Photorelease of HCl from *o*-Methylphenacyl Chloride Proceeds through the *Z*-Xylylenol

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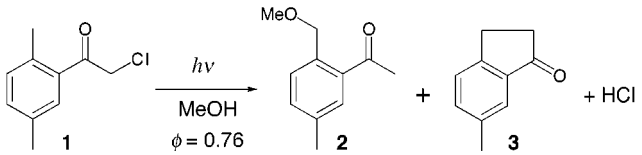
Substrates with photoremovable protecting groups ("caged compounds")[1] are in increasing demand for application in biochemistry, lithography, and combinatorial chemistry. Progress will depend on the development of substrates that satisfy diverse requirements. Rapid and efficient release of various functional groups is provided by desyl and *p*-hydroxyphenacyl[2] derivatives, which offer an alternative to the widely used *o*-nitrobenzyl cages. 2,5-Dimethylphenacyl (DMP) esters present another potentially useful active principle for the release of carboxylic acids.[3]

Photorelease of HCl from DMP chloride (**1**) to yield the solvolysis product **2** and indanone **3** in MeOH (Scheme 1) was observed in 1978 by Bergmark.[4] Netto-Ferreira and Scaiano (N-FS) investigated this reaction by nanosecond laser flash photolysis (LFP).[5] Our efforts to determine the release rates of DMP esters[6] by LFP led us to reinvestigate the model compound **1** as a benchmark. We found that the mechanism proposed by N-FS requires substantial revision.

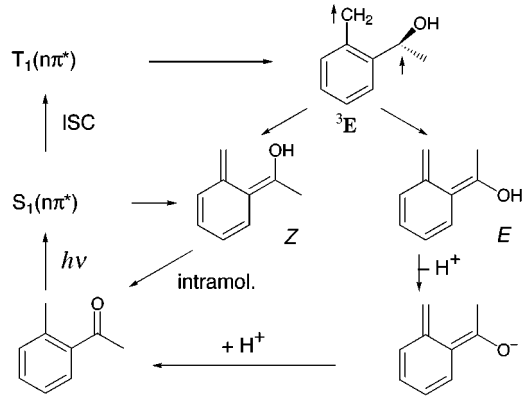
The product ratio of **2**/**3** = 1.4 reported by Bergmark[4] is that obtained after exhaustive photolysis of **1** (5×10^{-3} M) in MeOH. HCl release affects product distribution, but not the quantum yield: the ratio **2**/**3** is <1.1 at low conversions (<5%) or when MeOH is saturated with sodium carbonate. On the other hand, when HCl gas (1 equivalent) is added prior to irradiation, the ratio **2**/**3** rises to 1.4 even at low conversion.

The primary photoreaction of **1** is photoenolization. The established mechanism for photoenolization of 2-methylacetophenone is shown in Scheme 2.[7−9] Two isomeric xylylenols of *Z*- and *E*-configuration are generated via a triplet xylylenol intermediate, ^{3}**E**, formed by adiabatic 1,5-hydrogen transfer from the excited ketone triplet. Addition of piperylene does not affect the lifetime of ^{3}**E** (900 ns in degassed MeOH) due to its low triplet energy,[10] but reduces its yield by quenching of the triplet ketone precursor. The competing photoenolization from the excited singlet ketone yields only the *Z*-enol, which decays rapidly (τ =

Scheme 1



Scheme 2



730 ns in MeOH, ca. 20 ns in cyclohexane) by intramolecular reketonization. Ketonization of the *E*-enol, on the other hand, requires proton transfer through the solvent.

Bergmark and co-workers[4] assumed that fast intramolecular reversion of the *Z*-xylylenol of **1** would preclude competition by product-forming reactions, and this was supported by the LFP work of N-FS.[5] Two transient intermediates were observed in MeOH solution. The first, λ_{max} = 340 nm, τ = 270 ns, was attributed to a long-lived *anti*-conformer of the triplet ketone, ^{3}**1**, and the second, λ_{max} = 380 nm, τ = 20 μs, was assigned to the *E*-xylylenol.

Reinvestigation of **1** by LFP (XeCl excimer laser, 308 nm, 25 ns pulse width, 100 mJ pulse energy) indicated that the flow system used by N-FS had not completely excluded re-irradiation of photoproducts. We could reproduce the findings reported for the xylylenol transient, but the triplet species in MeOH (λ_{max} = 340 nm) and another transient observed in benzene solution (λ_{max} = 325 nm) were not seen when fresh solutions of **1** were used for each laser shot. Such transients appeared only upon re-excitation of the solutions with a second laser pulse. Yet, elimination of these spurious transients from consideration has no substantial impact on the reaction mechanism proposed by N-FS, as they had shown that their triplet transient was "not a major player in product (or enol) formation", and the transient observed in benzene was left unassigned.

Neither the intensity, i.e., the yield, nor the lifetime of the xylylenol transient ($\lambda_{max} \approx$ 385 nm, τ = 22.5 μs in MeOH) was affected by the presence of oxygen or by addition of piperylene (<5% change up to 1.5 M), in accord with earlier findings.[5] Previous authors concluded that the lifetime of the excited triplet ketone, ^{3}**1**, must be unusually short.[4,5] Failure to detect triplet xylylenol, ^{3}**E**, and *Z*-xylylenol by LFP was also attributed to unusually short lifetimes (≤20 ns) of these intermediates.[5] An alternative interpretation of these observations is that ^{3}**1** and, hence, ^{3}**E** are bypassed by efficient photoenolization from the excited singlet state of **1**. Given that the singlet pathway is expected to yield only the *Z*-xylylenol (Scheme 2), we were led to question the assignment of the observed xylylenol transient to the *E*-isomer. We now provide evidence that the 20-μs transient should be reassigned to the *Z*-xylylenol, which is formed

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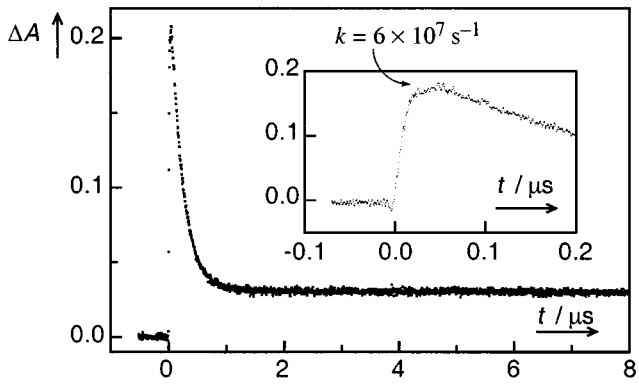


Figure 1. Formation (inset) and decay kinetics of the xylylenol transient (λ_{0bs} = 390 nm) formed by LFP of **1** in benzene solution.

predominantly by the singlet pathway, so that its yield does not depend on the presence of triplet quenchers.

A kinetic trace obtained by LFP of **1** in benzene solution is shown in Figure 1. In this solvent the xylylenol transient absorption decays much more rapidly (τ = 225 ns), but does not return to baseline on the microsecond time scale. The end absorption decays with a half-life of about 10 ms. Furthermore, formation of the absorbance at 390 nm is partly resolved (inset of Figure 1). We conclude that the reaction partly proceeds by the triplet pathway and that, consequently, both xylylenol isomers are formed in benzene. The resolved growth is attributed to the decay of ^{3}**E** and the fast (225 ns) and slow (10 ms) decays to the *Z*- and *E*-isomers of the xylylenol of **1**, respectively.

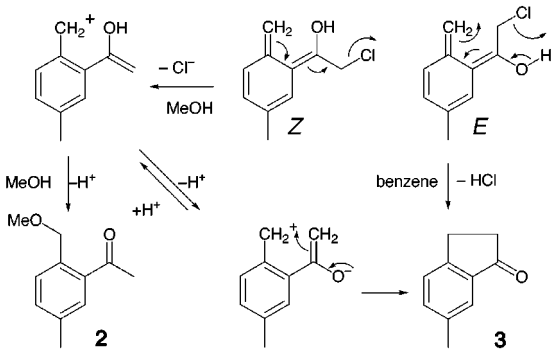
These assignments are established by quenching experiments. Addition of piperylene reduces the amount of ^{3}**E** and of both xylylenol transients, but has no effect on their lifetimes. Formation of the xylylenols by the triplet pathway, ^{3}**1** → ^{3}**E** → *Z* + *E* as in Scheme 2, is reduced by quenching of ^{3}**1**. Steady-state analysis leads to the Stern−Volmer relation $A^0/A^q = 1 + k_q{}^3\tau^0[q]$. A^0 and A^q are the absorbances of the xylylenol transients in the absence and presence of quencher q, respectively, k_q is the second-order rate constant for quenching of ^{3}**1** by piperylene, and $^3\tau^0$ is the lifetime of ^{3}**1** in the absence of quencher.

The amplitude ratio A^0/A^q of the long-lived xylylenol transient increased linearly with piperylene concentration (5 points up to 1.5 M) with a slope of $k_q{}^3\tau^0 = 1.1 \pm 0.1$ M^{-1}. Thus, the long-lived *E*-isomer forms exclusively by the triplet pathway. Assuming a quenching rate constant of $k_q = 5 \times 10^9$ M^{-1} s^{-1}, the lifetime of ^{3}**1** is estimated as $^3\tau^0 \approx 0.2$ ns. The Stern−Volmer plot for the *Z*-xylylenol had about the same initial slope, but reached a plateau at $A^0/A^q \approx 1.5$. Thus, formation of the *Z*-xylylenol is not fully quenched at high piperylene concentrations, because a large fraction (≈2/3) is generated by the singlet pathway.

Similar results were obtained with solutions of **1** in acetonitrile. Again, formation of the xylylenols occurred in part via ^{3}**E** ($k = 3.1 \times 10^6$ s^{-1}), and the enol decay was biexponential (*Z*-xylylenol: $k = 1.9 \times 10^5$ s^{-1}, about 90% of the transient amplitude at 390 nm; *E*-xylylenol: $k \approx 2 \times 10^2$ s^{-1}, about 10% of the amplitude).

The absence of the triplet pathway in MeOH indicates that hydrogen bonding reduces the rate of singlet−triplet intersystem crossing.[11] Addition of 0.1% of MeOH to benzene is sufficient to reduce the yield of *E*-xylylenol by about 50%. MeOH must be preassociated by hydrogen bonding to ketone **1** in the ground state, as the singlet state lifetime is a few picoseconds. Addition of 1% MeOH is required to reduce the yield of the *E*-isomer by about 30% in acetonitrile.[12] The decay rate constant of *E* increases to $k \approx 4 \times 10^2$ s^{-1} in the presence of 1% MeOH.

Scheme 3



Reassignment of the short-lived xylylenol transient (22.5 μs in MeOH, 225 ns in benzene) to the *Z*-isomer immediately rationalizes several observations. Unusually short lifetimes need not be invoked for any of the species ^{3}**1**, ^{3}**E**, or *Z*-xylylenol. Moreover, the previously puzzling[5] 100-fold increase in the lifetime of the xylylenol transient going from benzene to MeOH now falls in place. Ketonization of the *Z*-xylylenol formed from *o*-methylacetophenone by 1,5-sigmatropic return is also strongly retarded by hydrogen bonding to the solvent.[8]

Scheme 3 shows our rationalization of the subsequent medium- and acid-dependent reactions leading to products **2** and **3**. Only the *E*-xylylenol is disposed for concerted elimination−cyclization to form indanone **3**. Indeed, the low quantum yield in benzene ($\phi_{\mathbf{1}\rightarrow\mathbf{3}} = 0.11$)[4] indicates that only *E*-xylylenol reacts in this solvent, while the major (Figure 1) *Z*-isomer reverts to starting material. On the other hand, the high quantum yield, $\phi_{\mathbf{1}\rightarrow\mathbf{2}+\mathbf{3}} = 0.76$,[4] of HCl release in MeOH—where formation of the *E*-isomer is negligible—requires reaction via the *Z*-xylylenol. Rapid protolytic equilibration of the cationic enol formed by chloride elimination affects product formation:[13] The cation yields the solvolysis product **2** in acidic solution, and cyclization of the conjugate base forms **3** at low acid concentration.

In summary, we propose that HCl photorelease from DMP chloride (**1**) in MeOH solution proceeds by heterolytic elimination of chloride ion from the *Z*-xylylenol of **1**, the only photoenol formed in this solvent. The high solvolytic reactivity of this photoenol holds promise for the use of *o*-alkyl phenacyl as a photoremovable protecting group for other functions. Both xylylenols are formed in benzene solution, but HCl release takes place only from the *E*-isomer in this solvent.

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