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Acetazolamide as a singlet molecular oxygen quencher

Cristina Valencia*, Eduard Tobón, Carolina Castaño

Departamento de Química, Facultad de Ciencias, Universidad Nacional de Colombia – Sede Medellín, Calle 59 a No. 63-020 Núcleo del Volador, AA 3840, Medellín-Colombia

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ABSTRACT

According to literature the acetazolamide, which is commonly used as a diuretic, shows phototoxic properties. To contribute to the understanding of the role of this chemical as a generator of the very common toxic substance, the singlet molecular oxygen, $O_2(^1\Delta_g)$, in this paper we show a kinetic study about the photosensitized oxidation of acetazolamide and its photosensitizing nature in the generation of $O_2(^1\Delta_g)$. Contrary to our expectations, results show that this drug has a predominant activity as an $O_2(^1\Delta_g)$ deactivator and its ability to generate the singlet oxygen is small. To find the mechanism of this activity, chemical reactivity constants measured in several solvents were adjusted to first-order kinetics. We found very moderate values around $10^5\ M^{-1}\ s^{-1}$, which compared to the total rate, the sum of the physical and chemical rate constants, of around $10^7\ M^{-1}\ s^{-1}$, supports a physical type of quench as the main acetazolamide deactivation pathway of $O_2(^1\Delta_g)$. Additionally, due to a moderate solvent effect of the reaction between acetazolamide and $O_2(^1\Delta_g)$ it is possible to postulate the formation of an exciplex complex with small charge separation. Finally, quantum yield values for the generation of singlet oxygen, determined through steady-state experiments, are 0.056, 0.097, and 0.015 in methanol, ethanol, and acetonitrile, respectively. Therefore, we can conclude that acetazolamide is an efficient quencher of singlet molecular oxygen (mainly of the physical type) and its phototoxic activity may involve other species different from singlet oxygen.

1. Introduction

Acetazolamide, AZ, (N-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)acetamide), a carbonic anhydrase inhibitor, is used as an anticonvulsant, a diuretic, and in the treatment of glaucoma. However, the use of this and other sulfa drugs is associated with the development of adverse side effects [1–5]. It has been suggested that acetazolamide induces phototoxicity as a result of its interaction with ultraviolet or visible light radiation, which in some cases can be linked to the generation of active oxygen species [6]. However, acetazolamide phototoxicity could be due to the effects of its direct irradiation or could be due to indirect processes by the presence of photosensitizers, which could absorb radiation and then, if the spectral overlap between the sensitizer and the activator (drug) is fulfilled, could transfer the energy to the drug through a Förster-like mechanism. For example, the acetazolamide maximum absorption is at 264 nm, and the absorption extents to 350 nm (cut off), without any significant fluorescence. The photosensitizers could be compounds such as proteins with indole ring, which have a strong UV absorbance at 280 nm as well as the emission at 340–360 nm, which originates mostly from ring [7]. Once acetazolamide is in an excited state, it could generate processes such as the production of toxic species.

The evaluation of the photochemical instability of acetazolamide by means of direct irradiation or by the action of a photosensitizer has been reported in some studies [8–11]. These include the exposure of a dilute solution of acetazolamide to direct sun light during the course of 6 days, each day having approximately 8 h of exposure, without the observation of variations in the concentration of acetazolamide or product formation [8]. In other studies, the reactivity of acetazolamide was carried out under irradiation at 300 nm, also under a nitrogen laser at 337 nm, and under visible light using Rose Bengal or even tetraphenylporphine (TPP) as a photosensitizer ($\lambda > 400$ nm) [9]. Particularly interesting to us is a photosensitized reaction found in those studies which can be appreciated in Fig. 1. The singlet oxygen participation in the acetazolamide photodegradation was detected by using singlet oxygen quenchers such as histidine, 2.5-dimethylfuran, furfuryl alcohol, and sodium azide (NaN_3). They induce a pronounced retardation of the photodecomposition, demonstrating that acetazolamide participates in type II photodynamic activity, which implies the formation of singlet molecular oxygen [9]. In vitro studies related with photohemolysis test to evaluate the phototoxic effects of some diuretics including acetazolamide, revealed phototoxic hemolytic properties after irradiation with either solar, UVA, and/or visible

* Corresponding author.
E-mail address: gcvalenc@unal.edu.co (C. Valencia).

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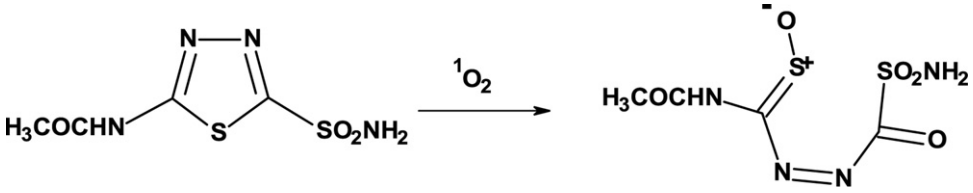

Fig. 1. Photosensitized oxidation of acetazolamide [8].

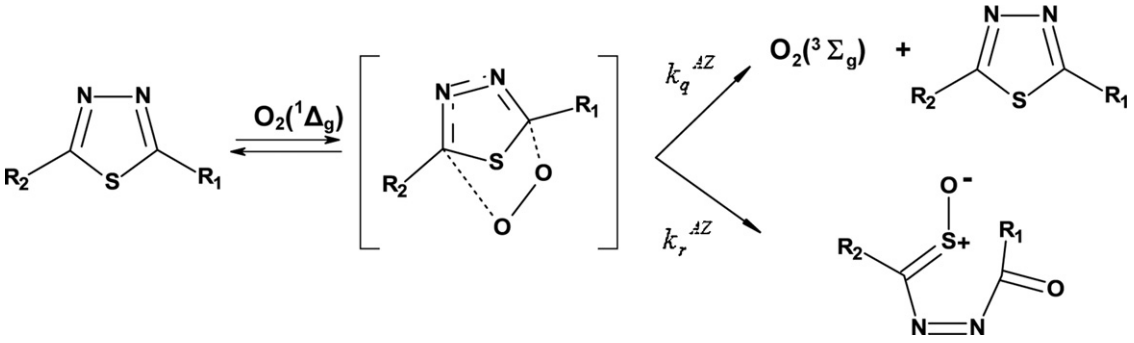

Fig. 2. Scheme of quenching of singlet molecular oxygen by acetazolamide ($R_1 = SO_2NH_2$ and $R_2 = CH_3CONH$).

light. Effects were significantly inhibited by the use of antioxidants such as ascorbic acid, alpha-tocopherole, or superoxide dismutase [10]. Preliminary molecular topology studies using the local Fukui reactivity indices [11] show that the reactivity of acetazolamide with electrophilic reagents could lead to reaction at the thiadiazol ring, in agreement with the product found by Vargas et al. [9], for the photosensitized reaction of acetazolamide.

Singlet oxygen, $O_2(^1\Delta_g)$, the first excited state of molecular oxygen [12], is more electrophilic and 92 kJ/mol higher energy than the ground state. It can react with electron-rich regions of many molecules, meeting spin conservation rule; e.g., olefins, aromatics, and conjugated double bonds, containing S, O, and N [13]. The $O_2(^1\Delta_g)$ is able to quench the triplet excited state of many organic compounds, and it is capable of oxidizing and degrading a number of biomolecules such as DNA (DNA strand breaks), proteins (causing protein crosslinks), and lipids [14]. In the human body, the singlet molecular oxygen is generated by photosensitization when a chromophore absorbs electromagnetic radiation in the UV–vis region. After the absorption process, the chromophore in a singlet excited state can undergo an intersystem crossing accessing thereby the triplet excited state, from which it can efficiently interact with molecular oxygen in the ground state to generate the singlet oxygen.

This active species of molecular oxygen can be deactivated by either physical or chemical quenching agents. The chemical reactions of singlet oxygen with organic molecules include the *ene* reactions and 1,4-addition to π-systems with endoperoxide formation [13]. The physical quenching implies the formation of an encounter complex or exciplex between the molecule in the excited state and the quencher in the ground state. This quenching process can occur by electron transfer or energy transfer.

The acetazolamide absorbs radiation in the UVC (200–290 nm) and UVB (290–320 nm) region, and even when the intensity of the UVB solar radiation is relatively low and varies with the latitude, time of the day and the season of the year, there may be some important contribution through the artificial radiation in this range of the electromagnetic spectrum. Moreover, it is possible that the diuretic drug can cause light-induced side-effects after administration if it interacts with endogenous or exogenous substances. Drug decomposition is not always observed, therefore it is also important to study phototoxicity by photosensitization with the intervention of other species, including the study of the quenching character, which the drug may present on the excited species generated by photosensitization.

The purpose of this study is to contribute to the investigation of the greater or lesser role of $O_2(^1\Delta_g)$ in the phototoxicity of acetazolamide. We work on the problem from two fronts: (a) by determining the capacity of this drug to participate in type II reactions [15] to produce $O_2(^1\Delta_g)$ and, on the contrary, (b) by determining the acetazolamide antioxidant effect against singlet molecular oxygen. Know ledge about the photostability and photosensitizing properties of a drug is important if we are to evaluate the origin of adverse effects.

2. Experimental set-up

All solvents used were HPLC or spectroscopic grade (purity ≥99%). The 9,10-dimethylanthracene (DMA) was purchased from Aldrich (99%), and the Rose Bengal (RB) was purchased from Fluka (95%). The acetazolamide, AZ (99%) (CAS number 59-66-5) and the sodium azide, NaN_3 (98%), were used without further purification, and were obtained from Sigma.

2.1. UV–vis spectra analysis of acetazolamide

The molar extinction coefficients, measured in a PerkinElmer Lambda 35 UV-Vis spectrophotometer (supplier Polco S.A.), were determined from absorbance readings at absorption peaks detected at 260 nm or above.

2.2. Photosensitized oxidation of acetazolamide

The initial chemical rate constants for the reaction of the AZ with $O_2(^1\Delta_g)$ in several organic solvents, k_r^{AZ}, were determined using steady-state kinetic experiments. Photodegradation studies were performed by irradiating samples with different AZ concentrations using RB as photosensitizer ($A = 0.7$ at 559 nm). A 300 W halogen lamp was used as the light source. Samples were irradiated in a 1 cm quartz water jacketed cell. The cell temperature was kept constant at $20 \pm 0.5\,^{\circ}C$ by external water circulation from a Lauda bath (RE 415 Series, Supplier: Analítica). A cut-off filter of 400 nm was used to carry out the experiment in the specific photosensitizer radiation

range. Assuming that the reaction of $O_2(^1\Delta_g)$ with AZ as a quencher is the main path of oxygen consumption, a plot of the concentration of drug remaining vs. the irradiation time follows first-order kinetics, can be obtained according to Eq. (1):

$$\ln\frac{[AZ]_0}{[AZ]_t} = k_r^{AZ}[O_2(^1\Delta_g)]t = k_{exp}^{AZ}t \quad (1)$$

where [AZ] is the acetazolamide concentration, $[O_2(^1\Delta_g)]$ is the steady-state singlet oxygen concentration, t is the radiation time, and where the slope is the experimental constant, k_{exp}^{AZ}. The acetazolamide consumption was monitored by HPLC using Agilent 1100 series equipment (supplier: Khymós S.A.) with a UV–vis detector and an Agilent Hipersil BD5-C18 column (4 mm × 125 mm, 5 μm), using CH_3CH_2OH/CH_3OH (75:25, v/v) as the mobile phase at a flow rate of 0.75 ml min^{-1}, with monitoring at 264 nm. Under the same experimental conditions, $[O_2(^1\Delta_g)]$ was determined by using DMA as actinometer [16] (reference quencher compound) and its consumption was monitored by the absorbance decrease on sensitized irradiation (RB as the photosensitizer) measured in a PerkinElmer Lambda 35 spectrophotometer. This follows pseudo first-order kinetics, according to Eq. (2):

$$\ln\frac{[DMA]_o}{[DMA]_t} = k_r^{DMA}[O_2(^1\Delta_g)]t = k_{exp}^{DMA}t \quad (2)$$

The ratio of the first-order slopes of the oxygen uptake by the DMA as actinometer (Eq. (2)) and the substrate AZ (Eq. (1)) with the same RB concentration, allows to obtain k_r^{DMA}/k_r^{AZ}.

The values of the total quenching rate constant (k_T^{AZ}) for the reaction of the AZ with $O_2(^1\Delta_g)$ in some organic solvents were determined also by steady-state kinetic experiments with competitive techniques using DMA as the actinometer and RB as the photosensitizer (λ_{max} = 559 nm) [17]. The photo-oxidation reaction of DMA with $O_2(^1\Delta_g)$ of known characteristics [18] was monitored (with UV–vis spectrophotometry) when was under irradiation with a halogen lamp of 300 W, at 20 ± 0.5 °C, and under a specific filter combination that allowed to irradiate only the photosensitizer. In this experiment we monitored the DMA absorbance. This reaction was analyzed with the Stern–Volmer relationship, by observing the inhibition of the photosensitized oxidation of DMA with the addition of AZ, as shown in Eq. (3):

$$\frac{k_{exp_O}^{DMA}}{k_{exp_{AZ}}^{DMA}} = 1 + \tau_{^1O_2}k_T^{AZ}[AZ] \quad (3)$$

where $k_{exp_O}^{DMA}$ and $k_{exp_{AZ}}^{DMA}$ are experimental measurements for the reaction of the pseudo first-order of DMA and $O_2(^1\Delta_g)$ in the absence and in the presence of different concentrations of the quencher [AZ], respectively, and $\tau_{^1O_2}$ is the singlet oxygen lifetime in the solvent employed.

Considering that the total quenching constant is the sum of the physical and chemical processes, the physical constant of quenching (k_q^{AZ}), is determined by solving Eq. (4):

$$k_T^{AZ} = k_q^{AZ} + k_r^{AZ} \quad (4)$$

To check the participation of excited oxygen, NaN_3 was used as the quencher in the DMA photosensitized reaction in ethanol as the solvent.

2.3. Generation of singlet oxygen

Based on the photosensitization mechanism proposed by Wilkinson et al. [19], we can define the quantum yield of $O_2(^1\Delta_g)$ as the number of molecules of $^1O_2$ generated for each photon absorbed by a photosensitiser. This measurement is an indication of the relative capability of the drugs to generate singlet oxygen from the triplet excited state. In the current research, the singlet oxygen generated was detected by the actinometrical measurement of the rates of the photosensitized reaction of molecules that quench unambiguously singlet oxygen. We used DMA as the actinometer and RB as the photosensitizer. Here, first-order kinetics may apply to the reaction, and the relationship between their pseudo first-order plot of DMA in the presence of RB and AZ, separately, as photosensitizers, represents the relationship between the quantum yields as can be seen in Eq. (5):

$$\phi_\Delta^{AZ} = \phi_\Delta^{RB}\frac{k_{exp}^{AZ}}{k_{exp}^{RB}} \quad (5)$$

Table 1
Extinction coefficients for acetazolamide (ε).

Solvent	λ_{max} (nm)	ε (L cm^{-1} mol^{-1})	Upper limit of absorbance [AZ]
Methanol	264	15,610	1.3887
Ethanol	264	12,425	1.1346
Acetonitrile	263	7800	0.7754
Pentanol	265	9757	0.8746
Ethyl acetate	264	7685	0.7458
Butanol	264	9846	0.8823
2-Propanol	264	10,866	0.9584
Terc-butanol	264	12,425	1.0984
Hexanol	265	8563	0.8045
Ethylene glycol	264	8392	0.7894
Dimethyl sulfoxide	278	7893	0.7761
Tetrahydrofuran	265	8039	0.8210

3. Results and discussion

3.1. Molar extinction coefficients

In order to determine the absorbance linear response range with the concentration of acetazolamide in various solvents, calibration curves were made. The results are presented in Table 1, where the AZ extinction coefficients, obtained from Beer–Lambert plots, are included.

3.2. Quenching of $O_2(^1\Delta_g)$

Rate constants for the photosensitized degradation of DMA were determined in organic solvents using RB as the photosensitizer at different irradiation time periods and the reaction of the DMA actinometer with the $O_2(^1\Delta_g)$ generated was compared with the response of AZ as a photosensitizer in the same solvents. No measurements were performed in nonpolar solvents due to solubility difficulties.

Fig. 3 shows an example of the DMA consumption UV–vis monitoring in the presence of $O_2(^1\Delta_g)$, generated by RB

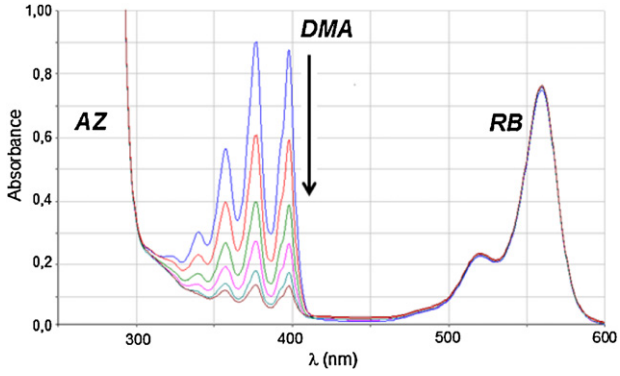

Fig. 3. UV–vis monitoring of the DMA consumption in ethanol.

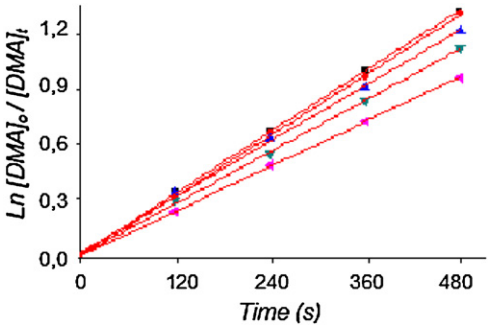

Fig. 4. Inhibition of the quenched constant with the AZ concentration in ethanol ((■) 0.0 mM, (●) 0.22 mM, (▲) 0.44 mM, (▼) 0.66 mM, (►) 0.88 mM).

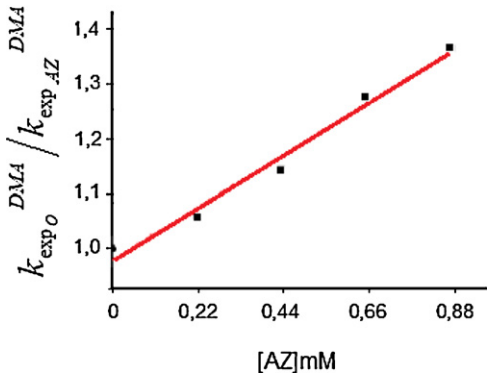

Fig. 5. Example of the Stern–Volmer relationship (Eq. (3)). The solvent is ethanol.

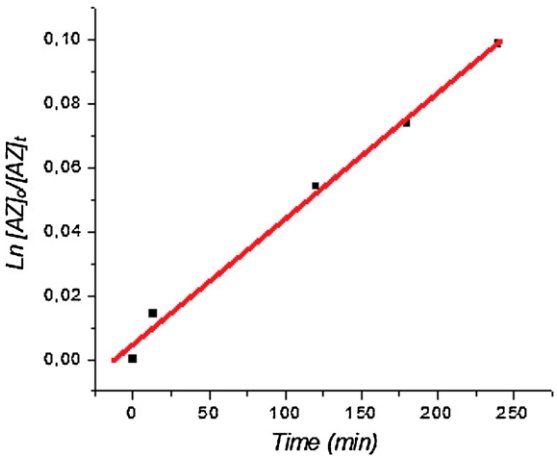

Fig. 6. Example of the application of Eq. (1). The solvent is ethanol.

Table 3
Quenching rate constants: k_T^{AZ} : total, k_r^{AZ} : chemical, and k_q^{AZ} : physical, determined for the reaction of AZ with $O_2(^1\Delta_g)$.

Solvent	$k_T^{AZ}/10^7$ $M^{-1}\,s^{-1}$	$k_r^{AZ}/10^5$ $M^{-1}\,s^{-1}$	$k_q^{AZ}/10^7$ $M^{-1}\,s^{-1}$	k_r^{AZ}/k_T^{AZ}	k_q^{AZ}/k_r^{AZ}
Methanol	1.84	2.35	1.82	0.0128	77.4
Ethanol[a]	2.05	2.28	2.02	0.011	88.6
Butanol	4.60	2.16	4.58	0.009	195.3
Acetonitrile	0.27	3.45	0.24	0.128	6.96

[a] An example of the determination of those data for the ethanol case is shown in Fig. 6.

photosensitization, in the presence and absence of AZ, and in ethanol as the solvent. We can observe how the DMA signal decays. This decay was fitted to a pseudo first order kinetic, according to Eq. (2). Fig. 4 shows the decrease in the quenching constant with an increase in AZ concentration.

The corresponding example of the Stern–Volmer relationship of Eq. (3) is shown in Fig. 5.

The slope of this plot corresponds to $\tau_{^1O_2} k_T^{AZ}$. Using these slopes and the corresponding $O_2(^1\Delta_g)$ lifetime values in each solvent, the k_T^{AZ} constants were obtained (Table 2). In this experiment, it was found that the autoxidation of RB was less than 1%.

The use of AZ inhibits the photosensitized degradation of DMA by the excited oxygen by means of a competition as a quencher (DMA vs. AZ). A significant quenching of $O_2(^1\Delta_g)$ by AZ was observed with extreme values of k_T^{AZ} in hexanol of $6.70 \times 10^7\ M^{-1}\,s^{-1}$ and $0.25 \times 10^7\ M^{-1}\,s^{-1}$ in ethyl acetate, a protic and an aprotic polar solvent, respectively. In a preliminary manner, we observed that solvents with higher values of β (the solvent capacity as hydrogen bond acceptor [20]) helps increase the charge density at positions susceptible to electrophilic attack, promoting interaction between AZ and $O_2(^1\Delta_g)$. Generally, a moderate solvent effect on the k_T^{AZ} values suggests a reaction mechanism with small charge separation [20].

Acetazolamide photosensitized oxidation followed by HPLC shows that the consumption achieved was 12% in 48 h. AZ and photoproduct signals are observed with a retention time of 2.751 and 3.209 min, respectively.

Plots used to obtain the chemical rate constants k_r^{AZ} for the reaction between AZ with $O_2(^1\Delta_g)$ follow first-order kinetics (see Fig. 6 using ethanol as solvent). Table 3 shows a comparison of the observed values of k_T^{AZ} in different solvents.

It is clear that k_T^{AZ} is greater than k_r^{AZ} in the solvents tested. The ratio of the chemical to the total rate constants is less than 1.3% in the three alcohols, and 12% in acetonitrile. Therefore, it can be deduced that the main mechanism of deactivation of $O_2(^1\Delta_g)$ by AZ is physical quenching.

The inhibition for the photosensitized oxidation of DMA by AZ and NaN_3, the last being an unambiguous $O_2(^1\Delta_g)$ quencher, is presented in Table 4. It should be noted that both quenchers, AZ and NaN_3, inhibit the photosensitized oxidation of DMA.

Table 2
Total quenching rate constant of pseudo first-order kinetics between $O_2(^1\Delta_g)$ and AZ.

Solvent	$k_T^{AZ}/10^7$ $M^{-1}\,s^{-1}$	r^2
Ethanol[a]	2.05 ± 0.01	0.97457
Hexanol	6.70 ± 0.01	0.98899
Acetonitrile	0.27 ± 0.02	0.9799
Methanol	1.84 ± 0.01	0.9755
Pentanol	2.74 ± 0.03	0.9543
Ethyl acetate	0.25 ± 0.02	0.98107
1-Butanol	4.60 ± 0.02	0.96567
Terc-buthanol	1.23 ± 0.01	0.99954
1-Propanol	1.60 ± 0.02	0.9785
2-Propanol	2.47 ± 0.02	0.9798
NN-DMF	2.32 ± 0.02	0.9711
Ethylene glycol	1.73 ± 0.02	0.9910

[a] Examples of plots from where these data were obtained are shown in Figs. 3–5.

Table 4
Effect of singlet oxygen quencher concentrations on the DMA photosensitized oxidation. RB was used as photosensitizer.

Quencher concentration in solution		$k_{exp}/10^{-3}$	r^2
AZ/mM	Sodium azide/mM		
0.0	0.0	3.43 ± 0.02	0.99962
25	0.0	2.90 ± 0.03	0.99918
0.0	0.40	1.53 ± 0.03	0.99711
25	0.40	1.42 ± 0.03	0.99625

3.3. Generation of singlet oxygen

Taking as the reference values of quantum yield of singlet molecular oxygen for RB, φ_{Δ}^{RB}, of 0.76, 0.68, and 0.25 in methanol, ethanol, and acetonitrile, respectively [19], the quantum yields for the generation of $O_2(^1\Delta_g)$ by AZ, φ_{Δ}^{AZ}, were 0.0562, 0.097, and 0.015, respectively (see Eq. (5)). Therefore, it is evident that the AZ is not an efficient generator of $O_2(^1\Delta_g)$.

4. Conclusions

Acetazolamide is also capable of efficiently quenching singlet oxygen by a mixture of physical and chemical processes, with predominance of the physical pathway, and is a weak photosensitizer of singlet oxygen. So it is possible that the adverse side effects of acetazolamide are not caused by a type II mechanism, indicating that their phototoxicity are caused by other reactions. This is very important when considering whether AZ should be used in the treatment of glaucoma, because AZ would inhibit the harmful action of $O_2(^1\Delta_g)$ which could be produced in the eye by the presence of other exogenous substances with photosensitizing ability.

The interaction mechanism between singlet molecular oxygen and acetazolamide, in which moderate solvent effects are observed agrees with the proposal by Vargas et al. on the product of photodegradation [9]. Thus, it is possible to suggest a five-membered heterocyclic reaction with $O_2(^1\Delta_g)$ [21], in which the reaction between AZ and singlet oxygen is an asynchronous concerted addition mechanism [2 + 4], of the Diels–Alder type, as shown in Fig. 2.

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References

[1] J. Ferguson, Photosensitivity due to drugs, Photodermatology, Photoimmunology & Photomedicine 18 (2002) 262–269.
[2] B. Henry, C. Foti, K. Alsante, Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? Journal of Photochemistry and Photobiology B: Biology 96 (2009) 57–62.
[3] D.E. Moore, Drug-induced cutaneous photosensitivity. Incidence, mechanism, prevention and management, Drug Safety 25 (5) (2002) 345–372.
[4] B. Quintero, M.A. Miranda, Mechanisms of photosensitization induced by drugs: a general survey, ARS Pharmaceutica 41 (1) (2000) 27–46.
[5] E. Selvaag, In vitro phototoxicity due to antidiabetic and diuretic drugs sulfonamide-derived oral, Journal of Toxicology – Cutaneous and Ocular Toxicology 16 (1) (1997) 77–84.
[6] F. Vargas, H. Mendez, J. Sequera, J. Rojas, G. Fraile, M. Velásquez, Phototoxicity induced by $^1O_2$ generation during the photodegradation of some diuretic drugs, Toxic Substance Mechanisms 18 (1999) 53.
[7] K.E. Sapsford, L. Berti, I.L. Medintz, Materials for fluorescence resonance energy transfer analysis: beyond traditional donor–acceptor combinations, Angewandte Chemie International Edition 45 (2006) 4562–4588.
[8] B. Ramesh, P. Srimannaraya, A.S. Reddy, P. Sitadevi, Densitometric evaluation of stability-indicating HPTLC method for the analysis of acetazolamide and a study of degradation kinetics, Journal of Pharmacy Research 4 (2) (2011) 429–433, ISSN: 0974-6943, Available at http://jpronline.info/article/view/5909/3018
[9] F. Vargas, M.V. Hisbeth, J.K. Rojas, Photolysis and photosensitized degradation of the diuretic drug acetazolamide, Journal of Photochemistry and Photobiology A: Chemistry 118 (1998) 19–23.
[10] E. Selvaag, A. Petersen, R. Gniadecki, T. Thorn, H.C. Wulf, Phototoxicity to diuretics and antidiabetics in the cultured keratinocyte cell line HaCaT: evaluation by clonogenic assay and single cell gel electrophoresis Comet assay, Photodermatology, Photoimmunology & Photomedicine 18 (2) (2002) 90–95.
[11] C. Valencia, E. Tobón, F. Figueredo, D. Henao, fototoxicidad de medicamentos sulfas y su reactividad frente al oxígeno molecular singulete, Revista de la Sociedad Química del Perú 74 (4) (2008) 311–322.
[12] M.C. DeRosa, R.J. Crutchley, Photosensitized singlet oxygen and its applications, Coordination Chemical Reviews 233–234 (2002) 351–371.
[13] E.L. Clennan, A. Pace, Advances in singlet oxygen chemistry, Tetrahedron 61 (2005) 6665–6691.
[14] H.H. Tonnesen, Photostability of Drugs and Drug Formulations, 2nd ed., CRC Press, Boca Raton, 2004 (Chapter 9).
[15] M.T. Allen, M. Lynch, A. Lagos, R.W. Redmond, I.E. Kochevar, A wavelength dependent mechanism for rose bengal-sensitized photoinhibition of red cell acetyl cholinesterase, Biochimica et Biophysica Acta 1075 (1991) 42–49.
[16] A. Albini, E. Fasani, Drugs: Photochemistry and Photostability, 1st ed., The Royal Society of Chemistry, Great Britain, 1998, pp. 75–76.
[17] A.L. Zanocco, E. Lemp, G. Gunther, A kinetic study of the reaction between boldine and singlet oxygen [$O_2(^1\Delta_g)$], Journal of the Chemical Society, Perkin Transactions 2 (1997) 1299–1302.
[18] R. Castro-Olivares, G. Gunther, A. Zanocco, E. Lemp, Linear free energy relationship analysis of solvent effect on singlet oxygen reactions with mono and disubstituted anthracene derivatives, Journal of Photochemistry and Photobiology A: Chemistry 207 (2009) 160–166.
[19] F. Wilkinson, W.P. Helman, A.B. Ross, Quantum yields for the photosensitized formation of the lowest electronically excited singlet-state of molecular oxygen in solution, Journal of Physical and Chemical Reference Data 22 (1) (1993) 113–262.
[20] M.J. Kamlet, J.L.M. Abboud, M.H. Abraham, R.W. Taft, Linear solvatation energy relationships. 23. A comprehensive collection of the solvatochromic parameters, pi, alfa, and bets, and some methods for simplifying the generalized solvatochromic equation, The Journal of Organic Chemistry 48 (1983) 2877–2887.
[21] C.W. Chen, C.T. Ho, Reactivity on photo-oxidation of selected five-membered heterocyclic flavor compounds, Journal of Agricultural and Food Chemistry 44 (1996) 2078–2080.