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Looking for Stable Carbenes: The Difficulty in Starting Anew

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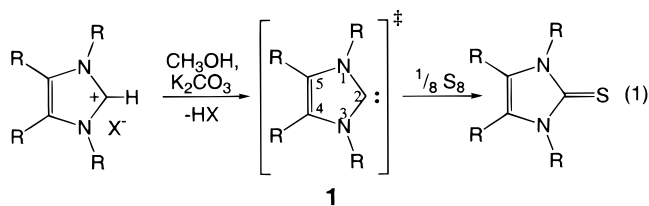
Introduction

A decade ago we initiated research, the goal of which was isolation of a stable carbene. Our success has helped to catalyze a resurgence of interest in readily available and easily handled carbenes. Research on stable (nucleophilic) carbenes is again a popular theme worldwide. Efforts in the general area of stable carbenes now focus not only on chemistry of the carbenes themselves but also on their applications to other chemical systems, where their chemical properties create technical opportunities that are unavailable with other functional groups. The quest for isolable carbenes is a long saga whose origin can be traced back to the first half of the 1800s. A recently published history of this quest provides an important backdrop for the research described in this Account.¹ It is the intent of this Account to delineate the events and environment that led to the report from DuPont laboratories of the first isolation of a stable crystalline carbene.

Anthony Arduengo was born in Tampa, Florida, in 1952. He studied chemistry at the Georgia Institute of Technology, receiving his B.S. in 1974 and Ph.D. in 1976. After beginning his career with DuPont, he moved to University of Illinois—Urbana as a member of the Organic Faculty. From 1984 to 1998, he worked as a member of the research staff at DuPont, advancing to Research Leader/Research Fellow. Professor Arduengo currently holds the Saxon Chair in Organic Chemistry at the University of Alabama (Tuscaloosa) and is adjunct professor of chemistry at the Technical University in Braunschweig, Germany. His research interests include unusual bonding arrangements, main group element chemistry, and various aspects of applied chemistry.

Getting Started

Although the isolation of an imidazol-2-ylidene did not occur until 1990, our interest in key compounds necessary for its synthesis originated in the 1970s. In an effort to find exceptionally stable carbenium ions that would make suitable substituents for dipole-stabilized thiocarbonyl ylides, our attention was drawn to imidazole-2-thiones.^{2,3} Imidazole-2-thiones are commonly prepared by reaction of an imidazolium ion with sulfur in the presence of methanolic potassium carbonate (eq 1).^{4–6} In this reaction, imidazol-2-ylidenes (carbenes) formed by deprotonation of the imidazolium cations were presumed to be intermediates.

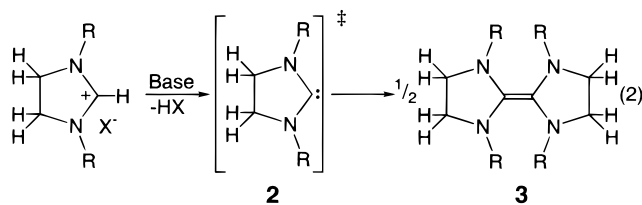


The imidazole-2-thione synthesis is remarkably insensitive to varied conditions that allow different substituents to be accommodated on the imidazole ring.⁷ The reaction can even be run under dry air; however, moisture is not well tolerated. This reaction system simply does not behave as if unstable or delicate intermediates are involved, and no olefin byproducts are observed from dimerization of the putative carbene intermediates.

Attention to History

Even though carbenes could reasonably be expected to be intermediates in imidazole-2-thione syntheses and there was some anecdotal evidence to suggest that these intermediates may possess unusual stability, pursuit of these particular carbenes did not seem warranted based on other literature precedents. H.-W. Wanzlick had recognized earlier that the electron-rich imidazole nucleus should be capable of stabilizing a carbene center at the 2-position, between the two nitrogens.⁸ Much of Wanzlick's work actually centered on the saturated imidazoline

ring (2), in which the double bond between carbons 4 and 5 is absent (eq 2).^{9–20} There are, however, reports by Wanzlick of his work involving unsaturated imidazole analogues^{21,22} and a closely related triazole system.²³ Nonetheless, no carbenes were reported as isolable in any of these cases.



Wanzlick's work on these carbene systems was influenced by earlier false claims of the isolation of carbenes.¹ Also playing an important role was the fact that Wanzlick's academic mentor (Doktorvater) was Helmuth Scheibler, for whom he held a great admiration and who had also been active in searching for stable carbenes (dialkoxycarbenes) some years earlier.²⁴ Additionally, Wanzlick's work occurred at a time when the discipline of organic chemistry, because of advances in technology, was still coming to terms with differences between what a molecule is (in its ground state) and how it reacts.

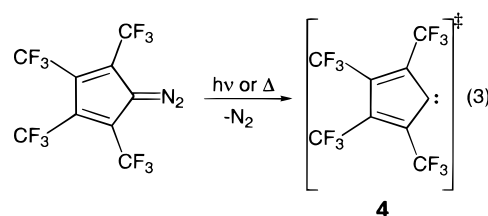
Before the advent of modern analytical methods, traditional organic chemistry was a science that was rich with the descriptive chemistry of how and with what a molecule or substance reacts. Chemists learned batteries of reactions that could be used to classify a substance by the functional groups that it contained. Thus, associated with every organic functional grouping are expectations of how and with what that functional group should react. With respect to carbene chemistry, the reader is referred to an important Account of "carbenic reactivity" in connection with cyclopropanation.²⁵ The idea that the reactive state of a molecule and its isolated ground state (unperturbed by external reagents) might differ was not a useful concept in organic chemistry because it could not be tested. The identity of a molecule was determined primarily by how it reacted with other compounds. Only in the last half of the 20th century did advances in technology enable chemists to probe a molecule's structure with a minimum of perturbation to its ground state. Wanzlick, and Scheibler before him, both relied primarily on reactivity to characterize their compounds. The one common analytical method that was applied by both Wanzlick and Scheibler was molecular weight determination or estimation. In both cases, results were at best inconclusive and at worst misleading.

Although Wanzlick did uncover a great deal of reactivity that seemed to be characteristic of nucleophilic carbenes, the carbenes themselves were never isolated. During the course of Wanzlick's investigation of imidazolin-2-ylidenes (2), an important article was published by D. M. Lemal and co-workers.²⁶ Lemal's work indicated that chemistry similar to that which had been attributed by Wanzlick to carbenes was also observed if one began with the olefin that was essentially the dimer of an imidazolin-2-ylidene

(3). Scrambling experiments allowed Lemal to show that, under his reaction conditions, carbenes were not intermediates, but rather carbene-like reactions could proceed directly from olefins. Although carbene-like reactivity can be observed from olefins (carbene dimers), this does not exclude the intermediacy of carbenes in Wanzlick's experiments. It is also noteworthy that dimers of imidazol-2-ylidenes (1) are observed only when the nitrogens are restricted to nonplanar geometries²⁷ or C⁴ and C⁵ bear powerful electron-withdrawing groups.²⁸ Within Wanzlick's research group, imidazolin-2-ylidenes were referred to as "das doppelte Lottchen", suggesting a mischievous duality between two carbenes and their dimer.²⁹ There has recently been a preliminary report that there may, indeed, exist an uncatalyzed equilibrium between imidazolin-2-ylidenes and their dimers, but further work is necessary to place these results in perspective against earlier reports.³⁰

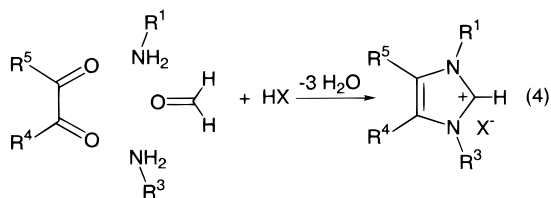
Temporary Diversions

With this volume of prior literature and the checkered history of stable carbenes as a backdrop, our interest in imidazol-2-ylidenes waned. However, curiosity about imidazol-2-thiones continued. We completed work to improve the imidazol-2-thione synthesis, and we showed that selenones and tellurones could be synthesized by similar procedures.⁶ Our interest in carbenes temporarily shifted to highly electrophilic carbenes such as 2,3,4,5-tetrakis(trifluoromethyl)cyclopentadien-1-ylidene (4). The chemistry of these highly electron deficient carbenes allowed the synthesis and isolation of a number of unusual compounds such as carbonyl, halonium, and nitrilium ylides.³¹



Getting Back into the Game

In 1988, a commercial need arose for catalysts in various polymer cross-linking applications.^{7,32–35} The imidazol-2-thiones seemed well suited to these applications because they are very powerful nucleophiles but are not strong bases. Other potential uses were also developed that could help drive commercialization of these thiones.^{36,37} Existing syntheses of the imidazol-2-thiones were not well suited for large-scale manufacturing processes because of material costs, yield, separation, and byproduct problems. A more convenient synthesis of imidazol-2-thione was developed,⁷ along with a new one-step synthesis of imidazolium ions (eq 4) that allowed the production of substituted imidazolium ions that were not accessible by conventional routes.³⁸ This new imidazolium ion synthesis would later prove essential for our reentry into the quest for stable carbenes.

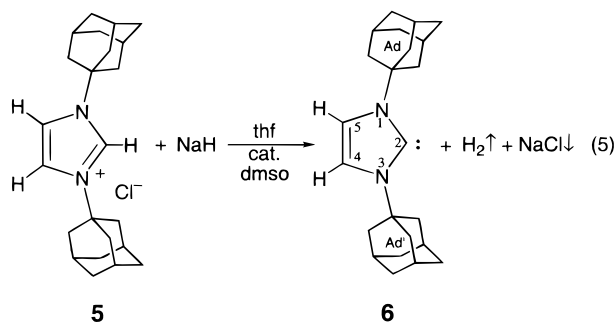


As progress toward commercialization of imidazol-2-thiones continued, we ran reactions with a very wide range of substituents that again seemed to underscore the extreme stability and tolerance of carbene intermediates in these reactions. Pilot-plant tests were not always conducted with the same attention to detail that one can achieve when working on a small laboratory scale. Adventitious water and air were sometimes present in the larger plant reactions. Nonetheless, the ease with which these reactions succeeded served to bolster our belief that the carbene intermediates were remarkably stable. Our industrial research environment at that time held in-depth scientific investigation and understanding as essential factors for the success of businesses that depend on technology and its applications. These factors combined to renew our interests in isolating stable carbenes from these reactions.

Novel imidazolium ions that were available from our new syntheses allowed us to attempt the generation of imidazol-2-ylidenes (**1**) that were not accessible to Wanzlick. This new technology made it possible for us to do more than simply repeat Wanzlick's chemistry, and therefore our hopes were high that these new experiments would lead to the actual isolation of stable carbenes. Thus, using a combination of steric and electronic effects, we decided to investigate the chemistry of imidazol-2-ylidenes bearing large substituents on nitrogen in hopes of isolating a stable carbene.

New Results

Our first attempt to isolate a stable carbene was through use of 1-adamantyl substituents on the imidazole nitrogens (eq 5). Anticipating that the desired carbenes would be marginally stable at best, for a base we chose sodium hydride with catalytic dimethyl sulfoxide (to generate the dimsyl anion) so that the byproducts (sodium chloride and hydrogen) could be easily separated from the carbene in a tetrahydrofuran (thf) reaction medium.



The deprotonation of imidazolium ion **5** proceeded smoothly, as monitored by hydrogen gas evolution to give

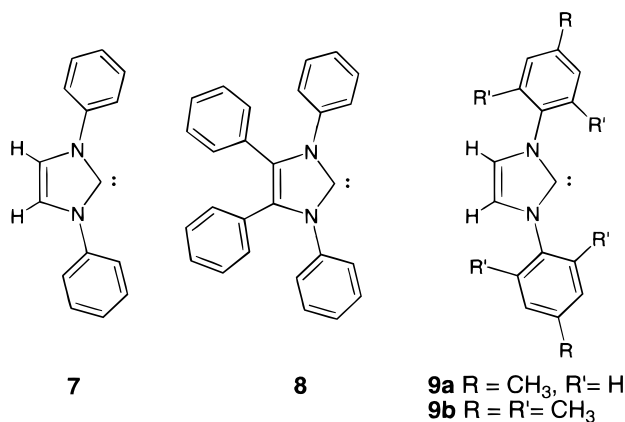
carbene **6**.³⁹ Imidazol-2-ylidene **6** proved to be a remarkably stable carbene both in solution and in the solid state. A solution of this carbene in thf-*d*₈, sealed under a few atmospheres of CO, has shown no decomposition or change after 7 years at room temperature. Carbene **6** crystallizes from many solvents, readily forming very large crystals (up to several millimeters on a side), and it does not decompose at its melting point of 240 °C.⁴⁰

The crystal structure of carbene **6** revealed features characteristic of a singlet carbene.³⁹ Particularly noteworthy was the valence angle of 102.2° at the carbene center. Although the structure of a singlet carbene had not been previously determined, numerous calculations were and have become available to predict the structure. Common among all the theoretical models of singlet carbenes is a small valence angle of about 102° at the carbene center.^{41–49} Thus, structural features of imidazol-2-ylidenes reflect those widely predicted for singlet carbenes.

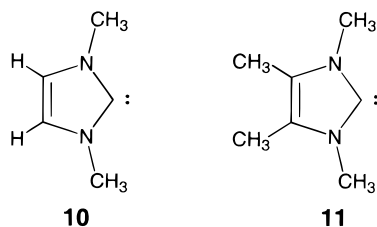
Comparison of the structure of carbene **6** with that of its precursor carbenium (imidazolium) ion **5** was also instructive. The C–N bonds to the carbene center actually lengthen relative to those of the carbenium ion. Although it was tempting to attribute this increase in bond length to a decrease in π -delocalization or $p\pi$ – $p\pi$ interaction in the carbene relative to the carbenium ion, it is important to remember that there are also substantial changes in hybridization at the carbene center that influence bond distances. These hybridization changes strongly affect the σ -system. As more s-orbital character is used to stabilize the in-plane lone pair of electrons at the carbene center, the N–C σ -bonds take on more p-character at the carbene center. This would be expected to lead to an increase in N–C² distances on the basis of σ -effects alone. Because σ -bonds are energetically more important than π -bonds, these σ -effects are likely to be important contributors to structural changes. In fact, if one considers ¹A₁ :CH₂ and the methyl cation, there are analogous changes in the C–H distances for this pair of molecules for which π -interactions cannot play a role.⁵⁰ Thus, structural changes that occur in an imidazol-2-ylidene upon protonation (decrease in C²–N distances and increase in the N–C–N angle) appear to be typical for protonation of all singlet carbenes.

After a detailed consideration of the structure of carbene **6** and a preliminary investigation of some of its chemistry, our attention was drawn back to Wanzlick's work. If carbene **6** was so stable, why had not Wanzlick isolated either of the two imidazol-2-ylidenes that he had studied?^{21,22} Wanzlick's two imidazol-2-ylidenes (**7** and **8**) both bore phenyl substituents on nitrogen. These phenyl substituents may have been unfortunate choices, either because of π - or σ -effects. We decided to synthesize aryl-substituted imidazol-2-ylidenes that would allow separation of possible π - and σ -effects. To this end, *p*-tolyl- (**9a**) and mesityl-substituted (**9b**) imidazol-2-ylidenes were prepared.

Both aryl carbenes **9a** and **9b** were isolated as stable crystalline materials.⁵¹ These aryl-substituted carbenes melt with decomposition around 150 °C, but they can be



isolated and manipulated with ease under a dry nitrogen atmosphere at room temperature. Thus, there appeared to be no special σ - or π -effects for aryl substituents. The X-ray structures of these carbenes revealed a central imidazol-2-ylidene ring that was very similar to that in **6**. It was also possible to show that mildly electron-accepting aryl groups are well tolerated as substituents on nitrogens of imidazol-2-ylidenes. This latter point was illustrated by the isolation of the 1,3-bis(*p*-chlorophenyl)imidazol-2-ylidene.⁵¹ The isolation of **9a,b** and 1,3-bis(*p*-chlorophenyl)imidazol-2-ylidene raised another question about the need for steric stabilization in the imidazol-2-ylidenes. When turned on edge, as in **9b**, these aryl substituents offer a steric effect in the plane of the carbene center that is similar to a that of simple methyl group. Was there a need for large bulky groups on the nitrogens?



The isolation of both **10** and **11** nicely illustrated that small substituents are also acceptable.⁵¹ The 1,3-dimethylimidazol-2-ylidene, **10**, is a moderately stable oil at room temperature, but tetramethylimidazol-2-ylidene (**11**) is a stable crystalline material at room temperature under nitrogen (it is pyrophoric in moist air). The X-ray crystal structure of **11** reveals geometric features very similar to those of all the earlier imidazol-2-ylidenes. The geometry of the central imidazole ring is hardly affected by the variety of substituents that we have studied. The crystal structure of **11** packs the molecules along 2-fold axes of a *C₂/c* space group, reducing the number of crystallographically unique atoms in this small molecule to 11 (including hydrogens). This fortunate packing situation allowed a detailed structural investigation using both X-ray and neutron diffraction techniques to produce a high-quality experimental electron density map of the molecule.

In contrast to what could be accomplished at the time of Wanzlick's original work, we were able to apply a number of exacting experimental techniques in order to

characterize the ground state of the stable imidazol-2-ylidenes. These methods included an electron density mapping by a combination of electron and neutron diffraction techniques,⁵² photoelectron spectroscopy,⁵³ and nuclear magnetic resonance (NMR) chemical shift anisotropy determination.⁵⁴ At the same time, a number of theoretical papers appeared which presented models for the bonding and structure in imidazol-2-ylidenes and diaminocarbenes in general.^{45–49,51} Although a variety of methods have been employed, with semantic issues aside, the agreement among these representations is good. The availability of accurate experimental data on imidazol-2-ylidenes has served as a grounding point for the various theoretical models. Unperturbed by external reagents, the ground-state electron distribution in imidazol-2-ylidenes bears a remarkable similarity to those in some of the more classical ¹A₁ carbenes, such as CF₂. For singlet CF₂ and an imidazol-2-ylidene model with only hydrogen substituents on the ring, a TCSCF wave function showed very similar mixing coefficients and electron populations at the two carbene centers.⁴⁸

The experimentally determined electron distribution in carbene **11-d₁₂** is quite interesting and provided us with a great deal of information about this simple imidazol-2-ylidene.⁵² These data may be viewed in several ways, and some of these representations are presented in Figures 1 and 2. The valence electron component of the experimental electron density is depicted in Figure 1. Figure 1a shows electron density around the carbene center itself. The illustrated plane is perpendicular to the molecular plane and incorporates the molecular 2-fold axis. In this cross section, the in-plane lone pair of electrons is visible to the right, and electron density in the π -direction is visible above and below the carbon. Clearly, the high in-plane electron density falls off to a minimum in the π -direction, consistent with the expected electron distribution for a singlet carbene. Figure 1b provides a view of a plane of electron density in the π -system 70 pm above the molecular plane. The electron density due to the nitrogen p π lone pairs of electrons is prominent. The π -component of the C⁴=C⁵ double bond is evident, but there are no other distinctive π -features. The illustration (Figure 1c) of the in-plane electron density reveals the high electronegativity of nitrogen relative to those of carbon and hydrogen (deuterium). The electron density of the in-plane lone pair of electrons at the carbene center is readily visible to the right, just outside the ring.

Another common view of such experimental electron density is found in so-called "deformation density" drawings. Deformation density is the difference between the observed electron distribution and that predicted for a "promolecule" made up of only spherically symmetric, noninteracting atoms located in their molecular positions. Deformation density is thus a representation of the electron distribution that is deformed into bonding regions between atoms. Such a representation makes it easier to see electron density that is responsible for bonding in a molecule. However, the problem of choosing

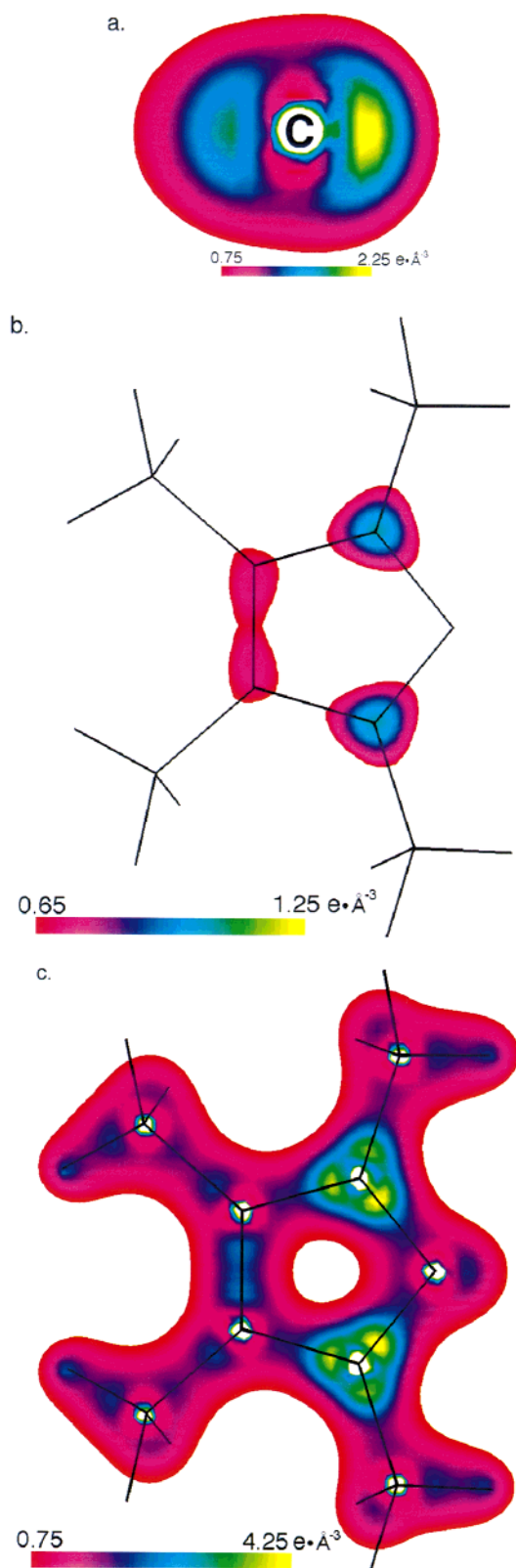


FIGURE 1. Valence electron density determined for 1,3,4,5-tetra-methylimidazol-2-ylidene. (a) Carbene lone pair electron density perpendicular to the molecular plane. The C lone pair density lies to the right of the carbon. (b) π -electron density 70 pm above the molecular plane. The nitrogen lone pairs and C–C double bond are obvious. (c) In-plane electron density. The framework σ -bonds and in-plane C lone pair are evident.

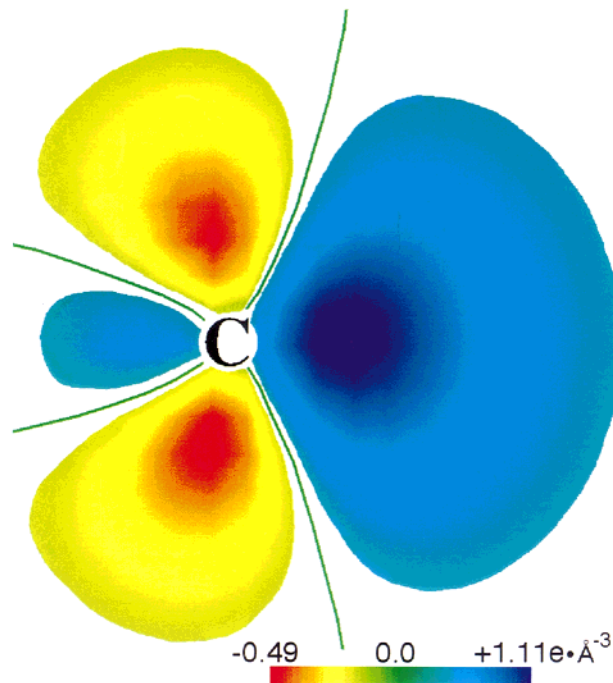


FIGURE 2. Deformation density profile at the carbene center in 11.

a suitable reference “promolecule” has been noted previously, and one should not overinterpret these drawings.^{55–57} Nonetheless, deformation density drawings are instructive. Figure 2 depicts the deformation density at the carbene in the same plane presented in Figure 1a. The carbene lone pair density is to the right of the carbon, and the p-density is in the plane of the drawing above and below the carbon. There is clearly a large surplus of electron density in the direction of the lone pair relative to a spherically symmetric isolated carbon atom. On the other hand, there is a deficit of electron density in the direction of the out-of-plane carbon $p\pi$ -orbital, as illustrated by the negative density regions (red and yellow) above and below the carbon. The deficit in electron density in the p-direction at the carbene center is striking, but one needs to remember that this deficit is relative to the two-thirds of an electron that would be placed in this region from the spherically symmetric carbon atom in the promolecule. The actual amount of electron density that one should attribute to the carbene $p\pi$ -orbital is difficult to quantify, because such an analysis is dependent on the basis set used to describe the molecule. Qualitatively, about one-third of an electron can be attributed to this π -region of space at the carbene center.

Such a precise experimental determination of electron density as described above, although highly informative, is not routinely practical. Measurement of NMR chemical shift anisotropy at the carbene center is more easily accomplished and provides information that also confirms the highly anisotropic nature of the electron distribution around the carbene center. For imidazol-2-ylidene **11**, the NMR chemical shielding tensor at the carbene center has been observed experimentally and theoretically modeled for comparison with the singlet carbenes $^1\text{CH}_2$ and $^1\text{CF}_2$.⁵⁴

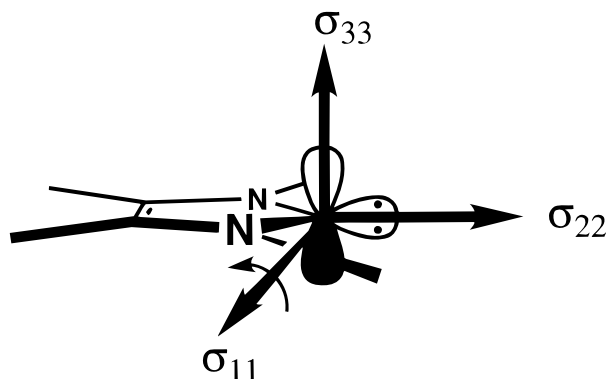
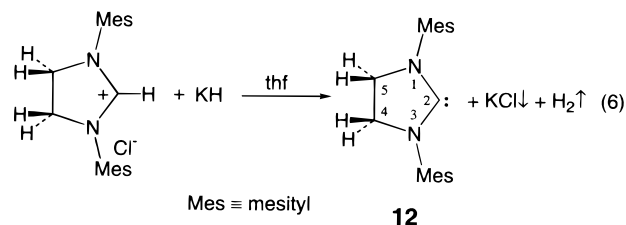


FIGURE 3. Components of the chemical shielding tensor at the carbene center in **11**.

The most characteristic component of the chemical shielding tensor in a singlet carbene is the σ_{11} component that relates the high density of the carbene in-plane lone pair with the formally unoccupied $p\pi$ -orbital at the carbene center. This tensor component is illustrated in Figure 3 and is orthogonal to the planes of the contoured density diagrams in Figures 1a and 2. This component is highly deshielding and is primarily responsible for the characteristically large downfield shift observed for carbene centers. Experimentally, measurement of the ^{13}C chemical shift of a carbene is a highly reliable method for characterizing a carbene. The imidazol-2-ylidenes exhibit ^{13}C resonances for the carbene center from about δ 210 to 220.^{39,51,58,59} The saturated imidazolin-2-ylidenes and diaminocarbenes generally have further downfield-shifted resonances for the carbene center of about δ 240–255, consistent with an even higher anisotropy at the carbene center due to a lower population of the carbene $p\pi$ -orbital.^{60–63} Various aminoxy- and aminothiocarbenes recently have been reported, and their chemical shifts range from about 250 to almost 300 ppm.^{64,65}

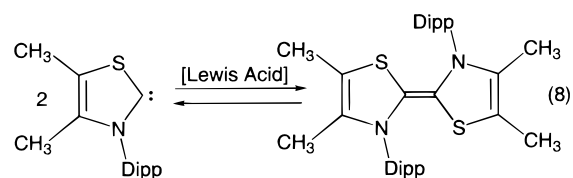
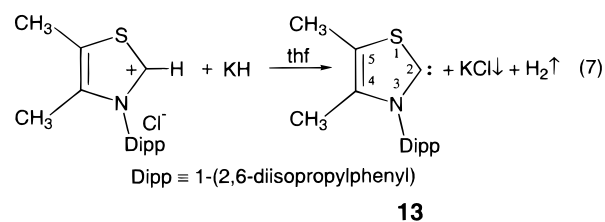
After initial reports of the isolation of stable imidazol-2-ylidenes appeared, interest in stable nucleophilic carbenes spread rapidly. The principles that had been used to create stable carbenes were soon applied to germanylenes⁶⁶ and silylenes.⁶⁷ Synthetic methods such as the reduction of the corresponding thiones also appeared and provided access to new structures.⁵⁸ The triazole ring system, which had been studied earlier by Wanzlick,²³ yielded its own contribution to a growing family of stable carbenes.⁵⁹ Amid this flurry of activity, our attention was again drawn back to Wanzlick's work. The question this time was whether saturated imidazolin-2-ylidenes could actually be isolated. The motivation for us to pursue these diaminocarbenes was the observation that many simple, unhindered imidazol-2-ylidenes were so stable and easy to make, and although delocalization undoubtedly played some role in the stabilization of the imidazol-2-ylidenes, electron density studies did not reveal a highly delocalized π -system. Similarly, comparison of imidazolium ions with their corresponding imidazol-2-ylidenes showed a substantial decrease in delocalization for carbenes compared to that for their obviously "aromatic" carbenium ions. Diaminocarbenes yielded to our efforts, and in 1995 we

reported the isolation and structural characterization of 1,3-dimesitylimidazolin-2-ylidene (**12**) (eq 6).⁶⁰



We were not the only research group to have identified the diaminocarbenes as likely targets. Alder et al. reported the isolation of an acyclic diaminocarbene (bis(diisopropylamino)carbene) in 1996.⁶¹ More recent reports of diaminocarbenes have also appeared.^{62,63}

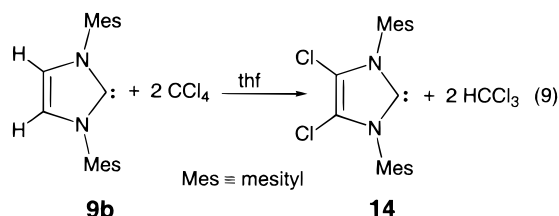
The range of stable carbene structures was now quite large, but all such structures reported up to 1996 possessed the common structural feature of nitrogen substituents on the carbene center.⁶⁸ The chemistry of vitamin B₁ suggested that sulfur should be a likely candidate for stabilization of an adjacent carbene center. This observation was not lost on Wanzlick, who had earlier studied a number of sulfur-containing carbenes.^{69–71} After efforts to find the right substituent for the nitrogen so that we could take advantage of steric effects, we were able to isolate a stable thiazol-2-ylidene (**13**) (eq 7).⁶⁴ Remarkably, not only the thiazolylidene could be isolated but its dimer (olefin) as well (eq 8).



Thiazol-2-ylidenes and their dimers provided first examples of a heterocyclic carbene for which the corresponding dimer could also be isolated. Indeed, there is a Lewis acid-catalyzed equilibrium between the carbene and dimer that can be observed under appropriate conditions.⁶⁴

There has always been an interest in the chemistry of heterosubstituted carbenes. Even before the isolation of stable analogues of these carbenes, there were early reports of reactivity derived from in situ-generated carbenes. Additional interest in this reactivity has surfaced now that these carbenes are easily handled, "bottleable" materials. Some of this chemistry has been previously reviewed,⁷² and additional reviews of this rapidly developing area will appear shortly.⁷³ Detailed comment on the reactivity derived from stable heterocyclic carbenes is

beyond the scope of this Account. We note, however, that there is an interplay between the study of reactivity of stable carbenes and insights into sources of stability for these compounds. One such case arose during a systematic study of the reactivity of imidazol-2-ylidenes and main group 14 halides. We discovered that carbon tetrachloride will actually chlorinate the 4- and 5-positions of imidazol-2-ylidenes (eq 9).⁷⁴ The resulting 4,5-dichloroimidazol-2-ylidenes possess remarkable stability and can even be handled in moist air without decomposition.



A range of stable carbenes can be made with electron-withdrawing groups in the 4- and 5-positions of the imidazole ring. Even 1,3-dimethyl-4,5-bis(trifluoromethyl)imidazol-2-ylidene has been synthesized and characterized.⁷⁵

The range of stable nucleophilic carbenes continues to grow rapidly to this day. Reports have now appeared from other laboratories of the isolation of aminooxycarbenes,⁶⁵ and as discussed above, spectroscopic properties of these new additions fit nicely into trends that emerged for ¹³C NMR spectra of carbenes. Even the parent imidazol-2-ylidene ring system bearing hydrogens on the nitrogens has now been characterized (although not isolated in a bottle).^{76,77} We finally decided to examine one of the same molecules that had eluded Wanzlick earlier. We were able to isolate 1,3,4,5-tetraphenylimidazol-2-ylidene and thus realize a dream that Wanzlick had for his research more than a quarter of a century earlier.⁷⁸

Epilogue

In the end, we were fortunate that we challenged the convention against doing further research in an area that seemed to be overworked by our predecessors. Our current research efforts continue to focus on design and synthesis of new structures and incorporation of stable carbene fragments into molecules that are engineered to perform useful tasks. The satisfaction of a successful end to a quest is always the best reward for the effort made, particularly so when the quest appears to be somewhat risky at its outset.

The skill, insight, and enthusiasm of H. V. R. Dias, S. F. Gamper, D. Khasnis, M. Tamm, T. K. Prakasha, J. R. Goerlich, R. Krafczyk, and M. Unverzagt made our work with nucleophilic carbenes possible. The excellent technical assistance of H. A. Craig, M. Kline, and U. Sharma contributed enormously to successes in this area. I am also grateful to the Alexander von Humboldt Stiftung for their support of a senior research prize that allowed completion of this text. Finally, I would like to dedicate this Account to the memory of my friend and colleague, Professor J. C. Martin.

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