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Weinreb Amides in Carbene Chemistry: A Time-Resolved IR Investigation into a Potential Intramolecular Stabilization Mechanism

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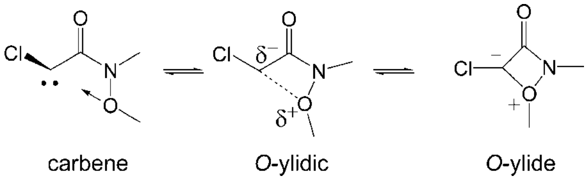
ABSTRACT



A chloromethylhydroxamiccarbene was generated photochemically in an attempt to form an intramolecularly stabilized carbene. A rapidly formed intermediate at 1645 cm^{-1} decayed with an observed rate of 1.99 × 10^6 s^{-1}. Other intermediates were also observed. These also decayed, albeit much more slowly ($k_{obs} = 3.47 \times 10^3$ and 1.98×10^4 s^{-1}). Multiple intermediates are apparently a function of both the proximal *N*,*O*-dimethylhydroxamic ester and multiple conformers of both the carbene and precursor.

The search for stable carbenes resulted in a clear set of concepts for stabilizing a singlet carbene center. Subsequently, heteroatoms bonded to the carbene carbon are a common motif in stable carbene chemistry. Strategies for stabilizing highly reactive carbenes are also known, and efforts to expand these strategies continue to evolve along with similar efforts in stable carbene chemistry,[1,2] *N*-heterocyclic carbene (NHC) chemistry,[,2] and remote NHC complexation.[3]

Intermolecular interactions are also known to stabilize carbenes and, in an early example of this, it was observed that dioxane could provide some stabilization to the singlet state of phenylcarbene.[4] Since this seminal contribution others have also looked for, and found, evidence for the solvation of other carbenes.[5−10] Ethereal solvents have often been used, and so the manner in which one describes such

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(1) Arduengo, A. J.; Dias, H. V. R.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530–5534.

(2) Sole, S.; Gornitzka, H.; Schoeller, W. W.; Bourissou, D.; Bertrand, G. *Science* **2001**, *292*, 1901–1903.

(3) Schuster, O.; Yang, L.; Raubenheimer, H. G.; Albrecht, M. *Chem. Rev.* **2009**, *109*, 3445–3478.

(4) Tomioka, H.; Ozaki, Y.; Izawa, Y. *Tetrahedron* **1985**, *41*, 4987–4993.

(5) Khan, M. I.; Goodman, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 6635–6636.

(6) Tippmann, E. M.; Platz, M. S.; Svir, I. B.; Klymenko, O. V. *J. Am. Chem. Soc.* **2004**, *126*, 5750–5762.

(7) Moss, R. A.; Wang, L.; Weintraub, E.; Krogh-Jespersen, K. *J. Phys. Chem. A* **2008**, *112*, 4651–4659.

(8) Moss, R. A.; Tian, J.; Sauers, R. R.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **2007**, *129*, 10019–10028.

(9) Moss, R. A.; Wang, L.; Odorisio, C. M.; Zhang, M.; Krogh-Jespersen, K. *J. Phys. Chem. A* **2010**, *114*, 209–217.

(10) Wang, J.; Kubicki, J.; Gustafson, T. L.; Platz, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 2304–2313.

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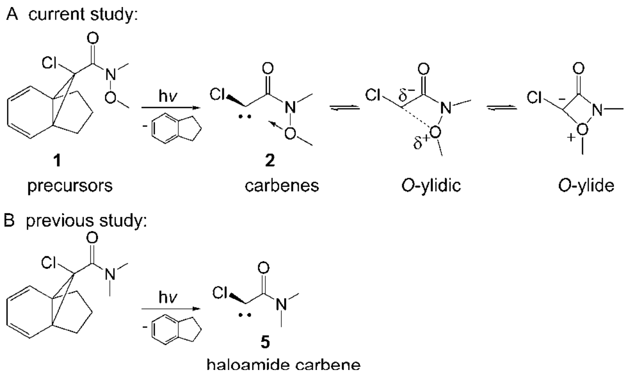
a complex is related to the length of the oxygen−carbene carbon bond (O−C bond). Useful descriptors have been provided by Moss,[7] where the term ylide was reserved for the true oxonium ylide, or “*O*-ylide”, where the O−C bond length is nearly the same as a fully formed O−C ether bond. The term “*O*-ylidic” would begin to apply when the O−C distance exceeds what is typical of this bond distance. Such definitions were found to be useful descriptors.

Ylides with O, S, or P have been featured in various synthetic organic transformations; and intra- and intermolecular examples are known.[11−14] With reactive intermediates, theoretical methods have yielded insight into intermolecular *O*-ylidic complexes[15] and only more recently have experimental results appeared for the direct characterization of intramolecular *O*-ylides.[16] In this work, we sought to expand our understanding of *intramolecular* O−C complexes with a systematic investigation of a carbene that was designed to form such complexes.

We introduced the functional group developed by Weinreb[17] onto a Jones−Moss non-nitrogenous carbene precursor[18] to generate precursor **1** (Scheme 1). The hypothesis was that a strategically placed intramolecular oxygen lone pair (such as that featured on the Weinreb amide *N*-methoxy group) is capable of donating electron density to the empty orbital of a singlet carbene (Scheme 1). To test this hypothesis, carbene precursor **1** was synthesized and with similar expectations to other chlorocarbonyl carbenes[19] photolyzed with the anticipation of generating the free singlet carbene. Time-resolved infrared (TRIR) spectroscopy was used to monitor intermediates.

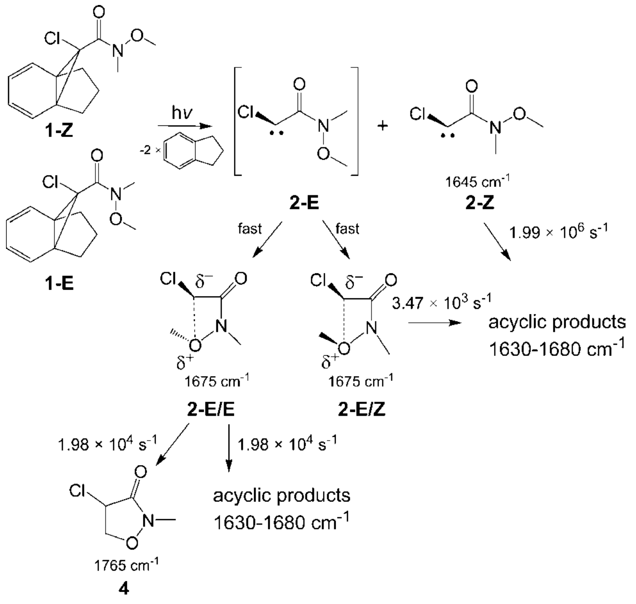
Scheme 1



Carbene precursor **1** was crystallized whereupon it was observed that the hydroxamic ester oxygens were in the *cis*, or *Z*, orientation (Supporting Information). However, a 1:1 ratio of conformers was observed in solution by NMR spectroscopy (Supporting Information). The precursor’s solution-phase properties and the presence of multiple precursor conformers posed interesting problems in our analysis (vide infra).

Photolysis of **1** in the absence of trapping agents resulted in a signal resolved at 1645 cm^{-1} that formed faster than the resolution of the instrument (ca. 50 ns). Consistent with the notion that the precursor is present as a mixture of two conformers, we have assigned this signal to overlapping signals from free singlet carbenes **2-*E*/*E***, **2*E*/*Z***, and **2-*Z*** (Scheme 2). A decay of the 1645 cm^{-1} signal ($k_{\text{obs}} = 1.99 \times 10^6\ \text{s}^{-1}$) correlated reasonably well with the formation ($k_{\text{obs}} = 1.86 \times 10^6\ \text{s}^{-1}$) of a second signal that was resolved at 1675 cm^{-1} (Figure 1). The latter signal is assigned to acyclic product formation arising explicitly from **2-*Z***. These signals overlap with an intense precursor depletion band and so the true maxima of a given peak may be obscured by such events (Supporting Information). For such experimental reasons, some secondary decay events were also resolved at 1675 cm^{-1}, but these are attributable to different intermediates: **2-*E*/*E*** and **2-*E*/*Z*** (Figure 2). This second decay event was fit to a double exponential equation that revealed two observed rates: $k_{\text{obs1}} = 1.98 \times 10^4\ \text{s}^{-1}$ and $k_{\text{obs2}} = 3.47 \times 10^3\ \text{s}^{-1}$, to be discussed below.

Scheme 2



One would expect the relative conformation of a free carbene to affect the reaction pathway, and ultimately the distribution of products. And, indeed, this has been shown

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[11] Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263–309.

[12] Uemura, M.; Watson, I. D.; Katsukawa, M.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 3464–3465.

[13] Clark, J. S.; Guerot, C.; Wilson, C.; Blake, A. J. *Chem. Commun.* **2007**, 4134–6.

[14] Vignolle, J.; Donnadieu, B.; Bourissou, D.; Soleilhavoup, M.; Bertrand, G. *J. Am. Chem. Soc.* **2006**, *128*, 14810–14811.

[15] Krogh-Jespersen, K.; Yan, S.; Moss, R. A. *J. Am. Chem. Soc.* **1999**, *121*, 6269–6274.

[16] Garcia-Garibay, M. A.; Dang, H. *Org. Biomol. Chem.* **2009**, *7*, 1106–14.

[17] Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.

[18] Hartwig, J. F.; Jones, M., Jr.; Moss, R. A.; Lawrynowicz, W. *Tetrahedron Lett.* **1986**, *27*, 5907–5910.

[19] Scott, A. P.; Platz, M. S.; Radom, L. *J. Am. Chem. Soc.* **2001**, *123*, 6069.

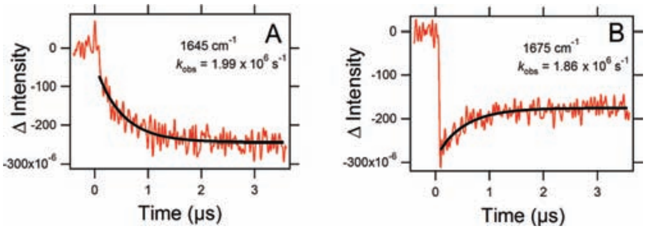

Figure 1. Kinetic traces observed at (A) 1645 and (B) 1675 cm^{-1} following 266 nm laser photolysis of **1** in argon-saturated dichloromethane; these traces are attributed to **2-*Z***. The red curves are experimental data; the black curves are the calculated best fit to a single exponential function.

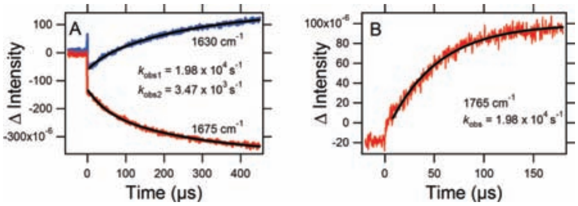

Figure 2. Kinetic traces observed at (A) 1630 and 1675 cm^{-1} and (B) 1765 cm^{-1} following 266 nm laser photolysis of **1** in argon-saturated dichloromethane; these traces are attributed to **2-*E*/*E*** and **2-*E*/*Z***. The red and blue curves are experimental data; the black curves are the calculated best fit to either a double exponential function for both the 1630 and 1675 cm^{-1} signals or a single exponential function for the 1765 cm^{-1} signal.

in several previous studies.[20−22] Moreover, the consequence of the carbene *precursor's* conformation, although not as common a topic, has also been addressed for a number of α-diazo ketones and esters.[23−25] Given such precedents, our mechanistic interpretation is based on the near simultaneous generation of **2-*E*/*E***, **2*E*/*Z***, and **2-*Z*** (Scheme 2). Theory predicts that the infrared signal of these conformers would be separated by just 14 cm^{-1} (**2-*E*/*E*** and **2-*E*/*Z*** = 1672 cm^{-1}; **2-*Z*** = 1658 cm^{-1}), with **2-*E*/*E*** 2.7 kcal/mol lower in energy than **2-*Z***. A calculated rotational barrier of 17.2 kcal/mol likely prevents interconversion of **2-*E*** and **2-*Z*** on the time scales explored here. It should also be noted that the interconversion of **2-*E*/*E*** and **2-*E*/*Z*** must be slower than other reaction pathways since a biexponential was observed for the decay.

Other support for our assignments comes from the similarities between carbene **2** and the structurally related haloamide carbene **5** (Scheme 1). In Freon-113, carbene **5** has a lifetime of 750 ns, as determined by TRIR spectroscopy, and the study of **5** was used to inform the assignments here.[6] Given the similarities between these two carbenes, we propose that **2-*Z*** is the initial species decaying with a 500 ns lifetime. We have excluded the possibility of β-lactam formation from **2-*Z***, although β-lactams are known to form from amido carbenes derived from *N*,*N*-ethyldiazoacetamide,[26−28] because new TRIR or ^{13}C NMR signals were not resolved in the regions indicative of a β-lactam.

Again, **2-*E*/*E*** and **2-*E*/*Z*** are calculated to be lower in energy than **2-*Z***. It is intriguing to speculate that **2-*E*/*E*** and **2-*E*/*Z*** have been further stabilized by the *N*-methoxy oxygen, and one metric of this is the internuclear O−C bond length. In the lowest energy conformation of **2-*E*/*E***, the O−C distance was calculated to be on the order of 2.43−2.67 Å, depending on the functional and basis set (Supporting Information). Such distances are shorter than the O−C bond distance reported by Garcia-Garibay and Dang, where an internuclear distance of 3.85 Å was observed in an intramolecularly formed oxonium ylide generated in the crystalline solid state.[16] Conversely, our calculated O−C distances are much longer than those found in typical ether or oxonium ylide O−C bonds (∼1.50 Å). When considering the definitions proposed by Moss, this suggests that the conformers of **2-*E*** are more "*O*-ylidic" in nature. It should also be mentioned that a fully formed *O*-ylide, as shown in Scheme 1, was not found during geometry optimizations. A stationary point was found when the O−C distance of **2-*E*/*Z*** was frozen at 1.74 Å; however, it was 3.3 kcal/mol higher in energy than **2-*E*/*Z***.

Next, we considered the origin of the double exponential required to fit the less rapid decay of the secondary intermediates observed at 1675 cm^{-1} (Figure 2). Some insight comes from the observation that **2-*E*** exists in two unique conformations where the Cl and O-methyl groups may adopt a further *cis* or *trans* relationship (Figure 3). These conformations were calculated to have the same C═O IR frequency and differed by less than 0.1 kcal/mol in energy (Supporting

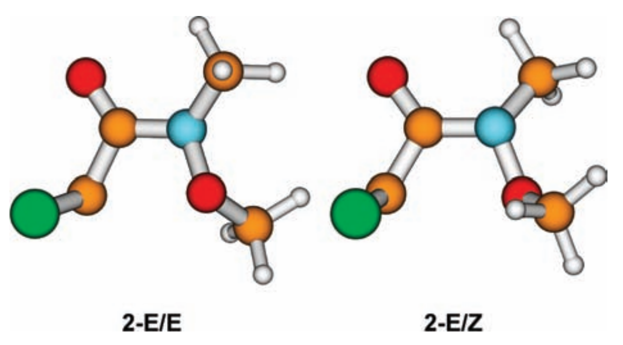

Figure 3. Optimized carbene geometries.

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(20) Kesselmayer, M. A.; Sheridan, R. S. *J. Am. Chem. Soc.* **1986**, *108*, 99–107.

(21) Kaplan, F.; Meloy, G. K. *J. Am. Chem. Soc.* **1966**, *88*, 950–956.

(22) Thamattoor, D. M.; Jones, M., Jr.; Pan, W.; Shevlin, P. B. *Tetrahedron Lett.* **1996**, *37*, 8333–8336.

(23) Wang, Y.; Yuzawa, T.; Hamaguchi, H.-o.; Toscano, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 2875–2882.

(24) Wang, J.; Burdzinski, G.; Kubicki, J.; Platz, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 11195–11209.

(25) Wang, Y.; Toscano, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4512–4513.

(26) More accurately, the β-lactams are thought to form from the excited state of the *N*,*N*-ethyldiazoacetamide used by Tomioka and others. This is an important distinction because our indan precursors would not suffer from this mechanism.

Information). Figure 3 shows why carbenes **2-*E*/*E*** and **2-*E*/*Z*** might be expected to yield cyclic and/or acyclic products. In carbenes like **2** and **5**, the singlet carbene lone pair seeks to conjugate with the adjacent C═O, which results in carbene carbon−Cl bonds rotating nearly perpendicular to the plane defined by the amide N─C═O (Figure 3).[19] Only in **2-*E*/*E*** do the carbene lone pair and vacant p orbital orient in such a way that only a slight rotation is required for favorable C−H insertion with the *O*-methyl C−H bonds. In **2-*E*/*Z***, however, the carbene lone pair points to the opposite face of the molecule, away from the *O*-methyl group entirely. Thus, carbene **2-*E*/*Z*** forms only acyclic products, but carbene **2-*E*/*E*** forms both acyclic products and cyclic product **4**, which theory predicts will appear at 1765 cm^{-1} (Scheme 2).

Photolysis of **1** in the presence of carbene traps afforded other insights. Photolysis in THF or dioxane resulted in TRIR absorbances near 1560 cm^{-1} (Supporting Information). This is consistent with the formation of *intermolecularly* formed carbene−ether ylides.[6] There was no evidence for the formation of additional species, such as cyclic **4**. From this it was concluded that the bimolecular rates for the reaction of all conformers of **2-*Z*** and **2-*E*** with these additives must be comparable, and/or the formation of **4** was now below the limit of detection. Bimolecular rate constants were determined by monitoring the 1645 cm^{-1} signal (Supporting Information) at varying concentrations of cyclohexene ($k_{\mathrm{cyclo}} = 6.5 \times 10^6\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$) or dioxane ($k_{\mathrm{diox}} = 9.37 \times 10^6\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$). The rate constants are similar to previous values reported for carbene **5** with the traps tetramethylethylene ($k_{\mathrm{TME}\text{-}\mathbf{5}} = 1.2 \times 10^7\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$) and THF ($k_{\mathrm{THF}\text{-}\mathbf{5}} = 1.6 \times 10^7\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$).[6]

Again, unique to this study were the "longer-lived" intermediates. Are these intermediates *O*-ylidic in nature? The TRIR spectra are masked somewhat from a multitude of events occurring in the same region, including precursor bleaching, and so we may only be resolving a given signal's shoulder and not the true maxima. Figure 2 in the Supporting Information shows stable peaks occurring above 1780 cm^{-1}, and across the region 1730−1630 cm^{-1}. On the basis of the unresolved rate of appearance, and similarity with known spectra, we have assigned the peaks above 1780 $\mathrm{cm}^{-\mathbf{1}}$ to Indane, the product of photolysis. Even though the 1630−1675 cm^{-1} region is composed of a mixture of ill-defined components,[29] the observation of "longer-lived" secondary intermediates, such as **2-*E*/*E*** and **2-*E*/*Z***, is still unprecedented among similarly substituted carbenes; and it is intriguing to speculate that the lone pair from the *O*-methyl group of the Weinreb amide is indeed stabilizing an *O*-ylidic carbene.

Certainly, Tomioka's use of triptycyl and ortho-substituents as "protecting" groups around the carbene center showed that diphenylcarbene's half-life could be extended from the ns into ms regime or longer with this strategy.[30,31] If we consider that the lifetime for haloamide carbene **5** was 750 ns, and that a subtle structural change results in intermediates with apparent lifetimes on the order of ∼250 μs, then this work may well indicate another general strategy for carbene stabilization—one potentially suited for further exploration and development.

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Supporting Information Available: Spectra, detailed descriptions of experimental procedures, and calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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[27] Tomioka, H.; Kitagawa, H.; Izawa, Y. *J. Org. Chem.* **1979**, *44*, 3072–3075.

[28] Zhang, Y.; Burdzinski, G.; Kubicki, J.; Platz, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 9646–9647.

[29] Steady-state photolysis (320 nm) of **1** in neat CH_2Cl_2 in a glass vial did not yield any isolable products although >50% of the **1** reacted; although **4** is calculated to be 72 kcal/mol more stable than **2-*E*/*E***, compound stability or TRIR photolysis at 266 nm may account for these differences. Photolysis in neat 2,3-dimethylbutene did yield a carbene addition product (Supporting Information).

[30] Tomioka, H.; Nakajima, J.; Mizuno, H.; Sone, T.; Hirai, K. *J. Am. Chem. Soc.* **1995**, *117*, 11355–11356.

[31] Monguchi, K.; Itoh, T.; Hirai, K.; Tomioka, H. *J. Am. Chem. Soc.* **2004**, *126*, 11900–11913.