

CHEMISTRY

Confirmation of Breslow's hypothesis: A carbene stable in liquid water

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In 1958, Breslow proposed that the coenzyme thiamine, also known as vitamin B₁, acted as a source of transient carbenes that facilitated the catalytic activity of various important enzymes. This was a controversial hypothesis, as, then and still now, carbenes are believed to be incompatible with water. Although evidence such as deuterium labeling experiments and the trapping of the so-called Breslow intermediate support Breslow's hypothesis, no spectroscopic evidence has ever been presented to prove that carbenes can exist or be generated in water. In this study, we disclose the synthesis and complete spectroscopic characterization by nuclear magnetic resonance and a single-crystal structure of a carbene that can be generated in water and isolated as a stable species, thus unambiguously validating Breslow's visionary hypothesis.

INTRODUCTION

Thiamine **1** (Fig. 1), more commonly known as vitamin B₁, is an essential micronutrient for human and other life. Phosphorylated forms of thiamine are essential for certain metabolic pathways (1). For example, **1**, in the form of its pyrophosphate cocarboxylase, is the coenzyme for a number of important aqueous biochemical pathways, such as the decarboxylation of pyruvic acid to acetaldehyde and the conversion of pyruvic acid to acetoin (2). The activity of these enzymes has been demonstrated to require bound **1** and is pH dependent (3). This behavior, coupled with the fact that all known crystal structures of the active sites of these enzymes contain water in the lattice (4–6), suggests that the observed catalytic processes are tolerant of water. The environment in the active site also contains a Mg²⁺ ion and the chemical reactions that do not occur in a protective hydrophobic pocket (6). Furthermore, recent studies on related transketolase demonstrate that a proton transfer to the amino group of the aminopyrimidine ring of bound **1** is assisted by a water molecule and is a key component of catalyst activation (7). In addition, **1** (8) and various other thiazolium and *N*-heterocyclic salts have been shown to catalyze related activated aldehyde reactions (Ümpolung) (9) in the presence of a base, in both aqueous and nonaqueous environments, such as the classical benzoin and acyloin condensation reactions. Although initially poorly understood, in 1958, on the basis of deuterium labeling experiments in D₂O and the fact that **1** itself could induce catalysis in water, Breslow (10) proposed that the active species generated from the thiamine residue was an *N*-heterocyclic carbene (NHC), thiazolylidene **1'**. The proposition that a carbene (11), a typically exceedingly reactive molecule featuring a divalent carbon atom and a nonbonding pair of electrons, could persist long enough to engage in exquisitely controlled chemical reactivity, let alone in water, was a visionary hypothesis. The mechanism is thought to occur in a similar fashion to the classic Lapworth pathway, proposed in

1903 (12), for the cyanide catalyzed benzoin condensation reaction. Although there has never been any spectroscopic evidence for the formation of a carbene in water, Breslow's hypothesis has been accepted by the scientific community to be correct. Another important compound proposed to be a key intermediate in these reaction pathways, the so-called Breslow intermediate, derived from the addition of an NHC to an aldehyde with subsequent tautomerization, has recently been isolated (13).

Subsequently, in 1968, Wanzlick and Schönherr (14) and Öfele (15) independently showed that NHC metal complexes could be formed by contact of an imidazolium salt with basic transition metal precursors, implying that the complexes might be generated via the formation of transient metal-free NHCs. For years, Wanzlick went on to attempt to isolate these so-called imidazolylienes but was not successful. These pioneering works paved the way for the seminal discoveries of Bertrand and colleagues (16) and Arduengo *et al.* (17) of the first bottleable carbene and NHC, namely, the liquid phosphinosilylcarbene **2'** and solid *N,N*-diadamantylimidazolylidene **3'**, respectively. The discovery of **3'** paved the way for the use of these imidazolylienes and related species such as cyclic alkyl amino carbenes (18) and carbones (19), as powerful ligands for transition metal-based catalysts and stabilizing species for reactive main-group compounds (20).

Neither of the first isolable carbenes **2'** or **3'** is air stable, presumably because of gaseous water in our atmosphere and other reactive species such as CO₂. However, Arduengo *et al.* (21) took carbene stability to a higher level with their report of the only known "air-stable" NHC **4'**, which features a doubly chlorinated imidazolylidene backbone and the carbene center flanked by two *N*-mesityl groups. The double chlorination of the backbone is thought to be key as it stabilizes the NHC lone pair via σ -inductive effects. In the manuscript, Arduengo claimed that stirred benzene solutions of this molecule open to air showed no decomposition after several days, meaning that, in principle, this carbene should be bench-top stable. It was not reported if this NHC was actually stable toward contact with water. However, it is inexplicable why benzene solutions of this compound stirred in open air do not readily react with water absorbed from the air, so the compound could, in principle, be unreactive toward liquid water. Subsequently, Denk and co-workers (22) showed that a tetrahydrofuran (THF) solution of the *t*-butyl-substituted NHC **5'**

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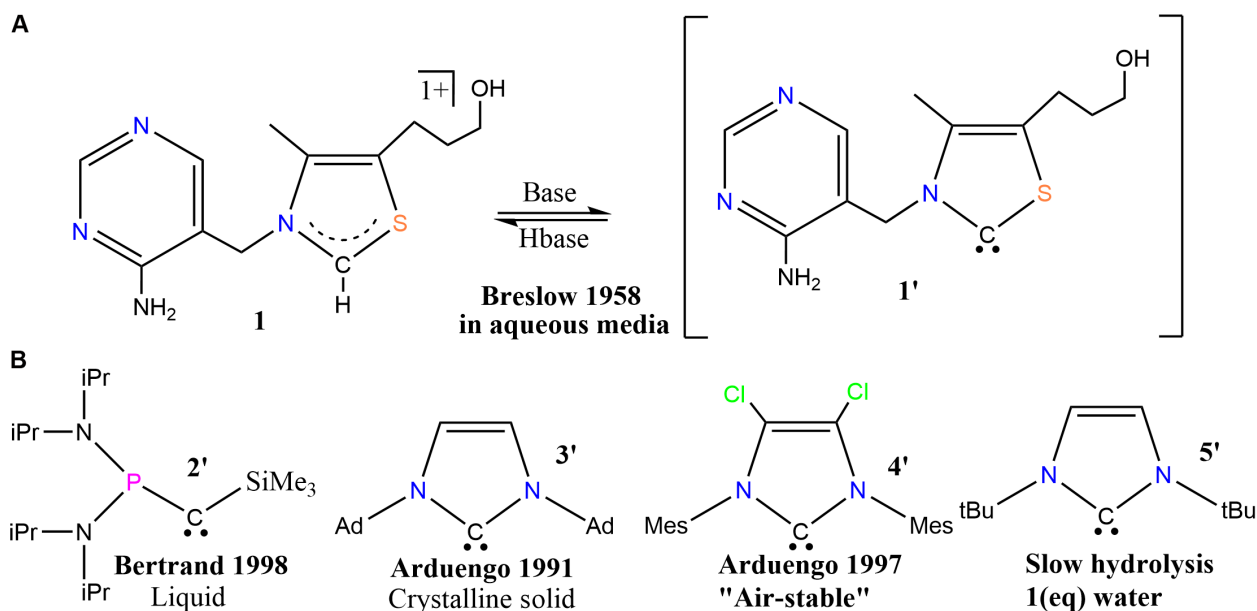


Fig. 1. Examples of carbenes. (A) Breslow's proposed NHC derived from thiamine (10). (B) Isolable carbenes of interest in chronological order (16, 17, 21–22).

undergoes slow hydrolysis over 3 months when it is reacted with one equivalent of water. A single example of an isolable thiazolylidene with a very bulky *N*-aryl group to prevent dimerization has been reported, but it is highly water sensitive (23). However, the presence of other acidic and reactive sites in thiamine and its derivatives, as well as a lack of steric protection, precludes the isolation or even observation by nuclear magnetic resonance (NMR) or other means of these proposed carbene intermediates. Here, we report, to our knowledge, the first truly water-stable carbene. This molecule appears to exist indefinitely in liquid water solutions, and we present spectroscopic proof that this carbene is not only stable toward water but can also be generated in water. While the carborane scaffold may not exactly mimic the active site of the enzymes Breslow had in mind, it does, in a way, mimic an active site by providing a protective pocket where the chlorinated cages both thermodynamically favors carbene formation and kinetically protects this divalent carbon center. Nevertheless, our study unambiguously confirms Breslow's hypothesis that under the right circumstances, it is possible to generate persistent carbenes in an aqueous environment.

RESULTS

Over the past decade, we have been developing ligands bearing functionalized carborane clusters for various applications (24). Most recently, we showed that it is possible to prepare anionic imidazolium salts **6** and the corresponding dianionic carbenoid **6'** appended with 10-vertex *closo*-carborane anions (10-vertex; CB_9^{1-} ; Fig. 2A) (25). Similar to what we have shown with polyhalogenated carboranyl NHCs bearing 12-vertex *N*-carboranyl groups (CB_{11}^{1-}) (26), we are interested in developing analogs of these ligands with the smaller 10-vertex cluster to implement in studies of weakly coordinating yet reactive organometallic and main-group ion pairs.

We learned that perchlorination of imidazolium salts bearing anionic 12-vertex hydrido *N*-carboranyl clusters is not possible (the reaction never goes to completion probably for steric reasons);

however, we found that smaller imidazolium anion **6** can be completely chlorinated, including the imidazolium backbone to produce **7** (Fig. 2A). The corresponding carbene **7'** can be easily formed in quantitative yield by the addition of two equivalents of lithium bis(trimethylsilyl)amide (LiHMDS). Analysis of the ^1H NMR of **7'** shows the expected absence of the single imidazolium proton, and the ^{11}B NMR shows movement of the resonances but retention of the local C_{4v} symmetry, which is consistent with the formation of a single compound in quantitative yield. The ^{13}C NMR spectrum is most instructive, as it shows a carbene carbon resonance markedly shifted downfield [239 parts per million (ppm) for **7'**] relative to carbenoid **6'** (200 ppm), which is consistent with a deshielding effect from the 20 electron-withdrawing Cl groups. Analysis of the ^7Li NMR shows a single Li peak that corresponds to $\text{Li}^+(\text{THF}_4)$, suggesting that in contrast to **6'**, **7'** is a free carbene in solution. The structure of **7'** was unambiguously determined via single-crystal x-ray diffraction, which shows that this species is a free dianionic carbene and not a carbenoid in the solid state (Fig. 2C). A space-filling model of the solid-state structure (Fig. 2B) shows the steric shielding provided by the cluster chlorides for both the σ -lone pair of electrons and the π orbital of the carbene center. The closest carbene carbon to Li^+ distance is greater than 10 Å away, confirming that **7'** persists as a free carbene in the solid state. All attempts to obtain a crystal structure with water in the lattice or bound to the Li^+ cations were unsuccessful, as they always resulted in the same structure even in the presence of water (vide infra).

The NMR samples were prepared in normal NMR tubes in the glove box, with the caps wrapped in electrical tape to slow down the diffusion of air into the samples, in lieu of using more expensive J Young-type tubes. We noticed that if the samples were left on the bench for several days, then the NMR spectra remained completely unchanged, showing no signs of decomposition via hydrolysis. This is rather unusual for most NHCs, except for the reports mentioned above, and this observation piqued our curiosity about the potential water stability of this compound. Adding tap water to the THF

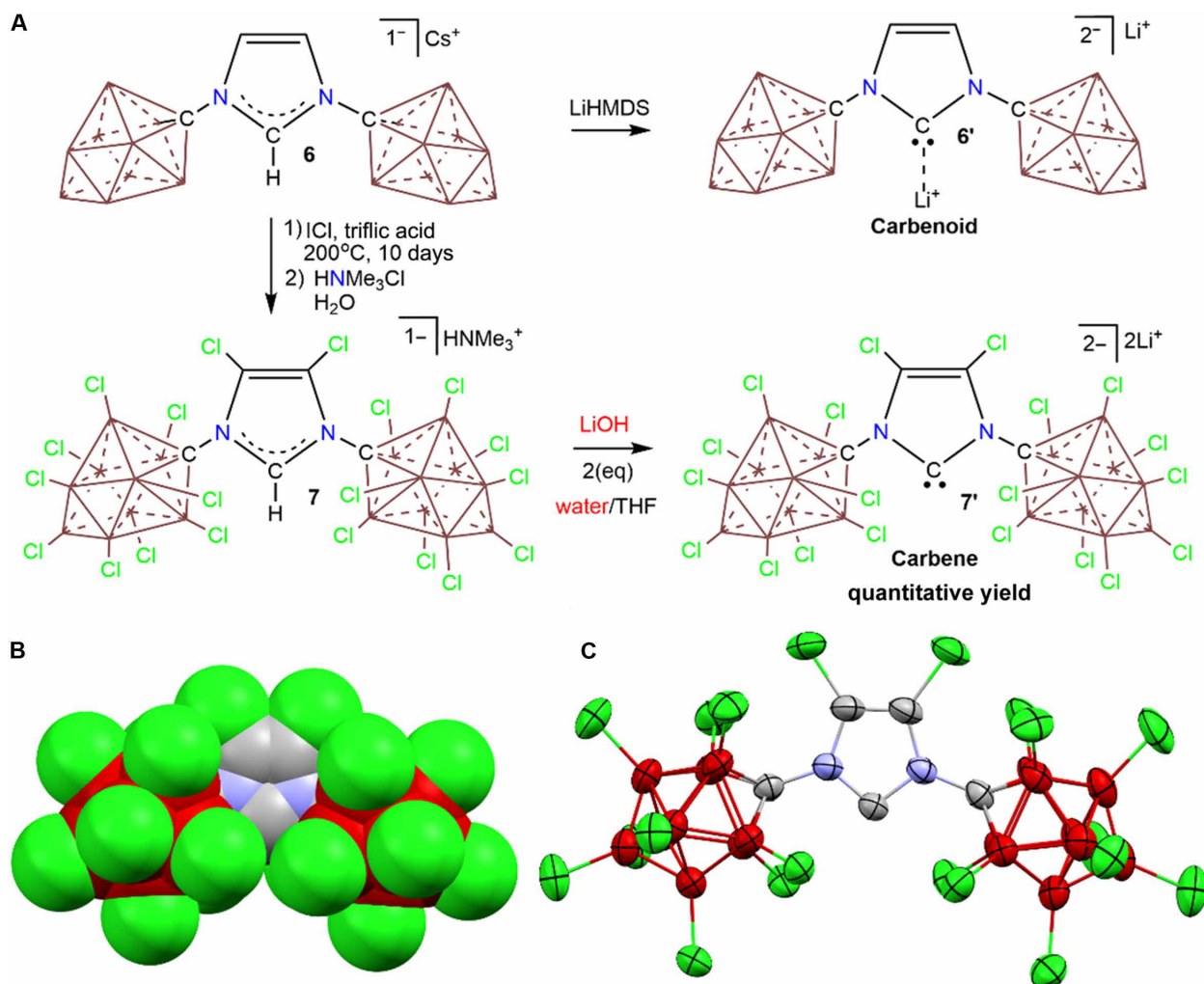


Fig. 2. Synthesis and determination of 7'. (A) Synthesis of carbenoid **6'** and carbene **7'**. The reaction is clean and quantitative when LiHMDS is used as a base and pure THF as the solvent. (B) Three-dimensional space-filling model. (C) Thermal ellipsoid plot drawn to the 50% probability. Color code: C, gray; B, brown; N, blue; Cl, green. Note that two Li(THF)₄⁺ counteranions are omitted for clarity.

solutions of the carbene to the point of water saturation (a monophasic solution), we noticed immediate protonation of the carbene and reformation of the starting material but no hydrolysis. We hypothesized that, perhaps, impurities, such as carbonic acid from CO₂ dissolution in the tap water, were leading to the observed protonation. Thus, we carefully distilled water under argon and repeated the experiment in a J Young tube, and, amazingly, the NHC remained completely intact with no signs of protonation or decomposition of any kind, even in this massive excess of water. Monitoring this sample and a few others over 6 months via NMR spectroscopy showed absolutely no decomposition of the carbene; thus, to our knowledge, it is truly the first water-stable carbene.

We next attempted to generate the carbene in pure water with LiOH but learned that the reaction did not proceed because of the insolubility of **7** in water. Thus, we added enough THF to the water suspension to solubilize **7** and found that **7'** is formed under these aqueous conditions, along with other unidentified by-products. However, we were able to optimize the conditions via adjusting the water/THF ratio and the order of addition to generate carbene **7'** as

the sole product (Fig. 3). The optimized conditions consist of dissolving the imidazolium salt in 1.0 ml of THF and subsequently slowly adding 2 equivalent of LiOH dissolved in 0.15 ml of pure water. Figure 3 shows the actual crude ¹³C NMR spectrum of the reaction mixture immediately after mixing the two solutions. The sole carbene carbon at 239 ppm and the backbone peak at 117 ppm show clean formation of carbene **7'** in water. The carborane carbon is not evident because of the coupling of this C atom with the different combinations of two different quadrupolar B nuclei (natural abundance: ¹¹B = 80%, spin 3/2; ¹⁰B = 20%, spin 3) in the cage. The only other resonances observed are that of THF solvent and that of liberated NMe₃ from HNMe₃⁺.

DISCUSSION

To confirm that carbene **7'** has special water stability compared to the reported water-resistant species **4'** and **5'**, we decided to synthesize these Arduengo-type NHCs and reinvestigate how they behaved in an excess of water. When a benzene or THF solution of compound

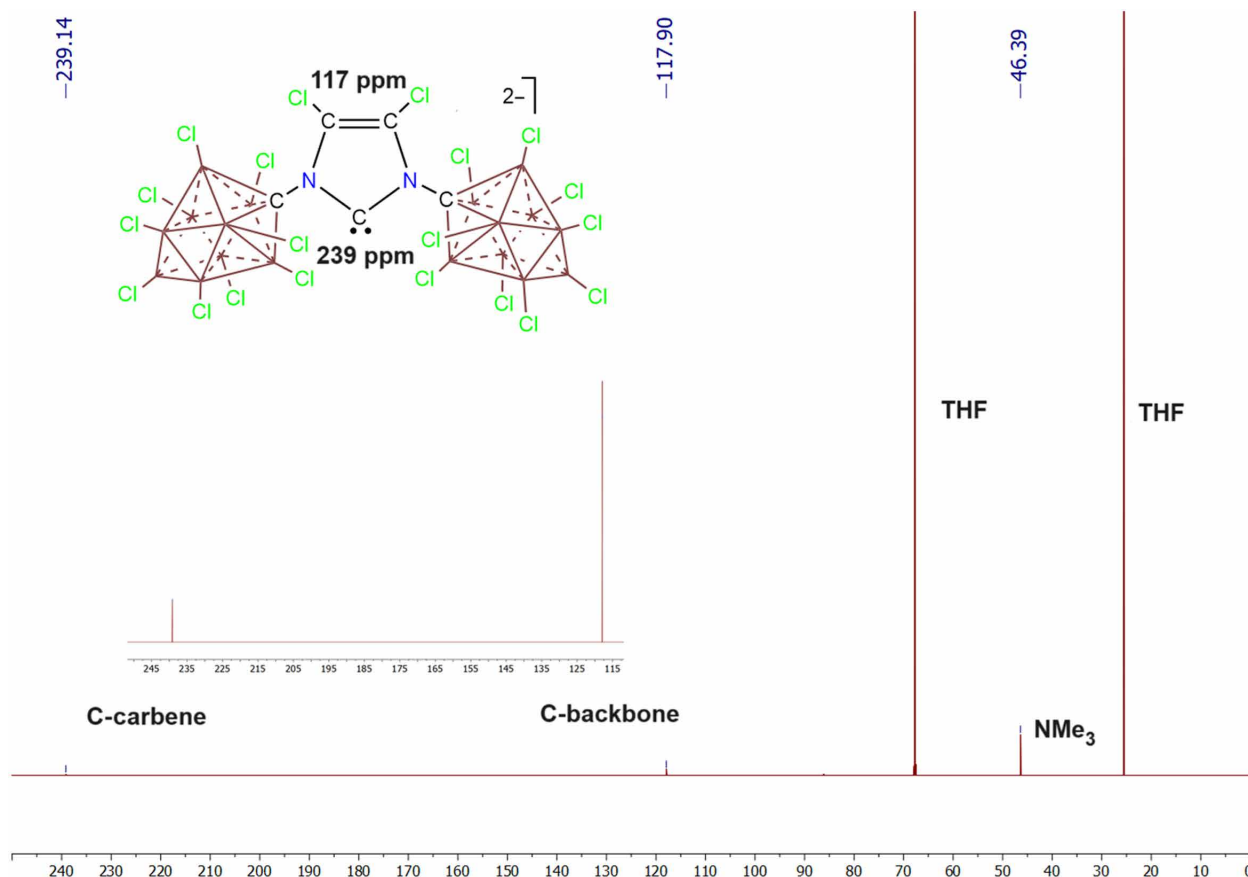


Fig. 3. NHC **7' formation in aqueous media.** Crude ^{13}C NMR spectrum of the generation of water-stable carbene **7'** with LiOH in water THF mixture. Inset shows the carbene carbon and back bone carbons at 239 and 117 ppm, respectively. The other resonances are THF from the solvent mixture and liberated NMe₃ from the counteranion of **7**.

4', so-called air-stable carbene of Arduengo *et al.* (21), is treated with one equivalent of distilled H₂O, it is completely consumed by the time the sample is loaded into the NMR spectrometer. The products consist of unidentified species and resonances suggestive of ring-opening hydrolysis (figs. S12 to S16). When a THF solution of NHC **5'** is exposed to 11 equivalents of H₂O, it completely undergoes ring-opening hydrolysis before an NMR spectrum can be recorded (figs. S16 and S17). If less than 11 equivalents are used, similar to Denk *et al.* (22), we observe the presence of NHC **5'** as well as the hydrolysis product in the ^1H NMR spectrum.

To gain insight into exactly why NHC **7'** is stable in water, we decided to calculate the pK_a (where K_a is the acid dissociation constant) of several imidazolium salts via density functional theory (DFT)-based quantum mechanics at the B3LYP/6-311G**++ level (figs. S23 and S24). This quantum mechanics-based method was validated via comparing our theoretical values to those of two reported experimental studies (27–28) on imidazolium salts (exp = 23.8 ± 0.5 , Calc = 24.8 and exp = 23.0 ± 0.5 , Calc = 25.6). Considering experimental error, DFT yields reliable estimates of the true pK_a of imidazolium salts. As seen in Fig. 4, the nonchlorinated imidazolium salts **3**, **5**, and **6** all have pK_a values well above 20. For Arduengo's so-called air-stable carbene precursor **4**, the pK_a is calculated to be 17.7, which is consistent with the combined electron-withdrawing effects of two aryl rings and two backbone chlorines. Given the fact that the pK_a of

water is 14.0, it is expected that carbenes **4'** to **6'** are not stable in water, as the equilibrium with the conjugate acid is highly favorable toward the imidazolium salt. On the contrary, the theoretical pK_a of perchlorinated imidazolium salt **7** is 11.9, making it at least two orders of magnitude more acidic than water with an equilibrium strongly favoring the carbene form. These findings combined with the kinetic protection, both in the σ and π planes of the carbene center, offered by perchlorination explain why **7'** is stable and unreactive toward water for at least 6 months. In addition, we observed that **7'** is not catalytically active in either benzoin or acyloin condensation reactions. Furthermore, we attempted numerous reactions with myriad transition metal precursors, heterocumulenes, and elemental selenium and observed absolutely no reaction except for complete decomposition at elevated temperatures. This precludes us from experimentally gauging the σ and π donor properties of this molecule. This unreactivity is expected as the lone pair of electrons is essentially sterically inaccessible to molecules beyond that of a proton, as highlighted in the space-filling model in Fig. 3. These strategies to sterically protect reactive intermediates often result in retardation of their typical behavior, but nonetheless allows for a snapshot of species that are normally not spectroscopically observable in the condensed phase. In addition, we included full molecular orbital energy analysis of all these carbenes in the Supplemental Materials (figs. S25 to S30), but the magnitude of the potential energies

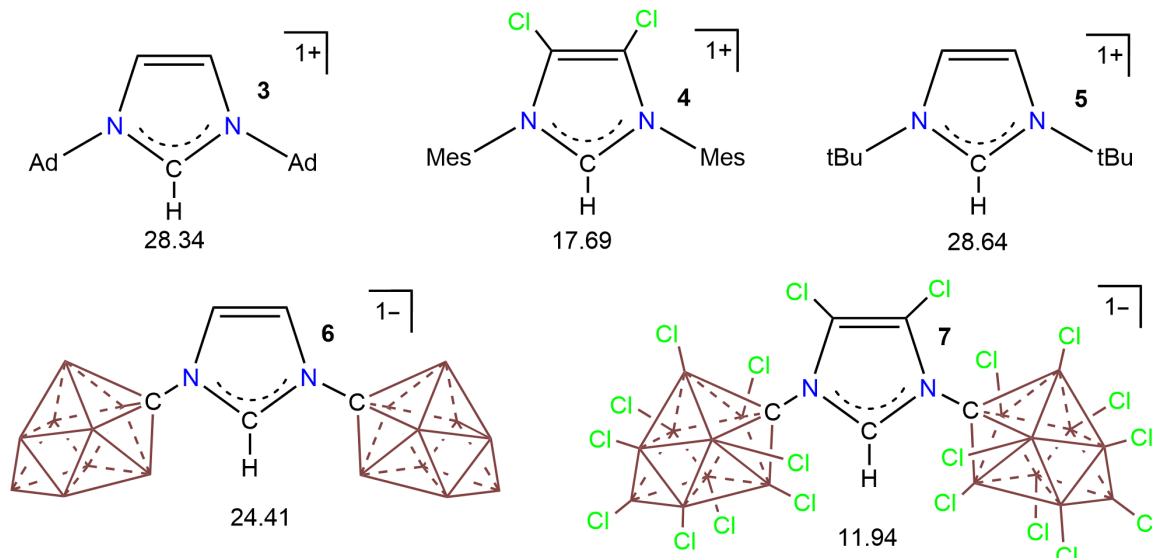


Fig. 4. Calculated pK_a values of relevant NHC conjugate acids. The calculated pK_a values of different imidazolium salts discussed in this manuscript. Unlabeled vertices: B-H for **6** and B for **7**.

are unreliable because of the dinegative charge, either with or without solvated Li^+ counteranions.

Over 80 years after Breslow's investigations lead him to the visionary hypothesis that a carbene could exist long enough in water to function as an active derivative of B_{11} , we provide definitive spectroscopic proof via NMR that Breslow was likely correct. Furthermore, the fact that we can grow crystals suitable for single-crystal x-ray diffraction in the presence water and actually generate stable carbenes in water shows how human ingenuity can be used to tame the most reactive chemical entities. While this carbene does not exactly mimic the protein active site, the steric protection provided by the carborane clusters and their role in equability may inform our understanding of how such reactive species can be prevalent in biological systems.

MATERIALS AND METHODS

As general considerations, unless otherwise stated, all manipulations were carried out using standard Schlenk or glovebox techniques (O_2 , H_2O < 1 ppm) under a dinitrogen or argon atmosphere. Solvents were dried on sodium-potassium alloy or potassium benzophenone ketyl and distilled under argon before use. Compound **6** was prepared according to literature methods (25). Reagents were purchased from commercial vendors and used without further purification. NMR spectra were recorded on Bruker Avance 300 MHz, Bruker Avance Neo 400 MHz, Bruker Avance 600 MHz, Bruker Avance III 700 MHz, Varian Inova 300 MHz, or Varian Inova 400 MHz spectrometers. NMR chemical shifts are reported in parts per million. ^1H NMR and ^{13}C NMR chemical shifts were referenced to residual solvent. ^{11}B NMR chemical shifts were externally referenced to $\text{BF}_3 \cdot \text{OEt}_2$. High-resolution mass spectrometry was recorded on Agilent Technologies 6210 (time-of-flight liquid chromatography–mass spectrometry) using electrospray ionization technique. Complete materials and methods for all of the compounds and calculations can be found in the Supplementary Materials. Complete crystallographic data for compound **7**

are available free of charge from the Cambridge Crystallographic Data Center (CCDC) under the reference number 1848698, respectively. The crystallographic data of these structures can be accessed via the CCDC website: www.ccdc.cam.ac.uk/Community/Requestastructure/Pages/DataRequest.aspx.

Supplementary Materials

This PDF file includes:

Supplementary Text

Figs. S1 to S31

Tables S1 to S3

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