framework for future studies of triazene containing anti-neoplastic agents and their structural derivatives.



Scheme 3. The S_N2 reaction between 1-methyltriazene and a halide ion results in a halomethane, molecular nitrogen and NH_2^-.



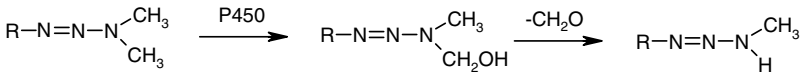
Scheme 4. The S_N2 reaction between 3-methyltriazene and a halide ion results in a halomethane and HN_3H^-.

2. Method

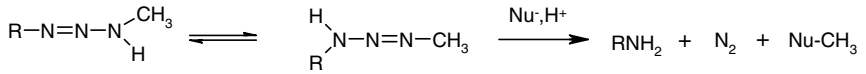
All calculations for this computational study were performed with Gaussian 98 [57]. Geometry optimizations were sequentially performed at the HF/STO-3G, HF/3-21G, HF/6-31G(d), HF/6-31+G(d), MP2/6-31G(d) and MP2/6-31+G(d) levels of theory. The frozen core approximation was used for the MP2 calculations. For iodine modified Huzinaga basis sets were implemented as described elsewhere [58,59]. Harmonic vibrational frequencies and zero-point vibrational energy (ZPVE) corrections were calculated analytically at the same level of theory as the corresponding geometry optimization. The ZPVE was corrected using a previously determined scaling factor [60]. All structures were characterized by harmonic vibrational frequency calculations. For brevity, only the results at HF/6-31G(d) and above shall be discussed.

3. Results and discussion

For this study six previously identified isomers of (mono)methyltriazene were utilized [56], namely, the (*E*) and (*Z*) isomers of 1-methyltriazene and two conformers each of the (*E*) and (*Z*) isomers of 3-methyltriazene (Fig. 3). Each reaction pathway involved the reaction between one of the methyltriazene conformers with a halide ion; fluoride, chloride, bromide or iodide. The various reactions will be discussed in terms of relative energy comparisons. Some relevant quantities are the reactant and product complexation energies ($E_R{}^w, E_P{}^w$), the central activation barriers ($E_R{}^*, E_P{}^*$), and the net activation barriers ($E_R{}^b, E_P{}^b$), in addition to the energy of reaction E^0. Additionally, interesting geometrical features along the reaction pathways will be discussed. The reaction between the conformers of 1-methyltriazene and the various halide ions of interest will be discussed first followed by a discus-



Scheme 1. The metabolic formation of monomethyltriazene from Dacarbazine, through hepatic cytochrome P450 enzymatic oxidation.



Scheme 2. The proposed mechanism of action for DNA methylation by a 1-methyltriazene occurs through a bimolecular nucleophilic substitution reaction resulting in molecular nitrogen, aryl amide and methylated DNA.