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Regio- and Diastereoselective Formation of 1,2-Azidohydroperoxides by Photooxygenation of Alkenes in the Presence of Azide Anions[1]

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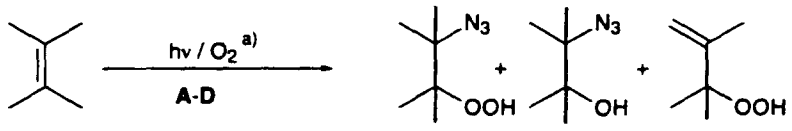
ABSTRACT : 1,2-Azidohydroperoxides are accessible from alkenes when irradiated in the presence of azide anions, oxygen and an appropriate sensitizer. The results of substrate/sensitizer variations indicate a reaction initiated by electron transfer to give the sensitizer radical anion and azidyl radicals. The latter efficiently add to alkenes producing carbon radicals which are trapped by molecular oxygen.

The mechanism of the singlet oxygen ($^1O_2$) ene reaction remains a matter of debate despite numerous intensive investigations in the last years.[2] In 1969 Kearns and coworkers reported the formation of azidohydroperoxides from alkenes when performing photooxygenation reactions in the presence of azide salts.[3] This was initially interpreted as proof of an intermediary perepoxide trapped by the nucleophilic azide anion. Subsequent investigations by other groups revealed, however, that singlet oxygen is efficiently physically quenched by azide.[4] Thus, an alternative mechanism has to be reponsible for the formation of the 1,2-azidohydroperoxides which has not been clarified until now. Despite the fact that a potentially useful synthetic protocol for one-pot 1,2-N,O-functionalization of alkenes was descovered, no further experiments were described in order to evaluate the scope and limitations of this reaction. As a consequence of the favorable quenching properties[5], azide salts are routinely applied to suppress singlet oxygen reactions, especially in biochemical investigations. In order to learn more about the photochemical behaviour of the azide/oxygen/sensitizer system, we performed a series of substrate and sensitizer variation experiments. α-Azidohydroperoxides apparently are logical precursors to α-aminoalcohols, an important class of compounds in organic chemistry.[6] For comparison of the photochemical route to these compounds with the thermal processes developed in the last years[7,8] we additionally investigated the regio- and stereoselectivity of the azidohydroperoxide formation.

In order to find the optimal sensitizer for the reaction, we compared the classical singlet oxygen sensitizer rose bengal with benzophenone and rhodamine B. Azide anions efficiently quench triplet excited benzophenone with formation of azidyl radicals (charge shift quenching).[9] This reaction should be also efficient with the cationic form of rhodamine B, whereas the anionic sensitizer rose bengal in its excited state was expected to be less reactive. All three sensitizers generate singlet oxygen as was shown with 2,3-dimethyl-2-butene **1a** as substrate. The product of the $^1O_2$ ene reaction, the allylic hydroperoxide **5a** dominated in the rose bengal sensitized reaction. Both benzophenone and rhodamine B sensitization gave predominately the azides **2a** and **3a** (Table 1).

Table 1: Product composition of 2,3-dimethyl-2-butene photooxygenations by ^1H NMR spectroscopy

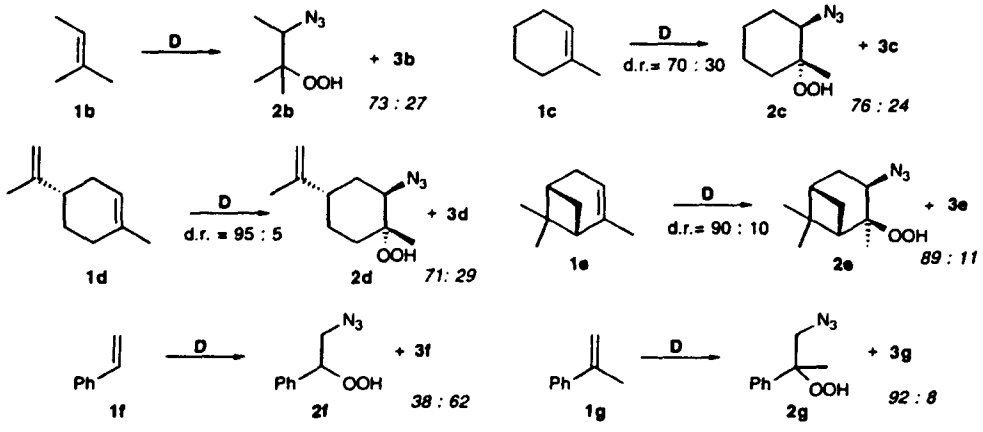


1a	2a : 3a : 5a
A: RB, MeOH, LiN_3	6 : 18 : 76
B: Ph_2CO, MeOH, LiN_3 [b]	46 : 24 : 13
C: Rh-B, MeOH, LiN_3	37 : 43 : 20
D: Rh-B, MeOH, 8% H_2O, NaN_3 [c]	70 : 10 : 20

[a] conditions: 1.5×10^{-2} M **1a**, 1×10^{-3} M sens. (RB=rose bengal, Rh-B=rhodamine B), 3.5×10^{-2} M azide, 48 h, 30°C, 300 W halogen spot; [b] additionally 17% [2+2] cycloadduct; [c] 24 h.

In the absence of water, appreciable amounts of the azidoalcohol **3a** were formed in the experiments **B-D**. This compound is a secondary product which also could be generated from **2a** *via* irradiation under the experimental conditions in the absence of oxygen with catalytic amounts of dyestuff. The formation of this reduction product could be suppressed by adding 8-10% of water to the reaction mixture. This effect is contrary to the results reported by Gollnick et al. for rose bengal photooxygenations.[4b]

Under the reaction conditions **D** alkenes **1b-1f** were transformed into the corresponding azidohydroperoxides **2** and the azidoalcohols **3**. In all cases mixtures of **2** and **3** were formed (Scheme 1). The regioselectivity was excellent for all examples investigated (> 98%) with exclusive formation of the higher substituted hydroperoxides. This is superior to the 1,2-N,O-functionalization *via* oxirane ring opening which often give regioisomeric mixtures.[10]

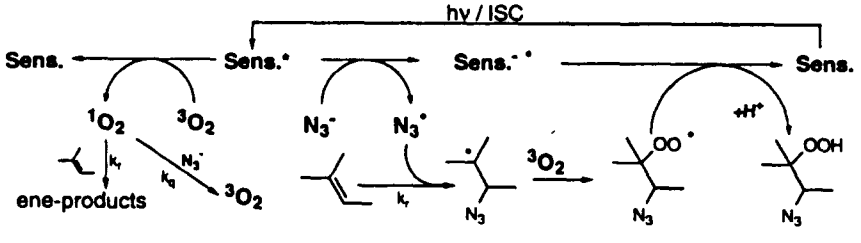


Scheme 1: Product composition for azidohydroperoxidation of alkenes **1b-1g**. For yields and conversion see text. Values in italics correspond to the 1,2-azidohydroperoxide / 1,2-azidoalcohol ratio (^1H NMR).

The diastereoselectivity of the azidohydroperoxidation was a crucial criteria in the initial report by Kearns et al.[3] In contrast to these results we only found moderate selectivity with 1-methylcyclohexene (**1c**) as substrate, a result which is in accord with the mechanistic scenario of an primary azidyl radical addition and with a low asymmetric 1,2-induction in cyclohexyl radicals.[11,12] Limonene (**1d**), the classical singlet oxygen probe[13], gave only one out of four possible stereoisomers (configuration assigned by NMR spectroscopy) in agreement with a much higher 1,4-asymmetric (cis) induction in 4-substituted cyclohexyl radicals.[14] In the α-pinene (**1e**) case the major diastereomer was the *cis*-1,2-azidohydroperoxide **2e** (and the respective azidoalcohol **3e**). The primary azidyl radical addition as well as the secondary oxygen trapping reaction were controlled by the steric shielding of the 1,1-dimethylmethylene bridge. Thus, both reactions preferentially occurred from the same side of the bicyclo[3.1.1] skeleton. The oxygen trapping reaction was very efficient in this case due to the fact that less than 2% of cyclobutane ring opening could be detected, a reaction which under free radical conditions dominates the chemistry of bicyclo[3.1.1]hept-2-enyls.[15] Styrene (**1f**) and α-methylstyrene (**1g**) were also reactive under these conditions, but not with $^1O_2$ (Typ II photooxygenation).

The 1,2-azidohydroperoxides **2** were purified by flash chromatography and characterized *via* IR (2091-2114 and 1251-1264 cm^{-1}) and ^{13}C NMR spectroscopy (typical signals: $\underline{C}(H)(C)_2N_3$ {61.4-62.2 ppm} and $\underline{C}(C)_3OOH$ {82.0-86.5 ppm}). Direct reduction of the crude photolysis mixtures with sodium sulfite (in MeOH/water) resulted in the pure 1,2-azidoalcohols **3**. The yields for the azidoalcohols were > 90% for all cases (conversion after 24h: 40-70%). Likewise, reduction of the crude photolysis mixtures with $LiAlH_4$ in diethyl ether gave the α-aminoalcohols **4**.[16,17]

The results described herein are in agreement with the mechanism described in Scheme 2: the electron transfer from azide [$E°(N_3^{\bullet}/N_3^-) = 1.32V$[9a]] to triplet rhodamine B [$E°$(Rh-B/Rh-B$^-$) = - 0.54 V; E_T = 2.0 eV[18]] is slightly exergonic ($\Delta G°$ ca. - 0.1 eV). Singlet oxygen, which is also produced by a competing energy transfer process, is rapidly <u>physically</u> deactivated by the azide anion (k_q). The <u>chemical</u> quenching process of $^1O_2$ leading to azidyl radicals is about two orders of magnitude slower[19] and cannot represent a major source for the formation of azidohydroperoxides. The physical quenching process, however, additionally suppresses the ene reaction of $^1O_2$ with alkenes which is about 3-10 times slower than the addition of azidyl radicals (e.g. with **1a**: k_r (azidyl radical) = 1.3 x 10^8 $M^{-1}s^{-1}$, k_r (singlet oxygen) = 4.7 x 10^7 $M^{-1}s^{-1}$).[9a,20] The electron transfer catalyzed (ETC) reaction is completed by the reduction of the alkylhydroperoxy radical with re-formation of the sensitizer.



Scheme 2: Proposed reaction mechanism: Electron Transfer Catalyzed (ETC) reaction

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