N-Heterocyclic Carbenes

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The Beginnings of N-Heterocyclic Carbenes

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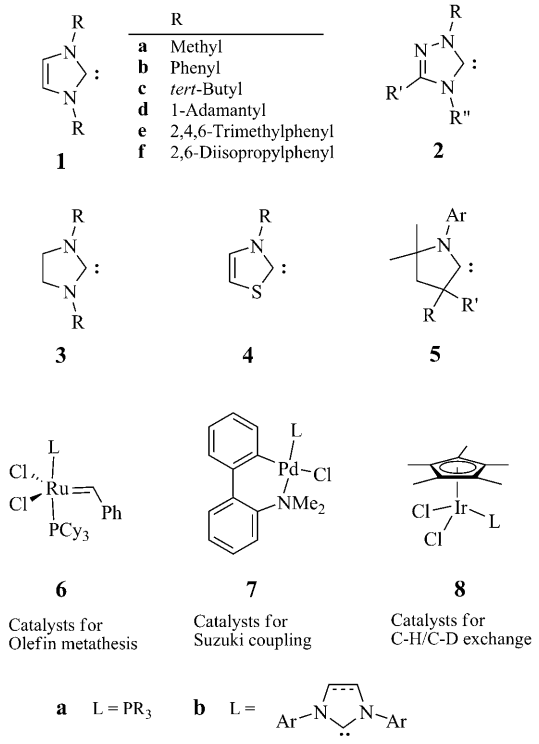
Carbenes (derivatives of divalent carbon) are usually short-lived reactive species.[1] It is only amongst the N- and P-substituted carbenes that stable, isolable compounds are found at room temperature.[2] The N-heterocyclic carbenes form the largest and most important group of stable aminocarbenes.[3] Here, the divalent carbon atom is part of a ring and is flanked by at least one nitrogen atom. The readily accessible imidazole-2-ylidenes (**1**) and dihydroimidazole-2-ylidenes (**3**) are particularly en vogue, but 1,2,4-triazol-2-5-ylidene (**2**), thiazole-2-ylidenes (**4**), and dihydropyrrole-2-ylidenes (**5**) have also been described (Scheme 1). Carbenes **1** and **2** are stable in the monomeric form irrespective of the R group, while **3**–**5** must be protected against dimerization by bulky substituents (**d**–**f**). N-Heterocyclic carbenes with six- and seven-membered rings are also known, but are still in their infancy.



Scheme 1. N-Heterocyclic carbenes and their metal complexes.

The practical significance of N-heterocyclic carbenes lies amongst other things in organic catalysis.[4] They can be used to advantage in numerous base-catalyzed reactions (ester exchange, epoxide opening, cyanhydrin formation). Above all, **2** and **4** demonstrate particular ability in the umpolung of aldehyde groups (benzoin condensation, Stetter reaction). Still more important are N-heterocyclic carbenes in organometalic catalysis.[5] Greater stability and reactivity were found with different catalyst types, for example, **6**–**8**, when phosphane ligands were replaced by N-heterocyclic carbenes (**a**→**b**). In addition, there are numerous catalytically active carbene–metal complexes which have no phosphane "role models". In contrast to phosphanes, N-heterocyclic carbenes have the advantage that their structure can be varied more simply and more extensively. This simplifies the optimization of the catalysts.

When and how did this historical success story begin? Fifty years ago the formula of an N-heterocyclic carbene, 1,3-diphenyldihydroimidazole-2-ylidene (**13**), appeared for the first time in a short note.[6] Wanzlick et al. carried out the thermolysis of **10** and obtained a product with the composition of **13**, which shortly later was demonstrated by molar mass determination[7,8] and Raman spectroscopy[7] to be the dimer **14** of the carbene **13** (Scheme 2). Shortly afterwards, **14** was also obtained by heating the diamine **9** with orthoformates (**9**→**11**→**14**)[8,9] and by deprotonation of the dihydroimidazolium salt **12**.[10] Numerous analogues of **14** (Ar instead of Ph)[8] and dimers of thiazole-2-ylidenes followed.[11,12]

Compound **14** reacts as "a half" with alcohols (→**11**),[13] acids (→**12**),[7] oxygen[7] and sulfur[14] (→**15**), aldehydes (→**17**),[7,15] ketones,[7,15,16] esters,[16] nitriles,[16] nitromethane,[7] and sulfones[17], that is, to give products which are formally derived from **13**. Wanzlick, therefore, assumed that **14** disassociated under the reaction conditions ("Wanzlick equilibrium").[18,19] Initially, he also supported this assumption by determination of the molar mass by the Rast method (melting point depression of camphor, ca. 180 °C), the result of which lay between the expected values of **13** and **14**.[6,7] The Rast method is simple to carry out, but is not reliable. In Wanzlick's case too, the result later had to be revised.[8] An excusable outcome, but the skeptics were immediately reminded of Wanzlick's doctorate supervisor Scheibler, who in 1926 erroneously reported the isolation of diethoxycarbene.[20] This "dead hand" followed Wanzlick, even though he subsequently experimented impeccably.

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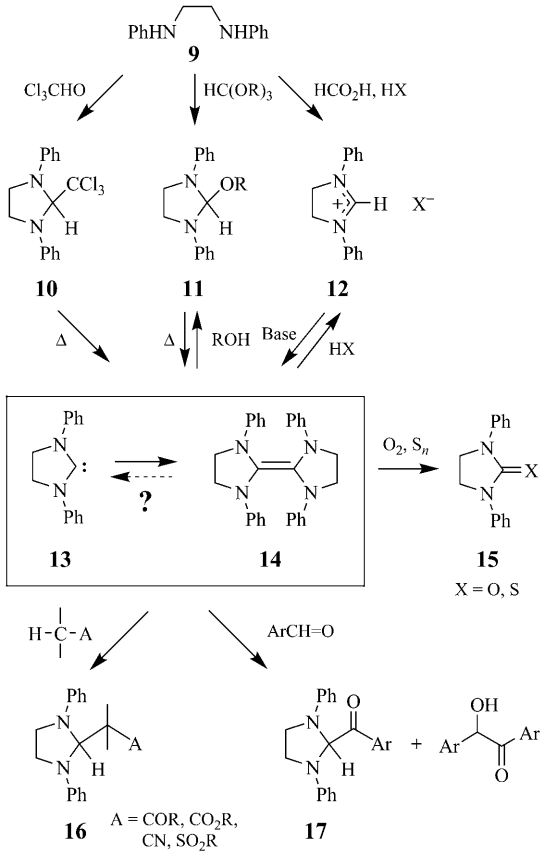
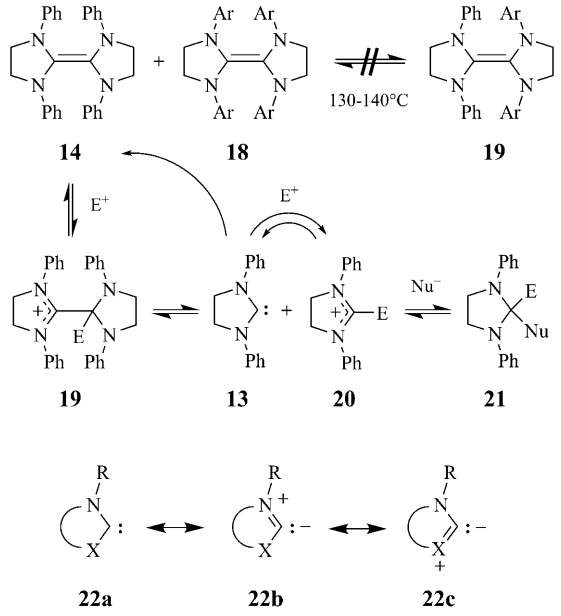


Scheme 2. Formation and reactions of 1,3-diphenyldihydroimidazole-2-ylidenes.



Scheme 3. Alternatives to the Wanzlick equilibrium.

The final nail in the coffin for an equilibrium **13**⇌**14** came from the "cross-over experiments" of Lemal et al.: no mixed dimer **19** was formed on heating a mixture of **14** and **18** (Ar = *p*-tolyl; Scheme 3).[21] Other tetraaminoethylenes also gave no cross-products.[22] Lemal et al. explained the reactions of **14** by the attack of the electrophile on the electron-rich double bond (**14**→**19**), followed by cleavage into two "halves" (**19**→**13** + **20**). Wanzlick et al. accepted this reaction course, but emphasized that, here too, carbene **13** would appear as an intermediate.[23] Quast and Hünig were able to trap selectively thiazole-2-ylidenes produced by electrophilic cleavage of the dimer.[12] Much later, the discussion on the Wanzlick equilibrium received a new lease of life when Denk et al. reported successful cross-over experiments with **14** and analogues.[24] This probably occurs through catalysis by traces of acids, since Liu and Lemal found no cross-over products in the presence of potassium hydride and under the conditions reported by Denk et al.[25] ("Real" Wanzlick equilibria are well known, but none of the type **13**⇌**14**.[19,26])

By 1965 it was actually clear how stable N-heterocyclic carbenes could be obtained: electrophiles had to be excluded as far as possible in the synthesis, and dimerization of the carbenes avoided through the use of bulky substituents. Even when the players of that time knew the route, the hurdles were high: Wanzlick's synthetic methods—starting from **10** or **11**—unavoidably generated electrophiles. (Dihydro)Imidazolium salts (**12**) were alternatives, which at that time, however, could not be prepared with bulky substituents. It was also less than fortunate that Wanzlick initially concentrated his efforts on the readily dimerizing dihydroimidazole-2-ylidenes. It was only later that he and Schönherr produced 1,3-diphenylimidazole-2-ylidene (**1b**)[27] and 1,3,4,5-tetraphenylimidazole-2-ylidene[28] from the corresponding imidazolium salts. They found in this case that dimerization did not take place and obtained the first metal complexes of the N-heterocyclic carbenes. The isolation of the carbenes was within reach, but perseverance and imagination were lacking in the search for the "right" solvent/base combination. Thus, it remained for Arduengo et al. to isolate the first stable imidazole-2-ylidene, **1d**, in 1991[29] and the first stable dihydroimidazole-2-ylidene, **3e**,[30] in 1995. They obtained the starting compounds by a new method for the preparation of imidazolium salts that Arduengo had developed at DuPont.[31] Only now was the hectic development of N-heterocyclic carbenes set in motion. Arduengo had repeatedly referred to Wanzlick's contribution and thus safeguarded them from oblivion.[32] (How quickly that happens is shown by work on the structure of **14**.[33] There, Wanzlick was neither mentioned nor cited.)

Even if Wanzlick had had more luck and success, the hoped for recognition would presumably have been denied him. When he reported his work at the Nordwestdeutsche Chemiedozenten-Tagung, 18–19 May 1963,[34] he reaped fierce criticism. Current opinion was not ready to accept the idea of nucleophilic carbenes after just being convinced of the electrophilic behavior of the then known carbenes. I remember this conference particularly well, because my lecture on "Nucleophilic Behavior of Diphenylcarbene"[35] met similar reservations. I deduced from evidence that the reaction of diphenylcarbene with alcohols occurred via diphenylcarbenium ions.[36] This was received as defamatory heresy, because in this case a quite "normal" carbene was involved (no nitrogen, anywhere). To escape excommunication I initially

put the project away in a drawer. Only much later was the protonation of diarylcarbenes indisputably proven by time-resolved spectroscopy.[37]

An additional acceptance problem arose from the uncritical handling of resonance structures (**22**, Scheme 3). Wanzlick's contemporaries considered N-heterocyclic carbenes—if they existed at all—as ylids **22b**,**c**. The contribution of the (presumably energy-rich) carbene resonance structure **22a** was considered negligeble. This one-sided viewpoint is attributable to Breslow,[38] who in his ground-breaking work on catalysis and on the H/D exchange of thiazolium salts (thiamine) had always formulated the intermediate thiazole-2-ylidenes as ylids—nowhere did a carbene structure appear. Also, of the reactions in Scheme 2, only the dimerization is untypical for ylids. Thus, Wanzlick's claim to a new class of compounds was considered to be unfounded. Only Arduengo's X-ray structure analysis of (dihydro)imidazole-2-ylidenes led to a change of mind. A narrowed N-C-N bond angle and extended C–N bonds compared to the (dihydro)imidazolium ions signaled a significant contribution of the carbene structure. The carbene character is confirmed by the low-field shift of the C2 signal in the ^{13}C NMR spectrum. As often in the history of science, a new idea finds acceptance only when methodological advances provides it with a solid foundation.

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