



Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: <http://www.elsevier.com/locate/molstruc>

Time-resolved spectroscopic and density functional theory investigation of the influence of the leaving group on the generation of a binol quinone methide

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ARTICLE INFO

Article history:

Received 18 September 2017

Received in revised form

3 November 2017

Accepted 5 November 2017

Available online xxx

Keywords:

Quinone methide

Time-resolved spectroscopy

Time-resolved resonance Raman

DFT calculation

ABSTRACT

Quinone methides are important reactive intermediates in photobiology and photochemistry, with little known regarding the photo-induced generation of reactive quinone methides species from relevant precursors in aqueous solutions. Here, the time-resolved spectroscopy methods including the transient absorption experiments and time-resolved Resonance Raman were employed to directly study the photophysics and photochemical processes of 6,6'-Bis(hydroxymethyl)-1,1'-binaphthyl-2,2'-diol (BQMP-a) in neat MeCN and 1:1 MeCN:H₂O aqueous solutions. In aqueous solution, the intramolecular excited state proton transfer (ESIPT) process was observed where the water molecules help deliver the proton on the hydroxyl group to the naphthol ring within 125 ps in the singlet excited state of BQMP-a. This solvent mediated ESIPT will then lead to the leaving of the H₂O group in 906 ps followed by the generation of the binol quinone methide (BQM-a) intermediate with a lifetime of 1.7 μs. As a result, the BQMP-a provides a different production rate of quinone methides compared with the 1,1'-(2,2'-Dihydroxy-1,1'-binaphthyl-6,6'-diyl) bis(*N,N,N*-trimethylmethanaminium) bromide system, which indicates the leaving group is an important factor in the generation of the reactive DNA alkylated intermediates.

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1. Introduction

By inhibiting DNA strand separation, interstrand cross-linking prevents DNA transcription, replication and gene expression effectively, then causes replication arrest and cell death. These alkylations can be among the most cytotoxic processes towards shutting down DNA replication processes. Recently, some bifunctional quinone methides were discovered to be key intermediates being used in cancer treatments and reported to show efficient nucleoside alkylation and DNA interstrand cross-linking by irradiation of the suitable precursors in water [1–7]. Freccero [5] pointed out that the binol quinone methides were able to alkylate N7 of guanines leading to an increasing the rate of depurination (at the oligonucleotide scale) and ribose loss (at the nucleotide scale) which was photocytotoxic on some cancer cell lines.

In light of the importance of quinone methides described above, there have been many studies on the photogeneration of *p*-quinone

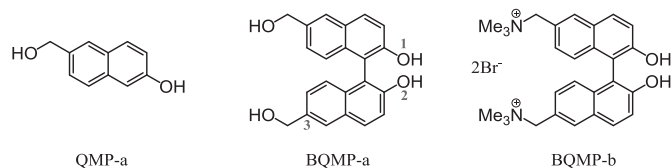
methide reported by Wan [8–10], Kresge [11,12], Freccero [13–16] and Richard [1,4,6] in the past decades. Both the alcohol analogue (Scheme 1, BQMP-a) and quaternary ammonium salts of phenolic Mannich base (Scheme 1, BQMP-b) are reported as the efficient leaving groups for quinone methide precursors [1,3,4,13]. While many studies examined the photogeneration of *p*-quinone methide, few studies have given direct pieces of evidence regarding the photochemical formation processes that generate QMs to the best of our knowledge. According to our recent study on the photolysis of the BQMP-b [17], water-assisted excited state intramolecular proton transfer (ESIPT) process was involved in generation of the Binol quinone methide. Unlike the BQMP-b, the alcohol analogue in BQMP-a showed good reversibility [5], which could improve their potential application for certain biological activity. Many studies have applied the reversibility of *p*-quinone methide (QM) photogeneration for efficient cross-linking and target-promoted alkylation of DNA [7,13,18,19], therefore, it is important to study the photo-induced process of BQMP-a and distinguish the difference between those two different leaving groups compared to BQMP-b.

In this paper, femtosecond and nanosecond transient absorption

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Scheme 1. The structures of QMPs.

(fs-TA and ns-TA) and nanosecond time-resolved resonance Raman (ns-TR²) have been used to directly examine the short time processes that occur for BQMP-a after the photoexcitation. So as to distinguish the significant influence of the bi-naphthol ring in the photochemistry, the photoreaction of the parent compound QMP-a (Scheme 1) which does not have another naphthol ring was also examined in MeCN and aqueous solutions using time-resolved spectroscopy techniques and these results were then compared to the results obtained for BQMP-a described here. The geometries and vibrational spectra of probable intermediate species were obtained from density functional theory (DFT) calculations (using the B3LYP method with a 6-311G** basis set). These results were employed to make assignments for the experimental vibrational bands of the binol quinone methide (BQM-a) intermediates characterized here. The time-resolved spectroscopy results reported here provide direct evidence that water assisted singlet ES IPT occurs to produce the binol quinone methides from bi-naphthol derivatives in aqueous solutions. Moreover, comparison to the other precursors, the high solubility in various solutions compared with other derivatives can increase BQMP-a's practical application in biological systems.

1.1. Experimental and computational methods

Samples of BQMP-a was synthesized according to the literature methods previously reported [5]. Spectroscopic-grade acetonitrile (MeCN), and distilled water were used. All of the mixed solvent ratios are volumetric ratios.

A. Time-Resolved Spectroscopy Experiments. The fs-TA and ns-TA experiments were used the experimental setups and methods which were described previously [17,20]. The ns-TR² experiments were also employed the same instruments described in detail previously [21–23].

B. DFT Calculations. The DFT calculations were finished by employing the (U)B3LYP method with a 6-311** basis set. A Lorentzian function with a fixed bandwidth of $\sim 10 \text{ cm}^{-1}$ was employed to compute the Raman spectrum from the vibrational frequencies and a frequency scaling factor of 0.986 was used to in the comparison of the calculated results with the experimental spectra. All of the calculations were done by using the Gaussian 09 program suite [24,25].

2. Results and discussion

2.1. Fluorescence study of BQMP-a

The fluorescence of BQMP-a was characterized in MeCN and H₂O mixed aqueous solutions with different contents of water after 266 nm excitation (Fig. 1a). As shown in Fig. 1a, addition of a small amount (2.78 mol L^{-1}) of H₂O into a MeCN solution can lead to an early red shift of the fluorescence emission band from λ_{max} 356 nm in pure MeCN to λ_{max} 360 nm for BQMP-a. With an increasing concentration of water, the intensities of the fluorescence decrease significantly and this suggests that the singlet excited state(s) of the BQMP-a may be involved in a reaction with H₂O. The quenching of

fluorescence at higher water concentration could be assigned to the competitive formation of naphtholates BQMP-a⁻ via ESPT to the solvent [26,27]. No new emission band is achieved at high water content, this indicates that BQMP-a⁻ is not emissive if it is formed. Another possibility is that the singlet excited state(s) of BQMP-a can produce quinone methide intermediate through an ES IPT process. Fig. 1b shows the modified Stern-Volmer quenching plots of the emission intensity of BQMP-a with addition of water to the MeCN solution and it can be fit by the following polynomial function reasonably well: $I/I_0 = 1 + K_{\text{sv}} [\text{H}_2\text{O}]^4$, where $K_{\text{sv}} = 2.5 \text{ M}^{-4}$. A similar phenomenon of a nonlinear water content dependence of the fluorescence quenching was also found in some previous studies [17,27]. Comparison to the complicated ES IPT process of the BQMP-b system [17], it has been suggested that multiple water molecules (like tetramers) can be involved in a long-range water-assisted ES IPT process for the BQMP-a system [25].

2.2. Fs-TA, ns-TA and TD-DFT study of BQMP-a

Fig. 2 shows fs-TA spectra of BQMP-a acquired in neat MeCN (267 nm excitation) with time delays from 0 ps to 3 ns after photoexcitation. The spectra of the early (before 1.3 ps), 1.3–16 ps and late (20 ps–3 ns) delay times are given separately in Fig. 2a–c to present the spectral changes more clearly. As shown in Fig. 2a, two bands at 351 nm and 443 nm are seen respectively, which can be assigned to an internal conversion (IC) from S_n to S₁. Afterwards, the band at 351 nm decreases a little in intensity with an additional absorption band at 585 nm growing in while the band at 443 nm shows a blue-shift to 439 nm and becomes much narrower which seems due to the vibrational cooling and solvent rearrangement processes. In the next 3 ns, a weak absorption band at ~ 360 nm shows up at the expense of the two strong bands at 439 nm and 585 nm (see Fig. 2c). The kinetics at 585 nm can be fit well by a bi-exponential function with two time constants 5.7 ps and 369 ps (see Fig. 2d). Therefore, the vibrational cooling and solvent rearrangement processes take place in about 5.7 ps. The following changes in the spectra are mainly attributed to an internal conversion from S₁ to S₀ process within $\tau_2 = 369$ ps, while the transient absorption at 360 and 445 nm at 3 ns corresponds to the triplet states that are formed with a fairly low quantum yield. The spectrum at 3 ns is identical to the ns-TA spectra of BQMP-a in neat MeCN both in open air and nitrogen purged conditions (Fig. S1). The phenomenon of quenching by oxygen further provides evidence that the species produced in the later time of fs-TA and ns-TA is a triplet species.

For comparison purposes, the fs-TA spectra of QMP-a acquired subsequent to 267 nm excitation in both pure MeCN and 1:1 MeCN:H₂O mixed solutions are shown in Figs. S2 and S3, respectively. Obviously, the spectral features observed at early times are almost the same in both the MeCN and 1:1 MeCN:H₂O solutions with the absorption band at 433 nm attributed to the singlet excited states of QMP-a, which subsequently go through an ISC conversion to generate triplet excited states with an absorption band at 466 nm. The photo-stability of QMP-a provides us more evidence in considering the involvement of two naphthol rings of BQMP-a in the proton transfer process.

Fig. S4 and Fig. 3 shows the evolution of the transient absorption of the BQMP-a in a 1:1 MeCN:H₂O solution. As discussed above, the broad transient absorption features with λ_{max} at 351 and 440 nm emerge at early times in Fig. S4a can be assigned to the transition from S_n to S₁ after 267 nm excitation. Later variations in the spectra observed in Fig. S4b can be due to the vibrational cooling process as discussed in a previous section. In Fig. 3a, the initial absorption band at 350 nm undergoes a bathochromic shift to 365 nm with an isosbestic point at ~ 390 nm. In addition, with the decrease of the

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