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Time-resolved pH jump study of photochemical cleavage and release of carboxylic acids from α-keto amides

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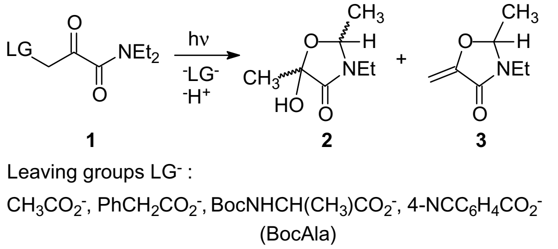
Abstract—Time-resolved pH jump experiments, using laser flash photolysis and bromocresol green as an indicator, showed that photochemical cleavage and release of carboxylic acids from various α-keto amides derivatives in aqueous media occurs on the microsecond timescale (18–136 μs), depending on carboxylate leaving group ability.

The photochemical reactions of α-keto amides have long been thought to proceed via intermediates, which possess zwitterionic character.[1,2] Recent studies have investigated the prospects for exploiting these zwitterionic intermediates to effect heterolytic elimination of carboxylate[3] and phenolate[4] leaving groups as a strategy for developing photoremovable protecting groups and cage compounds.[5,6] For example, photolyses of *N*,*N*-diethyl α-keto amides **1** with leaving groups LG = $CH_3CO_2^-$, $PhCH_2CO_2^-$ at the position α to the keto group result in efficient cleavage and release of carboxylic acids in essentially quantitative yields in aqueous media (Scheme 1).[3] The cleavage coproducts were found to be mainly the diastereomeric hemiacetal **2** and minor amounts of methyleneoxazolidinone **3**. In these cases the zwitterionic intermediate **4** would be involved in the elimination step.



Scheme 1.

The rates of elimination of the leaving groups from zwitterionic intermediates such as **4** (Fig. 1) have not been determined. One reason for this is that conventional nanosecond laser flash photolysis experiments have revealed no significant transient absorptions to monitor for kinetic information about the reaction. An alternate approach using time-resolved difference FT-IR spectroscopy seemed promising in this regard, because vibrations specific to the released carboxylate anion could be directly observed at pH 6 in buffer. This approach, using a rapid scan technique, provided an upper limit estimate of the release time of the γ-amino acid GABA of 30 ms.[3] However, further studies to resolve the rate constants using a faster step scan technique proved unfeasible due to the insensitivity of the method at 355 nm in the cases of our weakly absorbing α-keto amides.

Given the above difficulties in determining release rates, we have turned to a time-resolved pH jump method using laser flash photolysis,[7] which takes advantage of the pronounced increases in acidity, which are observed when the carboxylate derivatives of α-keto amides are photolyzed in unbuffered aqueous media. The pH jumps are sufficiently large to permanently change the color of an added pH indicator, bromocresol green (pK_a 4.90,

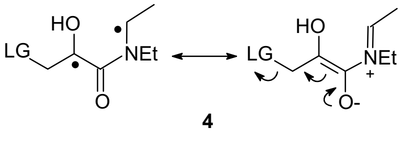


Figure 1. Intermediate with zwitterionic character.

Keywords: α-Keto amide; Photocleavage; Zwitterion; pH jump.

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20 °C[8a]). In this letter we report the rate constants for bleaching of the 620 nm band of this dye, which allow us to establish the mechanism for the loss of the carboxylate leaving groups that occurs in the rate determining step via zwitterionic intermediates **4**.

Steady-state photolyses ($\lambda > 300$ nm) were conducted with *N*,*N*-diethyl α-keto amides **1** substituted with various carboxylate leaving groups LG (Scheme 1) following previously described procedures.[3,4] In 50% aqueous acetonitrile, photocleavage was observed in all cases and resulted in formation of the corresponding carboxylic acid and the diastereomeric hemiacetal **2**,[3] which was accompanied by a minor product **3**.[3,4] The yields are given in Table 1. Quantum yields of reaction (λ 310 nm) for each LG^- were as follows: $CH_3CO_2^-$, $\Phi = 0.31$;[3] $PhCH_2CO_2^-$, $\Phi = 0.36$;[3] BocAla, $\Phi = 0.35$; $4\text{-}NCC_6H_4CO_2^-$, $\Phi = 0.32$.[9]

Prior to conducting the laser flash photolysis studies, we examined the pH jumps under steady-state photolysis conditions. For 0.04–0.05 M **1** with various carboxylate leaving groups ($LG = CH_3CO_2^-$, $PhCH_2CO_2^-$, BocAla, $4\text{-}NCC_6H_4CO_2^-$) in 50% aqueous CH_3CN the magnitude of the observed change in pH was 2.6–3.3 units starting from a pH of 6.1–6.6. When photolyses with bromocresol green were monitored by absorption spectroscopy, the 620 nm band of the anionic form of the pH indicator was observed to decrease in intensity, and a new absorption at 420 nm was observed to increase.

Table 1. Yields of photoproducts from steady-state photolyses of various α-keto amides, and rate constants for bleaching of bromocresol green

LG^-	Yield, %[a]				k, 10^3 s^{-1}[c]
	LG-H	**2**	**3**	**1**[b]	
$CH_3CO_2^-$	82	75	4.5	19	7.33
$PhCH_2CO_2^-$[d]	86	66	10	12	18.0
BocAla	81	78	0	18	31.8
$4\text{-}NCC_6H_4CO_2^-$	nd[e]	85	0	13	54.9

[a] Yields determined by NMR spectroscopy with DMSO, DMF, or glycine as standards in 50% D_2O in CD_3CN.

[b] Unreacted at end of photolysis.

[c] The average error was <5%.

[d] Yields taken from Ref. 3.

[e] Not determined due to overlap with starting material in the ^1H NMR spectrum.

The kinetics of the pH jumps, as reflected by the bleaching of the 620 nm absorption band of 20 μM bromocresol green, were studied by 355 nm nanosecond laser flash photolyses of 0.1–0.2 M[10] **1** in air-saturated 50% H_2O in CH_3CN at pH ca. 6 (unbuffered). The flowed samples were subjected to 10–20 3 mJ shots of a Nd-YAG laser at 30 or 60 s intervals. The summed ΔOD versus time plots in each case gave a satisfactory fit to a monoexponential function, which afforded the time constant for the bleaching kinetics of the bromocresol green. A representative kinetic plot (Fig. 2A) is shown for **1** ($LG = PhCH_2CO_2^-$), along with bleaching of the dye at time intervals (Fig. 2B). Control experiments with α-keto amide **1** (LG = H, no leaving group) showed no bleaching. The bleaching rate constants are summarized in Table 1.

For **1** the rate constants follow the order of leaving group ability, $CH_3CO_2^- < PhCH_2CO_2^-$, <Boc-alanine, $< 4\text{-}NCC_6H_4CO_2^-$ (Table 1), and a plot of log k versus $-pK_a$ of the released acid is 0.74 ± 0.07 (R^2 0.9919).[8b,c]

The pronounced leaving group effects on the rate constants for bleaching of bromocresol green in the case of **1** are consistent with rate determining elimination of the carboxylate groups in the unstable zwitterionic intermediate **4**. Subsequent proton release would be considered to occur mainly in a non-rate determining step along pathway a, which leads to the principal cleavage coproduct, diastereomeric **2** (Scheme 2). An inverse

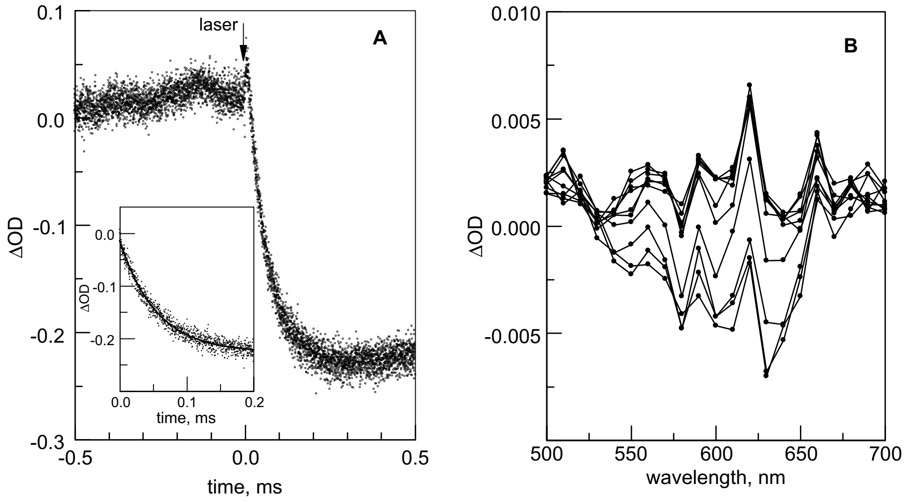
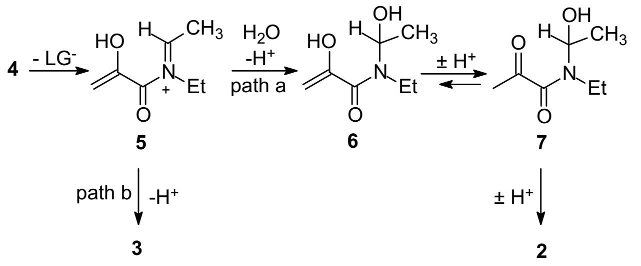


Figure 2. (A) Kinetics of bleaching of bromocresol green at 620 nm upon laser flash photolysis of **1**, $LG = PhCH_2CO_2^-$ (15 laser shots summed); inset shows the fit to a single exponential decay function made after the transient spike due to cuvette luminescence. (B) Spectral response at time intervals for one shot at each wavelength.



Scheme 2.

solvent isotope effect of 0.74 ± 0.02 is observed, which would be consistent with the enolate group of **4** being a stronger base in D_2O than in H_2O such that elimination occurs more rapidly in the deuterated solvent.[11]

Proton release via path a would involve addition of water to imminium ion **5**[12] to produce enol **6**. Pseudo first-order rate constants for hydration of imminium ions range from 10^6 to $10^8\ s^{-1}$ for the few examples reported.[13,14] The remaining steps along path a, such as tautomerization[15] and cyclization to give hemiacetal diastereomers **2**, would be slow acid-catalyzed reactions of relatively stable compounds that are considered to have no bearing on the bleaching rates.

Deuterium labeling studies support two mechanistically distinct pathways in the formation of **2** and **3**. In the case of diastereomers **2** deuterium is incorporated into the methyl group α to the carboxamide group, consistent with a prior tautomerization step (path a).[3] No deuterium is incorporated into the methylene group of the double bond of **3**, which rules out a tautomerization mechanism for the formation of this product.[4] The absence of deuterium in **3** shows that it is not formed via **2**. In addition, a control experiment shows that diastereomers **2** are not formed from **3**, which is stable in the presence of CH_3CO_2D at pD 2.8 in 50% D_2O in CD_3CN for >14 d.

In summary, the photoelimination of carboxylic acids from α-keto amides results in a rapid, permanent change in pH sufficient to cause bleaching of the 620 nm absorption band of the pH indicator, bromocresol green. In the case of *N*,*N*-diethylamides **1** the time constants for bleaching span 18–136 μs, depending on carboxylate leaving group ability, which is consistent with a rate determining elimination step in the photogenerated ground state zwitterionic intermediates.

Acknowledgements

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10. High concentrations of **1** were required because the molar extinction coefficients were $<10\ L\ mol^{-1}\ cm^{-1}$ at the 355 nm photolysis wavelength. For each experiment the absorbance at 355 nm was 0.5–0.7.
11. (a) An inverse solvent isotope effect usually signifies the existence of a preequilibrium protonation step that is followed by a rate determining step.[11b,c] Since the pH rapidly changes in our unbuffered experiments, significant protonation of **4** in competition with elimination could result in complicated kinetics and non-monoexponential bleaching. We suspect the isotope effect could be due to weaker solvation of the intermediate in D_2O than H_2O; (b) Keefe, J. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1983**, *105*, 265–279; (c) Keefe, J. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1981**, *103*, 2457–2459.

12. An approximately planar imminium ion **5** would have four combinations of *s*-cis and *s*-trans conformers. For brevity only one is shown in Scheme 2.
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