

The Mechanism of Photoinduced Acylation of Amines by *N*-Acyl-5,7-dinitroindoline as Determined by Time-Resolved Infrared Spectroscopy

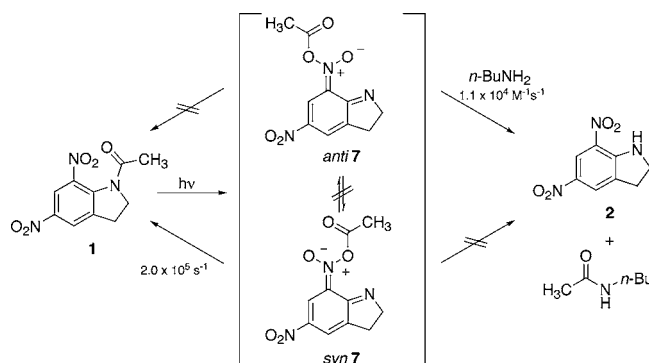
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ABSTRACT



The photochemistry of *N*-acetyl-5,7-dinitroindoline (**1**) was studied in acetonitrile using nanosecond time-resolved infrared (TRIR) spectroscopy. Upon photolysis, two nearly but not completely overlapping sets of transient IR bands are observed that are assigned to two non-interconvertible conformers of mixed acetic nitronic anhydride **7**. While *syn*-**7** reverts rapidly to **1**, *anti*-**7** is long-lived and is able to acylate amines. Results of density functional theory calculations support conclusions based on experimental TRIR data.

Photolabile protecting groups and caged compounds have been widely used in organic synthesis for nearly three decades.¹ Their attractiveness comes from the possibility of controlling both the location and the time of release by exposure to light alone. A large variety of such protecting groups have been developed, each of them tailored for specific uses. Among them, the *N*-acetyl-7-nitroindolines are of particular interest because their photolysis in the presence

of a nucleophile under both neutral and relatively mild conditions leads to acylated products. This reaction was first explored by Amit et al., who first used the 5-bromo-7-indoline moiety as a photoactivatable leaving group to form both acids and esters² and later extended this methodology to form amides.³ Helgen and Bochet have expanded the synthetic utility of this reaction by photolyzing *N*-acetyl-5,7-dinitroindoline (**1**) in dry acetonitrile in the presence of a variety of primary and secondary amines to form, along with

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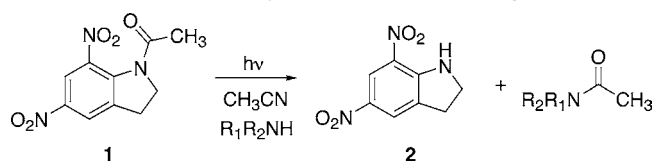
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5,7-dinitroindoline (**2**), mono- and disubstituted amides in high yield and excellent purity (Scheme 1).⁴ Nicolaou et al.

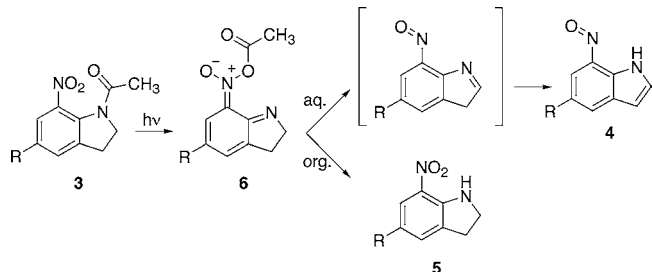
Scheme 1. Synthesis of Amides Using **1**



have applied a similar synthetic strategy using a resin-bound analogue to synthesize various amides with ease of purification.⁵ More recently, this methodology has been applied to the syntheses of *N*-glycosylated amino acids⁶ and various carbamates.⁷ In aqueous media, though the aromatic byproduct differs, carboxylic acids can be photochemically generated. Specifically, 7-nitroindoline derivatives have been used as hydrolytically stable “caged” glutamate, GABA, and glycine, releasing these neuroactive amino acids rapidly upon photolysis.⁸

Although the course of this reaction differs in aqueous and organic media as evidenced by the different aromatic products (Scheme 2), it nevertheless seems plausible that both

Scheme 2. Solvent-Dependent Reactivity of Purported Intermediate **6**



reactions proceed via a common intermediate. Wan, Corrie, and co-workers have used a variety of steady-state and laser flash photolytic techniques to study the mechanism of this reaction in both water and wet acetonitrile using water-soluble indoline **3** ($R = \text{CH}_2\text{CO}_2\text{CH}_3$) (Scheme 2).⁹ Along with acetic acid in both cases, in 100% water the major product is nitrosoindole **4** ($R = \text{CH}_2\text{CO}_2\text{CH}_3$), while in wet

acetonitrile the major product is nitroindoline **5** ($R = \text{CH}_2\text{CO}_2\text{CH}_3$). The ratio of these products varies smoothly upon varying the water content of acetonitrile. These and other data suggest that both products could potentially derive from one common acetic nitronic anhydride intermediate, the product of acyl transfer to a nitro-oxygen (i.e., **6**). Interestingly, this initial step qualitatively resembles the hydrogen transfer that initiates release of alcohols from nitrobenzyl ethers and esters.¹⁰ Two different solvent-dependent reactions are potentially available to an intermediate of structure **6**; in organic media, standard nucleophilic attack on the activated carbonyl and protonation yields a nitroindoline **5**, while in aqueous media loss of acetate and deprotonation yields a 3*H*-nitrosoindole, which tautomerizes to an isolable nitrosoindole (i.e., **4**) (Scheme 2). Although the data are compelling, nevertheless no direct structural evidence is available concerning the nature of purported intermediate **6**. In this letter, we present a time-resolved infrared (TRIR) spectroscopic study of *N*-acyl-5,7-dinitroindoline (**1**) in acetonitrile that confirms the intermediacy of **6** ($R = \text{NO}_2$), as well as computational data that also support this conclusion.

The synthesis of **1** has been previously reported.¹¹ Laser photolysis (355 nm, 90 ns, 0.4 mJ) of **1** in both acetonitrile and acetonitrile-*d*₃ produces the TRIR difference spectrum shown in Figure 1a. Instantaneous bleaching of the starting material (negative bands) is accompanied by instantaneous growth of transient IR bands at 1800, 1580, and 1160 cm^{-1} . The bands at 1800 and 1160 cm^{-1} decay incompletely over 20 μs with concomitant and incomplete recovery of the bands due to the ground state ($k_{\text{obs}} = 2.0 \times 10^5 \text{ s}^{-1}$). Absorbance near 1800 cm^{-1} is usually indicative of a carbonyl substituted with a highly electron-withdrawing group. Upon closer examination of the absorption bands at 1800 and 1160 cm^{-1} , it appears that two different intermediates (with distinct reactivity) having similar IR spectra (i.e., similar structure) are both formed within the laser pulse. Because IR bands are typically broadened in solution relative to the gas phase, we cannot discern two clear absorption maxima. We can, however, distinguish between the two species by examining their kinetic behavior at the two extremes of the observed absorption bands. Specifically, the higher-energy edge of the band at 1800 cm^{-1} and the lower-energy edge of the 1160 cm^{-1} band both exhibit a first-order decay over 20 μs , while the lower-energy edge of the band at 1800 cm^{-1} and the higher-energy edge of the 1160 cm^{-1} band are persistent for more than 180 μs (Figure 1a). If a band is due to only one species, then each edge of the band would display identical kinetic behavior, such as is observed for the depletion band near 1300 cm^{-1} . Interestingly, as the short-lived species decays, the depletion bands due to **1** recover to a similar extent (ca. 30%) and at the same rate, implying that the short-lived intermediate does indeed revert to **1**. The positive band

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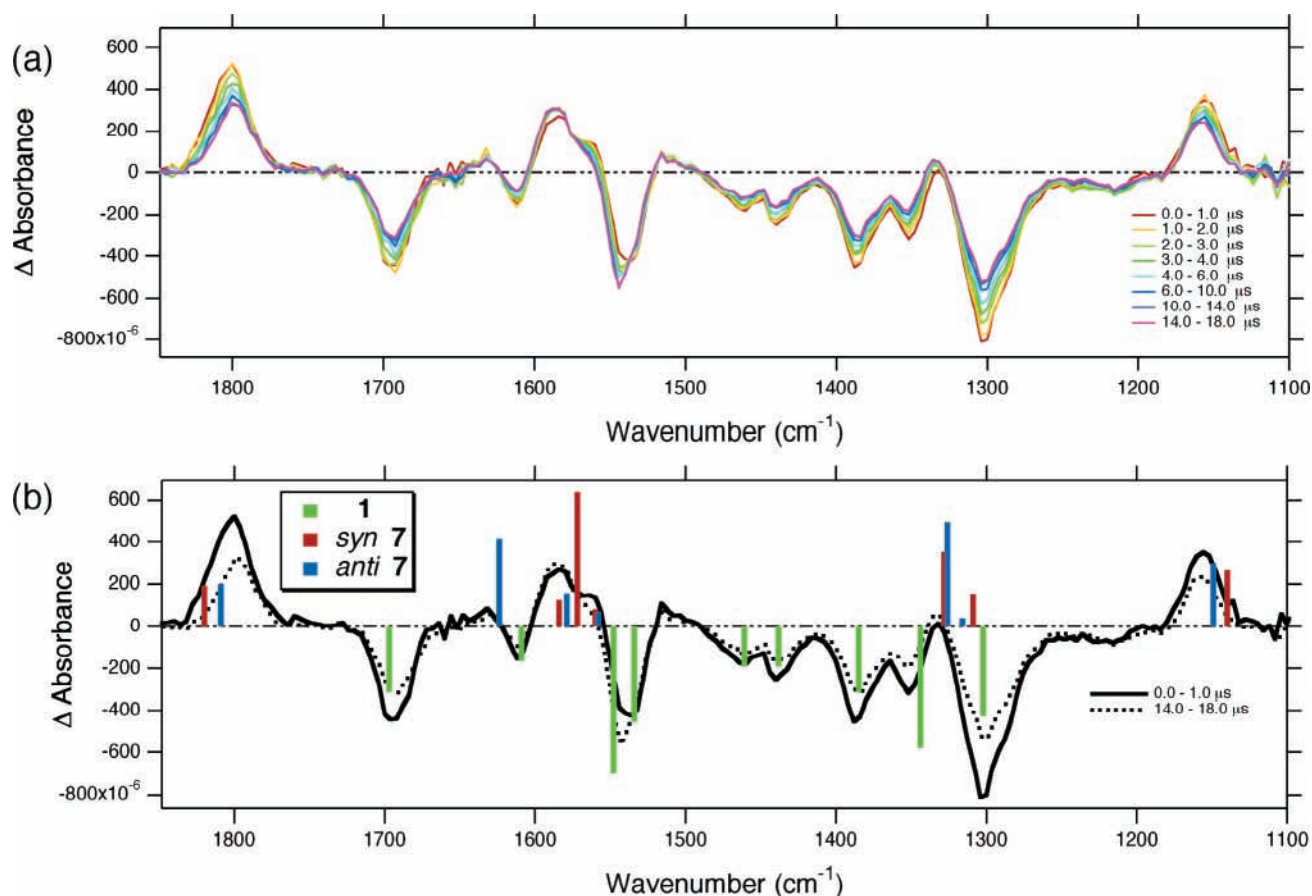


Figure 1. (a) TRIR difference spectra averaged over the time scales indicated following laser photolysis (355 nm, 90 ns, 0.4 mJ) of a solution of **1** (2 mM) in either acetonitrile (1850–1650 cm^{-1} and 1250–1100 cm^{-1}) or acetonitrile- d_3 (1650–1250 cm^{-1}) and (b) TRIR difference spectra from panel a overlaid with bars representing calculated IR frequencies (scaled by 0.96¹²) and relative intensities. Negative signals are due to depletion of reactants, and positive signals are due to new transients or products.

at 1580 cm^{-1} does not display this behavior due to complicating overlap with depletion bands.

Based on these observations, we assign the positive absorption bands to two non-interconvertible conformers of the acetic nitronic anhydride (*syn*-**7** and *anti*-**7**). These kinetically distinct yet structurally similar intermediates would be expected to display different reactivity, based on the differing proximity of the acyl group to the indoline nitrogen. To corroborate the assignment of the transient IR bands, we performed geometry optimizations and frequency calculations at the B3LYP/6-31G* level of theory on both *syn*-**7** and *anti*-**7** (see Supporting Information for computational details). As an internal check of calculation accuracy, we also performed geometry optimizations and frequency calculations on indoline **1**. All three structures optimized to stable minima. The difference in energy between *syn*-**7** and *anti*-**7** was calculated to be 1.7 kcal/mol favoring the former. The calculated IR bands are overlaid with the TRIR spectrum in Figure 1b. The calculated frequencies for both conformers of **7** are similar to each other (as would be expected based on their structural similarity) and match well with the experimentally observed bands. In the calculated geometry of *syn*-**7**, the acyl carbon and indoline nitrogen

are only 2.8 Å apart (well within the sum of the van der Waals radii), consistent with this species easily reverting to **1**. Interestingly, the relative position of analogous vibrational modes calculated for *syn*-**7** and *anti*-**7** match well with the expectation that the *syn* conformer will be short-lived and the *anti* conformer will be persistent. This is most clearly seen for the carbonyl stretch near 1800 cm^{-1} , where the calculations predict the *syn* conformer to have a carbonyl stretching frequency that is higher energy than the *anti* conformer. Indeed, when we monitor the decay at 1810 cm^{-1} ca. 50% of the signal decays, whereas at 1785 cm^{-1} , less than 10% decays (Figure 2). Similar behavior is observed for the band near 1160 cm^{-1} . Again, this is in contrast to the depletion bands between 1300 and 1400 cm^{-1} , which are completely symmetric.

We also examined the behavior of **7** in the presence of added *n*-butylamine, to confirm that this species is the active electrophile in the photochemical acylation reaction. Indeed, the persistent band due to *anti*-**7** decays only in the presence of this added nucleophile and at an observed rate proportional to the concentration of added amine. Additionally, we observe the growth of the product (*N*-butylacetamide) at 1670 cm^{-1} at the same rate as the decay of *anti*-**7** (data not shown).

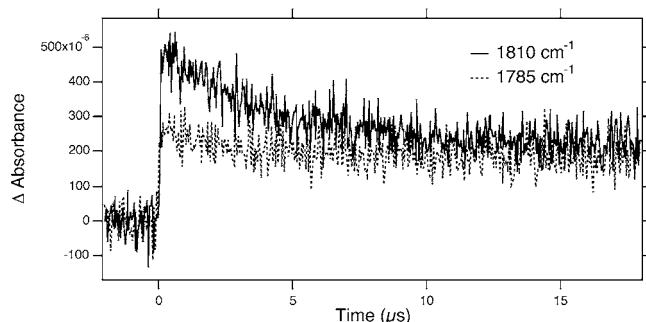


Figure 2. Kinetic traces observed following laser photolysis (355 nm, 90 ns, 0.4 mJ) of a solution of **1** (2 mM) in acetonitrile.

A second-order rate constant of $1.1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ was derived (Supporting Information). We were unable to add enough *n*-butylamine to observe the reaction with *syn-7* without obscuring the IR window.¹³ In addition, we were also unable to add enough methanol-*d*₃, to observe trapping of *anti-7* without obscuring the IR window.

The data suggest that *syn-7* and *anti-7* are non-interconvertible species at room temperature. To confirm this, we attempted to locate computationally a transition state corresponding to rotation about the C7–N bond. Although we were unsuccessful, and therefore do not have an exact calculation of the energetic barrier, we nevertheless have suggestive evidence that this barrier is substantial. First, from the optimized geometries (discussed above), the C7–N bond length in **1** is 1.47 Å, but in both *syn-7* and *anti-7* the analogous bond length is 1.34 Å, a substantial shortening implying increased double-bond character. Second, we performed a number of single-point energy calculations, using *anti-7* as a starting point, corresponding to various

rotations about the C7–N bond. The maximum energy of these unoptimized structures lies at approximately 90° rotation, as intuition predicts (see Supporting Information). We then performed a series of single-point energy calculations at various C7–N bond lengths with the maximum energy rotation. The minimum energy of these unoptimized structures lies at approximately 1.43 Å (see Supporting Information). These calculations provide us with an estimate of the rotational barrier that is on the order of 42 kcal/mol. Thus, it seems reasonable that *syn-7* and *anti-7* are indeed independent entities with unique chemistry.

We have shown by TRIR spectroscopy that photolysis of nitroindoline **1** initially yields two non-interconvertible conformers of mixed acetic nitronic anhydride **7**. One of these conformers, *syn-7*, reverts to **1** rapidly, while the other, *anti-7* is much longer-lived. The subtle difference between these conformers was detected by vibrational spectroscopy. Thus, our TRIR results indicate that *anti-7* is the potent photochemically generated electrophile responsible for the acylation of amines and alcohols discussed above. Apparently, in an aqueous environment, in the absence of nucleophiles, an elimination pathway becomes favorable, resulting in nitrosoindoles.¹⁴ In organic media such as methylene chloride/dioxane mixtures or acetonitrile, this pathway is unfavorable, and standard carbonyl addition/elimination chemistry predominates.

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Supporting Information Available: Experimental details, derivation of second-order rate constant, LFP data, and computational details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(13) We also examined the photochemistry of **1** by laser flash photolysis (LFP) using UV detection. By LFP, *syn-7* and *anti-7* are indistinguishable, so the transient absorption band was symmetric. Additionally, the derived second-order rate constant was the same in both the LFP and TRIR experiments (Supporting Information).

(14) Subtle structural changes can have an effect on the mechanism because 5-nitro-7-nitrosoindolines were observed as products in the photolysis of carbamate derivatives of **5**.⁷