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Ultrafast Time-Resolved Infrared Spectroscopy Study of the Photochemistry of *N,N*-Diethyldiazoacetamide: Rearrangement in the Excited State

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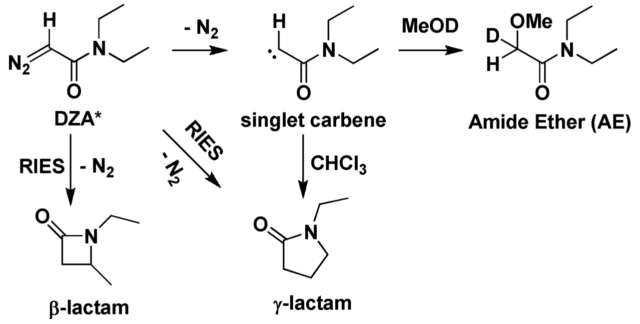
Photolysis of *N*,*N*-diethyldiazoacetamide (DZA) produces a nearly equal mixture of β- and γ-lactams (Scheme 1),[1,2] and the reaction has potential application in the synthesis of penicillins.[3] The formation of β-lactams contrasts with the photochemistry of diazoesters, which fail to produce lactones.[1] Rando[1,2] pointed out that diazocarbonyl compounds are planar[4] and that diazoamides necessarily have an alkyl group in proximity to the incipient carbene center promoting cyclization, but the single alkyl group on the ester is disposed away from it, making the alkoxyl group unavailable for cyclization.[2] Further studies by Tomioka et al.[5,6] using carbene quenchers demonstrated that the γ-lactam product was formed from both a trappable singlet carbene and a second, untrappable intermediate. As methanol, an excellent carbene trap, failed to depress the yield of β-lactam, it must be formed entirely from a non-carbene pathway. Tomioka et al.[5] proposed that the β-lactam was produced from the singlet excited state of the diazoamide (Scheme 1). Similar conclusions have been made concerning the photochemical Wolff rearrangement,[7] and such processes were named by Liu as examples of "rearrangement in the excited state" (RIES).[8] The mechanism of Scheme 1 predicts that the β-lactam and a portion of the γ-lactam are produced on different time scales (faster via RIES and slower with carbene intermediacy). As these two lactams have distinct carbonyl vibrations, we were encouraged to test that prediction using ultrafast time-resolved IR spectroscopy.

Scheme 1. Reaction Pathway for *N*,*N*-Diethyldiazoacetamide (DZA) upon Photolysis



The FT-IR absorption spectra of DZA in chloroform solution before and after 266 nm photolysis are shown in Figure S1 in the Supporting Information along with their calculated frequencies. The band at 1745 cm^{-1} is easily attributed to the β-lactam on the basis of its characteristic absorption at this high wavenumber, consistent with calculations and the literature.[1,2] The band at 1669 cm^{-1} is confidently assigned to the γ-lactam upon comparison with the spectrum of an authentic sample. The ultrafast time-resolved transient absorption spectra produced with 270 nm laser pulses (300 fs) are given in Figure 1. Significantly, these two lactams are formed at different rates. Within 2 ps of the laser pulse, β-lactam was detected as a broad band at 1760−1700 cm^{-1} that subsequently narrowed and shifted to the blue within 50 ps, a result typical of vibrational cooling (VC) of newly born species.[9] β-Lactam was formed instantaneously (<0.4 ps), and the long growth time constant of 29 ps probed at 1745 cm^{-1} was due to VC (Figure S2a). After 50 ps, the VC subsided, and the β-lactam band centered at 1745 cm^{-1} maintained the same intensity over 3 ns. However, the mechanism for γ-lactam formation is different. The γ-lactam band observed at 1669 cm^{-1} was formed on two time scales: a fast component was present within 50 ps of the laser pulse, and a slow component gradually grew over 50−1000 ps with a time constant of 190 ± 42 ps (Figure S2b). According to calculations (Figure S1, Table S1), the singlet carbene overlaps with γ-lactam and thus also significantly contributes to the instantaneous rise of the band at 1669 cm^{-1} (see below).

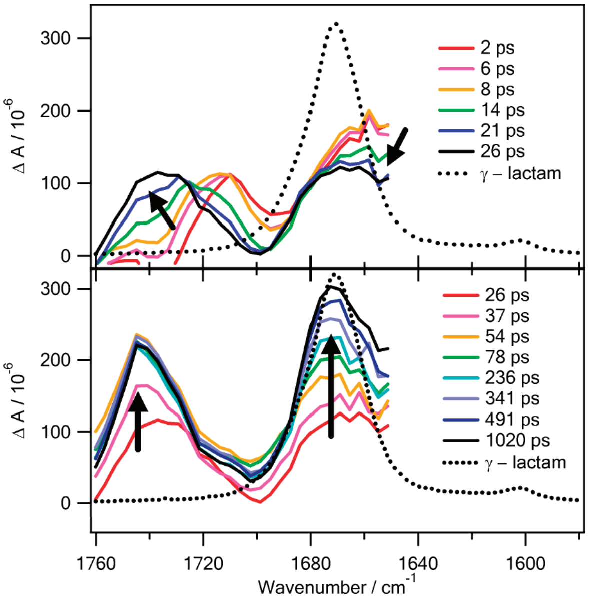


Figure 1. Transient IR spectra produced upon 270 nm photolysis of DZA in chloroform. The dashed curves are the FTIR spectra of authentic γ-lactam.

A DZA solution in CH_3OD was bleached with 266 nm light, and the resulting FT-IR spectra are shown in Figure S3 along with the calculated frequencies. The carbonyl stretching bands for both β- and γ-lactams in CH_3OD were slightly red-shifted (relative to those in chloroform) and split into doublets, which are attributed to mono- and dihydrogen-bonded carbonyl stretching bands, as reported by Minato.[10] In addition, a strong band at 1640 cm^{-1} was

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observed (Figures S1 and S3), which is assigned to the amide ether (AE) product formed from the reaction of the singlet carbene with methanol.[2] The time-resolved transient IR spectra produced with 270 nm laser pulses (300 fs) in CH_3OD are shown in Figure 2.

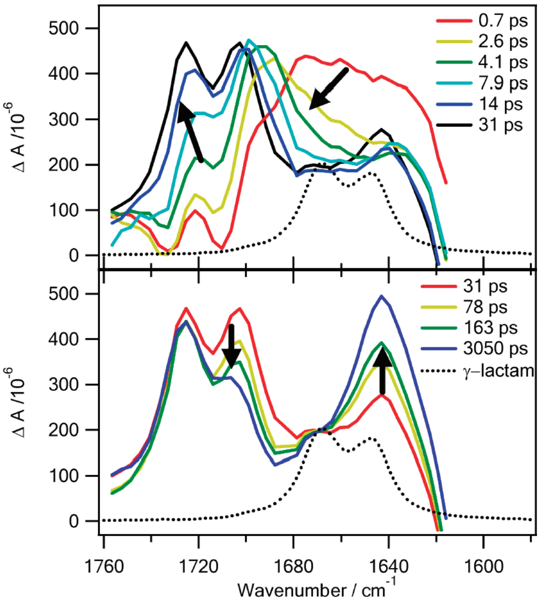

Figure 2. Transient IR spectra produced upon 270 nm photolysis of DZA in CH_3OD. The dashed curves are FTIR spectra of authentic γ-lactam in this solvent.

The β-lactam band centered at 1733 cm^{-1} was again formed immediately after the laser pulse, and it had constant intensity between 30 ps and 3 ns. The rising time constant of 5.8 ps at 1733 cm^{-1} (Figure S5a) indicates that VC was faster in methanol than in chloroform. One of the vibrational bands of the γ-lactam severely overlapped the AE band centered at 1640 cm^{-1}. However, the intensity of γ-lactam probed at 1665 cm^{-1} remained constant from 10 to 3050 ps (Figure S5b), in contrast to the slow growth observed in chloroform (Figure S2b). Thus, our data indicate that there are two pathways for the formation of γ-lactam: the fast formation in both chloroform and CH_3OD is from the excited state of diazoamide via the RIES mechanism, and the slow growth observed only in chloroform is from singlet carbene (Scheme 1). The latter mechanism is absent in CH_3OD, indicating that alcohol efficiently traps the carbene species.[6,7,12,13]

Singlet carbonyl carbenes have orthogonal geometries, in contrast to their planar precursors.[11] The orthogonal conformation assists γ-lactam formation because the empty carbene p orbital points toward a γ-CH bond (Tables S2 and S3). We speculate that in methanol, solvent molecules surround the nascent singlet carbene as a result of hydrogen bonding. This provides a solvent shell that insulates the carbene center from the reactive C−H bond. Thus, cyclization is suppressed, and OH insertion to solvent is preferred. Singlet carbene rotation from the nascent planar to the relaxed orthogonal conformation has been observed in chloroform.[14]

Our data also indicate that β-lactam is entirely formed from the excited state of the diazoamide precursor, consistent with studies of Tomioka et al.[6] Moreover, Tomioka demonstrated that methanol does not completely suppress γ-lactam formation relative to cyclohexane (67% of the γ-lactam is carbene-derived, and 33% is formed by a RIES mechanism).[6,7] If we assume that the extinction coefficients of γ-lactam and AE are similar, as predicted by the calculations reported in Table S1, the yield of γ-lactam formed from the RIES pathway is ~30% (see the transient absorption spectrum at 3050 ps in Figure 2), which is consistent with the previously reported chemical analyses.[6,7]

Significantly, a new transient species with a band peaking at 1706 cm^{-1} was observed in CH_3OD. Even though this band overlapped one of the β-lactam doublet peaks, it had a decay time constant of 102 ± 12 ps (Figure S6b), and remarkably, its decay correlated with the growth of the AE band at 1640 cm^{-1} (109 ± 10 ps, Figure S7). The carrier of the transient band at 1706 cm^{-1} is assigned to the singlet carbene on the basis of computational results (Figure S3). Another assignment of the carrier of this band is the cation formed by protonation of the singlet carbene, but this is not consistent with theory (Table S1). The singlet carbene was readily detected in CH_3OD relative to chloroform because (1) quantum-mechanical calculations predict that the vibrational band of the singlet carbene in methanol is less obscured by other species (Figures S1 and S2), (2) this band has a larger intensity in methanol than in chloroform (Table S1), and (3) VC is faster in methanol than in chloroform and obscures the carbene spectra to a lesser extent.

The transition states for β-lactam and γ-lactam formation from the singlet carbene were located with density functional theory (DFT) methods (Figure S8, Tables S2 and S3). The energy barrier for γ-lactam formation (4.4 kcal/mol) is predicted to be 1.8 kcal/mol less than that for β-lactam (6.2 kcal/mol), consistent with the selective formation of γ-lactam from singlet carbene. Transition state theory predicts that the lifetime of the relaxed singlet carbene is 271 ps at 298 K. This is consistent with the 190 ± 42 ps growth time constant for γ-lactam in chloroform.

In summary, our experiments indicate that in chloroform, both β- and γ-lactams are formed from the diazoamide precursor via RIES, and γ-lactam is also formed by isomerization of relaxed singlet carbene. In methanol-O-*d* both carbene decay and the rise of amide ether product are observed directly. The predictions of DFT calculations are consistent with these experimental observations.

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Supporting Information Available: Descriptions of the spectrometers, Figures S1−S8, and Tables S1−S3. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The fast component observed in $CHCl_3$ is consistent with the observation that singlet carbene is observed in $CHCl_3$ and overlaps with γ-lactam.
(13) We posit that the diazo excited state abstracts a hydrogen atom from a C−H bond to form a singlet biradical, which cyclizes to form the two lactams. The putative biradicals were not observed.
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