

# Quantum computations of the UV–visible spectra of uric acid and its anions

Muhannad Altarsha<sup>a</sup>, Gérald Monard<sup>a,\*</sup>, Bertrand Castro<sup>b</sup>

<sup>a</sup> *Equipe de Chimie et Biochimie théoriques, UMR 7565 CNRS-UHP SRSMC, Université Henri Poincaré-Nancy I, Faculté des Sciences, B.P. 239, F54506 Vandoeuvre-les-Nancy Cedex, France*

<sup>b</sup> *Sanofi-Aventis, 371, Rue du Professeur Joseph Blayac, 34184 Montpellier Cedex 04, France*

Received 5 January 2006; received in revised form 8 January 2006; accepted 9 January 2006  
Available online 28 February 2006

## Abstract

UV–visible spectra of uric acid as a function of pH have been studied and compared with experimental data. Different quantum methodologies have been employed: CIS–ZINDO, CIS–HF and TD–DFT. Solvent effects were modeled using the COSMO model. To account for the change in maximum absorbance along a variation of pH, different forms of uric acid have been taken into account: uric acid represented the major species at low pH, urate monoanions represented the major components of urate solution at pH 7, and urate dianions represented the major components of urate solution at pH above 10. Our computational results show CIS–ZINDO and CIS–HF quantum methods do not reproduce well experimental absorption spectra whatever the pH. In contrast, TD–DFT in conjunction with the COSMO continuum model gives very good agreement with experimental data and strongly indicates at medium and high pH uric acid solution is composed of a mixing of the different possible existing species. At neutral pH, uric acid exists as a mixture of a major monoanion component and a minor monoanion component, while at high pH, several dianion species seem to coexist.

© 2006 Elsevier B.V. All rights reserved.

**Keywords:** Uric acid; TD–DFT; ZINDO; CIS; COSMO; Absorption spectra; Electronic transitions

## 1. Introduction

In human species, uric acid is one of the final products of the degradation of purine nucleotides [1]. Accumulation of uric acid in kidneys can lead to severe disorders. More particularly, in cancer patients, cellular disorders or aggressive chemotherapy increase purine metabolism and therefore, the release of large quantities of uric acid in blood. To prevent and cure hyperuricemia, it is common to use as a drug urate oxidase: a nonhuman proteolytic enzyme that oxidizes uric acid to allantoin [2–4] (see Fig. 1).

The catalytic properties of urate oxidase has been experimentally studied [5–7], but no detailed modeling of catalytic events inside this enzyme has been published so far. To assess a possible theoretical mechanism for urate oxidase, it is necessary to be in agreement with experimental findings. One of them is a stopped-flow absorbance and fluorescence spectrophotometry performed by Kahn and Tipton [6]. These authors have found two intermediates in the mechanism: a first

intermediate with an absorbance maximum at 295–297 nm, and a second intermediate at 298 nm. The true product of urate oxidase, the 5-hydroxyisourate, has been identified with an absorbance maximum at 302 nm, while allantoin, the product of the natural hydrolysis of 5-hydroxyisourate in water, has been found with an absorbance maximum around 240 nm.

Before trying to reproduce these experimental facts inside the urate oxidase enzyme, it is necessary to test and calibrate quantum computations to verify quantum methodologies can be accurate enough for a possible comparison between calculated and experimental spectra. To assess and compare most of today's available methodologies, we have chosen to try to reproduce the variation of uric acid spectra as a function of pH. Bergmann and Dikstein [8] have determined uric acid present an absorbance maximum at 285 nm at pH 2, an absorbance maximum at 292 nm at pH 8, and an absorbance maximum at 294 nm at pH 12. This was the first experimental evidence uric acid presents two  $pK_a$ s in solution: a first  $pK_a$  around 5 and a second  $pK_a$  around 10 [9,10,5,11]. Shukla and Mishra [11] also studied the electronic absorption of uric acid at different pH. They identified two absorbance peaks in range 200–300 nm. At pH 2.7, uric acid presents two absorption peaks at 283 and 230 nm. At pH 7, these absorption peaks are red-shifted to near 290 and 233 nm. At pH 10.6, absorbance maxima are found at 293 and 220 nm. Moreover, Shukla and

\* Corresponding author.

E-mail address: gerald.monard@cbt.uhp-nancy.fr (G. Monard).

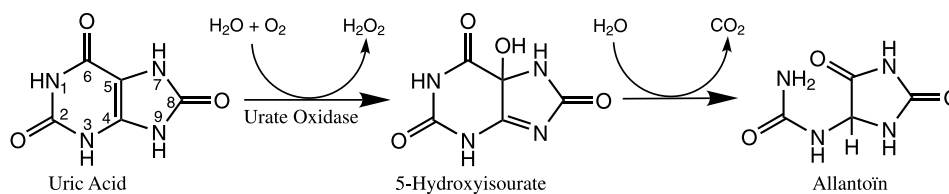


Fig. 1. Reaction catalyzed by urate oxidase (E.C.1.7.3.3).

Mishra have also computed the electronic transitions of uric acid and one of its monoanion (monoanion 3, depicted  $\text{UAN}_3^-$  in Fig. 2) using CIS–CNDO [12] computations on AM1 [13] or PM3 [14] optimized geometries. They found relative good agreements between their experimental and calculated spectra. However, as recently proposed [15,16], uric acid at neutral pH can be conceived of a mixture of two monoanions: a majority of  $\text{UAN}_3^-$  with a minority of  $\text{UAN}_7^-$ , while in high pH the urate solution is composed to three different dianions (see Fig. 3):  $\text{UAN}_3^- \text{N}_9^-$  in majority with small amounts of  $\text{UAN}_3^- \text{N}_7^-$  and  $\text{UAN}_7^- \text{N}_9^-$ .

We present here an extensive study of the UV spectra of uric acid, its monoanions, and its dianions in the experimental range of 200–340 nm using different quantum methodologies available. After presenting our computational details, we present our results using the semiempirical ZINDO [17] method using configuration interaction with single excitations (ZINDO–CIS), then the CIS method associated with Hartree–Fock calculations (HF–CIS) [18], and the time-dependent density functional theory (TD–DFT) [19–22].

## 2. Computational details

Semiempirical ZINDO–CIS calculations and HF–CIS computations have been handled using the GAUSSIAN 98 software [23]. TD–DFT calculations have been performed using the GAUSSIAN 03 version [24]. To assess basis set effects, several basis sets have been used for ab initio and DFT computations: 3-21G, 6-31G, 6-31G\*\*, 6-31++G\*\*, and aug-cc-pVDZ. Three different exchange–correlation potentials have also been evaluated: BPW91 [25,26], BLYP [25,27], and B3LYP [27–29]. Because experimental spectra have been obtained in solution, solvent effects through the use of a continuum model have been employed. The dielectric constant was the one from water: 78.54. Different continuum models have been used, all derived from the PCM model from Tomasi et al. and available in the last two versions of Gaussian: the original PCM [30], the improved IPCM model which use a static isodensity surface for molecular cavity [31], and the CPCM model [32,33] which represent an implementation of COSMO model from Klamt et al. [34] in the GAUSSIAN software. ZINDO UV spectra have been computed on PM3 optimized geometries. In these semiempirical calculations, when needed solvent effects were taken into account both during the PM3 geometry optimization and the ZINDO–CIS calculation. CIS UV spectra computations with and without solvent effect have been performed on gas phase geometries obtained after Hartree–Fock geometry optimizations. TD–DFT UV spectra

calculations with and without solvent effect have been made on geometries obtained after DFT geometry optimizations in gas phase.

## 3. Results and discussion

### 3.1. ZINDO semiempirical method

ZINDO–CIS calculations of UV spectra of uric acid, one of its monoanions ( $\text{UAN}_3^-$ ) and one of its dianions ( $\text{UAN}_3^- \text{N}_7^-$ ) are reported Table 1. It contains for each method and each molecule the two highest electronic transitions in the range 200–340 nm (i.e. the two electronic transitions having the highest oscillator strengths). In gas phase, maximum wave lengths for uric acid,  $\text{UAN}_3^-$  and  $\text{UAN}_3^- \text{N}_7^-$  are, respectively, 318, 303 and 296 nm. These are all far away from experimental data and in reverse order: from uric acid to its dianions, the experimental absorbance maximum increase from 285 to 294 nm while according to ZINDO–CIS calculations absorbance peaks should decrease in length. Use of the PCM solvent model worsen the results: the absorbance maximum for  $\text{UAN}_3^-$  becomes 314 nm while the absorbance maximum for  $\text{UAN}_3^- \text{N}_7^-$  increases to 308 nm. Changing solvent model, either IPCM or COSMO, does not lead to better UV spectra: in each case, the absorbance maximum order between uric acid, its anions and dianions is reversed. Overall, ZINDO–CIS calculations cannot reliably reproduce experimental UV spectra of uric acid and its related anions.

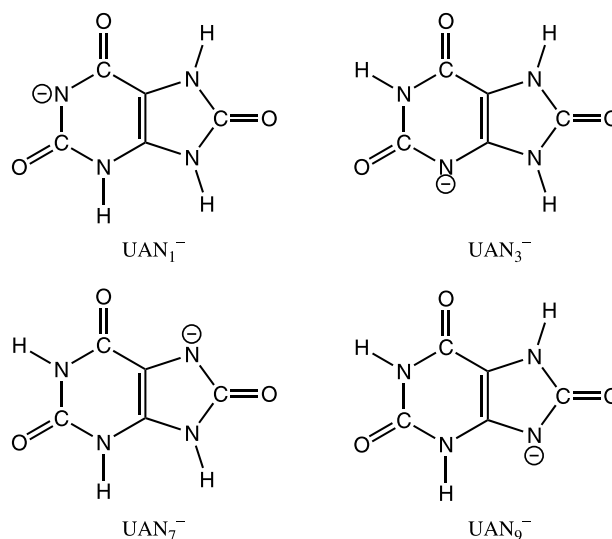


Fig. 2. The four possible urate monoanions obtained after proton abstraction on one NH site of uric acid.

Download English Version:

<https://daneshyari.com/en/article/5418473>

Download Persian Version:

<https://daneshyari.com/article/5418473>

[Daneshyari.com](https://daneshyari.com)