Efficient Photoinduced Electron Transfer in Papaverine N-Oxide: Regioselective Intramolecular Hydroxylation of Papaverine as an Alternative Disconnection for the Synthesis of Cularine Alkaloids

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Abstract: The photochemistry of papaverine N-oxide in polar aprotic and protic solvents has been studied in detail. Complex energy and charge transfer phenomena between chromophores occur in papaverine. Irradiation in protic media results in the formation of an emissive charge transfer state with concomitant intramolecular hydroxylation.

Cularines form a group of isoquinoline alkaloids characterized by a dibenzoxepine structure.1 The most common approach for the synthesis of cularines starts with an appropriately substituted 1-benzylisoquinoline (Scheme 1, A) and reserves construction of the oxepine ring as the last step.2 through an Ullmann3 reaction or a biosynthetic analog of phenolic coupling.4 This method lacks an efficient synthesis of 7,8-dioxygenated benzyl-isooquinolines, obtained mainly via Reissert compounds which are prepared following several modifications of the Pickted-Spengler reaction.5 One strategy uses the Bischler-Napieralsky reaction for this purpose, but this is of limited value due to unfavorable regioselectivity at the cyclization step.6

Scheme 1. Retrosynthetic analysis for cularine construction

However, disconnection B, with a designed reversed phenolic coupling where the benzylic portion carries the phenol function, is a possibility that merits investigation. The isoquinoline could be prepared, without regioselective obstacles, using the Bischler-Napieralsky approach starting with tyramine and a suitably substituted phenylacetic acid. Here, it would be desirable to introduce the OH group ortho to the benzylic position after construction of the 1-benzylisoquinoline. Aromatic hydroxylation of isoquinoline-type alkaloids is possible in some cases by the sequence bromination, halogen-lithium metal exchange, and oxidation of the resulting organometallic intermediate.7 However, a simple alternative for this procedure is direct hydroxylation of the benzene ring by photolysis of amine N-oxides. Only two general processes account for the photochemistry of aromatic-amine N-oxides: ring rearrangement and N-deoxygenation.8 Brønsted or Lewis acids inhibit most of the rearrangement reactions and their use leads to efficient deoxygenation. Sammes9 applied this method to study oxygen transfer from pyridine N-oxides to bridged aromatic rings and achieved efficient intramolecular hydroxylation. Thus, use of the isoquinoline moiety as the N→O carrier to do the hydroxylation intramolecularly was an attractive possibility.
To study the hydroxylation reaction, we selected as model system the readily available alkaloid papaverine (PAPN) and its N-oxide (1, PAPNO). The known photochemistry of PAPNO follows the general behavior of azanaphthalene N-oxides. Rearrangement reactions complicate oxygen cleavage required for hydroxylation. ISQNO gives ring enlargement to 1,3-benzoxazepines in aprotic media and rearrangement to isocarbostyrils with proton donors. Free and hydrogen bonded N-oxides photoreact differently, while the fully protonated molecules undergo deoxygenation instead of isomerization. There is now agreement that rearrangement involves the S1 state, while oxygen cleavage requires crossing to the T1 states. This implies that deoxygenation could be induced in PAPNO by generation of protonated or coordinated triplet states. Here we report new photochemistry and photophysics of PAPNO. Irradiation (125-W medium-pressure Hg lamp, \( \lambda > 300 \) nm) of a deoxygenated solution of 1 (500 mg, 1.41 mmol) and BF3·OEt2 (1 mL, 1.15 g, 8.13 mmol) in CH2Cl2 (100 mL), until total disappearance of the N-oxide (6 h), afforded a complex, tarry reaction mixture. This result was surprising considering the reports of efficient hydroxylation with pyridine N-oxide and clean deoxygenation of isoquinoline N-oxide using BF3 in both cases. Following a laborious work-up, we isolated 4% papaverine (2, PAPN), 4% 6'-OH–PAPN (3) and 3% 2'-OH–PAPN (4). We tried in turn the photoreaction with other Lewis (ZnCl2, CdCl2, CuCl2) or Brønsted acids (CF3CO2H, HCl, H2SO4) in different solvents (CH2Cl2, CH3OH, or H2O). Trifluoroacetic acid (TFA) in CH2Cl2 provided good isolated yields, i.e., 30% 3, 10% 4 with only 20% 2, but the reaction was still tarry due to considerable photopolymerization (~40%). Dilution of the N-oxide (10 times) gave clean conversions, this finding supporting the intramolecular nature of the photoreaction. In a typical procedure, photolysis of a dilute solution of 1 (100 mg, 0.282 mmol) in 0.1 M TFA CH2Cl2 (200 mL) under N2 yielded a distribution of 60% hydroxylation and 40% deoxygenation products. The disappearance of the starting N-oxide required only 10-15 min! Under these conditions the regioselectivity of the reaction was high, amounting the 2'-OH isomer 4 to less than 3%. TFA in aqueous solution produced similar results, though the yield of hydroxylation (40%) was reduced by an increase in deoxygenation (60%) via T1 of PAPN'-OH.

In view of these results, we studied relevant aspects of the photophysics and photochemistry of PAPN and PAPNO, since consideration of the partitioning and dynamics of the initial excited state should be crucial to optimize further the hydroxylation reaction. Little is known about the photophysics of PAPN and its N-oxide. This is due to the complexity of the electronic properties of isoquinoline (ISQN). Papaverine is a covalently linked donor-spacer-acceptor assembly D(S)A. The donor (D) is 1,2-dimethoxybenzene, the spacer (S) is the methylene bridge, and the acceptor (A) is dimethoxyisoquinoline. The absorption spectrum of dimethoxytoluene (DMT) in CH2Cl2 features a long wavelength band at 282 nm (\( \epsilon 2393 \)), while methyldimethoxylisoquinoline (MDM–ISQN) has bands at 325 nm (\( \epsilon 2909 \)) and 298 nm (\( \epsilon 3938 \)). The spectrum of PAPN is in a good approximation equal to the sum of the spectra of the two components. Thus there is little electronic interaction in the ground state (weak electronic coupling). Clearly, excitation of PAPN with \( \lambda > 300 \) nm will lead to initial local excitation of the ISQN chromophore. In contrast, the spectrum of PAPNO exhibits a band at 377 nm (n-hexane) that is not present in PAPN. This band shifts deeply to the blue as the solvent polarity is increased irrespective of hydrogen bonding ability. Undoubtedly, this is the (\( \pi, \pi^* \)) transition with strong internal charge-transfer character of the N→O group. The spectrum of PAPNO in 0.1 M TFA CH2Cl2 shows a band at 346 nm (\( \epsilon 7403 \)) that overlays the corresponding band of PAPN'-H. In acid, PAPNO is protonated, and since PAPN'-OH and PAPN'-H are isoelectronic species, their photophysics will be similar. This suggests that PAPN'-OH can be studied using PAPN'-H without photochemistry complications! In this sense, the photophysical analysis of papaverine is applicable to the photochemistry of its N-oxide.
The fluorescence spectrum of DMT in CH₂Cl₂ consists of an unstructured band at 317 nm (ϕᵢ = 0.20). MDM-ISQN exhibits a weakly structured emission band with maximum at 352 nm (ϕᵢ = 0.15). In 0.1 M TFA the band is unstructured and shifts to 383 nm (ϕᵢ = 0.18). These emission maxima and quantum yields are similar to those previously reported for the isolated units. By contrast, in PAPN the localized emission (LE) of MDM-ISQN is strongly quenched (CH₂Cl₂, λ₁LE = 354 nm, ϕ₁LE = 0.02) and decreases markedly with solvent polarity and hydrogen bonding ability (H₂O, λ₁LE = 358 nm, ϕ₁LE = 5 × 10⁻⁴). This means that in hydroxylic solvents protonation takes place in the excited state producing (PAPN'-H)*. Ground state protonation with TFA quenches the emission further irrespective of solvent polarity (ϕ₁LE = 2 × 10⁻⁴). The large difference in ϕ₁LE for PAPN and isolated MDM-ISQN shows that the electron-rich DMT is involved in a nonradiative decay process of the ISQN S₁ state that is much faster than normal fluorescence or intersystem crossing (ISC). Full electron transfer (ET) from DMT to S₁ of MDM-ISQN*-H, with formation of a singlet charge separated state (CS), is the additional decay process (Scheme 2). We conclude from application of the Weller treatment¹⁵ to the ET energetics in PAPN that photo-induced ET is exergonic for the protonated species.¹⁶ The driving force for charge separation CS (−ΔG₉S) is sufficiently positive to get complete ET even in apolar environments. Thus a CS state or “giant dipole” state can be generated.¹⁷ The observation of CS emission in both PAPN'-H and PAPN'-OH supports this conclusion. In fact, the dominant feature in the emission spectrum of PAPN'-OH is a broad band extending 450 - 800 nm with maximum around 500 nm (CH₂Cl₂, λ₁CS = 508 nm, ϕ₁CS = 0.034).

A)

B)

Scheme 2. A) Excited state dynamics and equilibria in PAPNO. B) Hydroxylation mechanism.

We studied the dynamic behavior of the CS state using time-resolved emission techniques. Secondary ET processes deplete the CS state by charge recombination, which can occur either by radiationless processes to S₀ and T₁ or by a radiative pathway to S₀ leading to a broad “exciplex-like” emission. The dominant processes competing for S₀ of ISQN in PAPNO are ISC to the ISQN triplets and chemical reaction (rearrangement). The photophysics of isolated ISQN*-H are dominated by fluorescence and ISC¹⁸ (ϕᵢ = 0.79, ϕISC = 0.21, ϕᵢC = 0). As the two processes are competitive, the absence of significant fluorescence from PAPN'-H and PAPN'-OH precludes ISC as the dominant path to depopulate S₁. This means that in these systems the only source of ISQN T₁ is not ISC from S₁. Since ET is the principal process to depopulate S₁ of PAPN'-OH, some ISQN T₁ responsible for deoxygenation (~ 40%) must arise as a decay product of the CS state. From spectroscopic measurements, S₁ in PAPN'-OH lies at 3.7 eV, CS is between 2.7 - 2.9 eV, and T₁ is at 2.6 eV. Thus the CS state is higher in energy than T₁ and charge
recombination with formation of an excited triplet state may be a significant decay path for the CS state. This pathway to T₃ places a constrain to reduce the efficiency of the ensuing deoxygenation. However, this limitation can be bypassed if the energy of the CS state is lowered below T₃. The lowest triplet of ISQNO is a \((\pi,\pi^*)\) state with a transition of strong CT nature, \(^{19}\) thus in polar solvents T₃ of ISQN in PAPNO will be less stabilized than the ground state. In contrast, the CS species will be more stabilized in polar solvents. Therefore, increased solvation in hydroxylic solvents could place the CS state below T₃, decreasing the fraction of T₃ and the resultant deoxygenation. Experiments in CH₃OH or aqueous CH₃CN clearly showed CS formation under neutral conditions. In contrast, the CS species will be more stabilized in polar solvents. Therefore, increased solvation in hydroxylic solvents could place the CS state below T₃, decreasing the fraction of T₃ and the resultant deoxygenation. Experiments in CH₃OH or aqueous CH₃CN clearly showed CS formation under neutral conditions.

\[ \text{REFERENCES AND NOTES} \]

13. The spectroscopic properties of all compounds are in complete agreement with the assigned structures. Compounds 3 and 4, previously unknown, gave satisfactory elemental analyses.
16. The reduction potential of aromatic N-oxides is strongly pH dependent, the protonated N-oxide being a much better electron acceptor. For instance, quinoline N-oxide E½/V vs. SCE (pH) = -1.164 (7), -0.772 (1.8), ΔE½ ~ 0.4 V, see Ochiai, E. *Aromatic Amine Oxides*; Elsevier: Amsterdam. 1967; pp. 91-96.
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