Pergamon

Tetrahedron Letters, Vol. 38, No. 49, pp. 8435-8438, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10273-8

Evidence for Azidyl Radical Initiated Olefin Isomerization. One-way Isomerization of (Z)-Urocanic Acid[1]

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Abstract: *(Z)-Urocanic acid (cis-UA), unlike its (E) isomer (trans-UA), undergoes photoisomerization in the presence of nitro blue tetrazolium (NBT^{2+}) and sodium azide. Evidence is presented that the photoisomerization involves the reversible addition of the azidyl radical to the double bond.*
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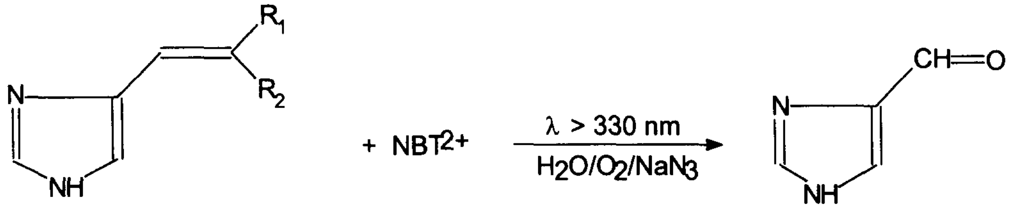
(E)-Urocanic acid [(3-(1H-imidazol-4(5)-yl)-2-propenoic acid, (UA)] is a metabolite of histidine that accumulates in the mammalian epidermis. Its (Z) isomer, formed by exposure of the skin to sunlight, is of considerable current biomedical interest.[2,3] We have recently shown that the irradiation of UA with 2'-deoxyadenosine or 2'-deoxyguanosine leads to a photooxidative cleavage of the acrylic acid side chain to 1H-imidazole-4(5)-carboxaldehyde (ImCHO).[4] Sodium azide catalyzes the photooxidation. The reaction is most readily accomplished by using long wavelength light (λ > 330 nm), sodium azide, and nitro blue tetrazolium (NBT^{2+}), a highly electron affinic photosensitizing dye, in place of the nucleoside (eq. 1). Under these conditions, yields of ImCHO as high as 68% were observed.



(1)

(E)-UA: $R_1 = CO_2H$, $R_2 = H$
(Z)-UA: $R_1 = H$, $R_2 = CO_2H$

ImCHO

We now report that in the absence of oxygen, there is a novel one-way, azide-catalyzed, NBT^{2+}-photosensitized isomerization of (Z)-UA to the (E) isomer. This observation bears on the mechanism of the azide catalyzed cleavage chemistry.

Neither (Z)- nor (E)-UA (1.0 *mM*) photoisomerized when separately irradiated in argon degassed buffered (pH 7.0) aqueous solutions containing NBT^{2+} (0.13 *mM*), using uranium yellow filtered light from a mercury arc ($\lambda > 330$ nm). However, when sodium azide (20.0 *mM*) was added to the (Z)-UA/NBT^{2+} solution, as much as 97% isomerization to (E)-UA was observed (by HPLC) under these irradiation conditions. *(E)-UA remained unchanged (i.e. it was neither isomerized nor degraded) when irradiated under the same conditions.* When the reaction was done under oxygen less than 1% isomerization was observed. The level of catalysis depends on the concentration of added azide (see Table 1).

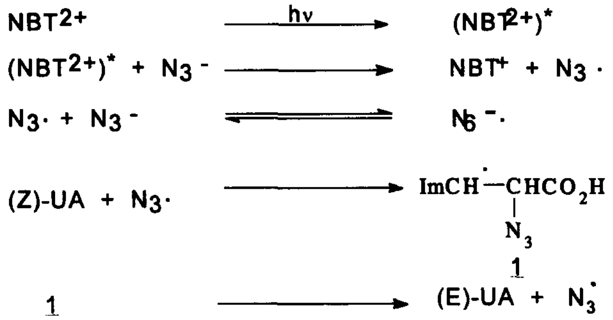
Table 1.Sodium Azide Catalysis of the Photosensitized isomerization of (Z)-UA[a]

NaN_3 (mM)	% (Z)-UA lost	% (E)-UA formed
0	b	< 1
5	23	23
10	24	26
20	45	47

[a] Irradiation of 0.13 *mM* NBT^{2+} and 1.0 *mM* (Z)-UA in the presence of indicated amount of NaN_3 at $\lambda > 330$ nm, under argon, for 3 min .[b] Loss too small to be measured ((Z)-UA HPLC peak actually slightly increased).

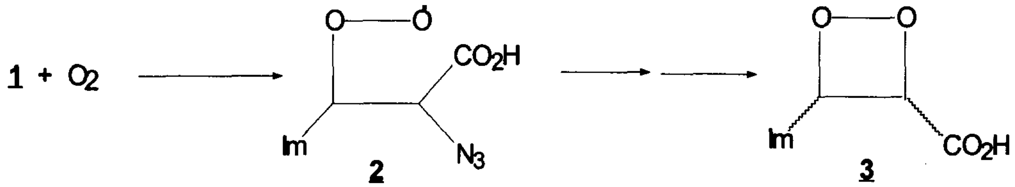
We measured the quantum efficiency for the NBT^{2+}-sensitized isomerization of 1.0 *m*M (Z)-UA in the presence of 20.0 *mM* azide, using the third harmonic (355 nm) of a Nd:YAG laser. A value of 0.0874 ± 0.0072 was determined over a range of conversions to the (E) isomer of 4 - 30%. Traces of oxygen were found to significantly inhibit the reaction. In fact, in the absence of rigorous degassing an apparent induction period was observed which corresponds to the requisite consumption of adventitious oxygen in order for the reaction to occur. A mechanism for the isomerization was suggested by the report that azidyl radicals can be readily generated through photooxidation of azide anion by, for example, benzophenone in acetonitrile.[5] The azidyl radicals were detected by their interception by alkenes using the spectroscopic signature of $N_6^{\cdot-}$, a species which exists in equilibrium with the azide radical and excess azide anion. A recent application of this chemistry utilized the photosensitized oxidation of azide anion with rhodamine B in aqueous methanol to synthesize 1,2-azidohydroperoxides from alkenes.[6] In our system, the source of the azidyl radical would be through oxidation of the azide anion by the NBT^{2+} excited state. Though not observed in the earlier studies,[5,6] one might anticipate alkene isomerization by the reversible addition of the azidyl radical. Our proposal, involving an addition-elimination sequence of the azidyl radical to UA is outlined in Scheme 1.[7] This Scheme represents a radical chain mechanism with the dimerization of 1 representing one potential termination step.

Scheme 1



We probed the validity of this scheme in two ways. First, because the visible absorption of $N_6^{\cdot -}$ (λ_{max} = 700 nm) is well characterized,[5] we used laser flash photolysis with an intensified CCD detector to verify that the azide anion can be photooxidized by NBT^{2+}. Photolysis of an acetonitrile solution of NBT^{2+} (0.13 *mM*) and 10.0 *mM* tetrabutyl ammonium azide (TBA) (to enhance solubility) using the 355-nm pulsed excitation from a Nd:YAG laser indeed produced the characteristic $N_6^{\cdot -}$ absorption. (We were unable to detect the new absorption when water was used as the solvent; it is known that the equilibrium constant for the formation of $N_6^{\cdot -}$ is 10^3-fold lower in water than in acetonitrile).[5b] In addition, to see if independently generated azidyl radical would indeed induce one-way isomerization of UA we decided to take advantage of the known ability of benzophenone to generate this species (see above). Since benzophenone itself photosensitizes UA isomerization (both (E) → (Z) and (Z) → (E)),[8] it was necessary to employ a concentration of azide sufficient to quench all of the ketone excited state and thus block the benzophenone/UA interaction. The necessary conditions were ascertained by using (E)-UA as the substrate, since this isomer is unaffected by azide catalysis (see above). With 1.0 *mM* (E)-UA in 40% EtOH/H_2O, we found that 100.0 *mM* sodium azide completely eliminated (E) → (Z) isomerization. Nevertheless, photolysis of an identical solution, but with (Z)-UA, gave 15% isomerization to the (E) isomer.

Thus, the mechanistic elements of Scheme 1 seem reasonable.[9] It behooves us, then, to consider the implications of these observations for our previously reported azide catalysis of the NBT^{2+}-sensitized oxidative cleavage reaction (see eq. 1). Since oxygen quenches the (Z) → (E) isomerization (see above), it is reasonable to presume that the two sets of observations, and the function of the azide as a catalyst in each, are related. In our earlier report we suggested that the azide anion served to intercept a UA radical cation created by photoinitiated electron transfer to the sensitizing dye (or the nucleoside). Clearly, the present observations suggest an alternative, i.e. that the primary step is photooxidation of the azide anion to the azidyl radical which adds to the acrylic acid to give 1. Oxygen may then intercept the resulting radical[6] to form the peroxy radical 2 which was postulated[4] to be a key intermediate en route to the dioxetane 3 and ultimately cleavage (Scheme 2). It should be noted that the evidence does not rule out our previous mechanism for azide-assisted alkene cleavage and clearly more needs to be done to determine which (if not both) of the pathways are operative in the cleavage chemistry.



Finally, we noted at the outset that the *photochemical* formation of (Z)-UA from the naturally occurring (E) isomer is of considerable biomedical interest. The current study is strongly suggestive that *ground state* radical processes are unlikely to contribute to (E)→(Z) isomerization in biological systems.

References and Notes

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7. Here UA is shown in non-ionized form for simplicity but, depending upon the pH of the medium, it can exist in dissociated form.
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9. We presume that 1 decomposes solely to (E)-UA because of the greater thermodynamic stability anticipated for this isomer, see for example, Chatgilialoglu, C.; Ballestri, M.; Ferreri, C.; Vecchi, D. *J. Org. Chem.* **1995**, 60, 3826-3831.

(*Received in USA* 23 *September* 1996; *revised* 22 *July* 1997; *accepted* 17 *September* 1997)