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N-Heterocyclic Carbenes (NHCs): An Introduction

Ruchi Bharti, Monika Verma, Ajay Thakur and Renu Sharma

Abstract

In 1991, the isolation and characterization of nitrogen heterocyclic carbene (NHCs) prompted the discovery of a new class of chemical compounds. NHCs have developed academic curiosity as one of the most potent tools in organic chemistry, exhibiting its utility in commercially relevant protocols. NHCs are cyclic compounds with a divalent carbon atom bonded to at least one nitrogen atom. The size of the carbene ring, the substituent moieties on the nitrogen atoms, and the extra atoms within the heterocycle can be changed to produce a variety of distinct NHCs with various electrical properties. They make excellent ligands in coordination chemistry because of their ability to act as donors and the consequent stable bonds with most transition metals. Free NHCs have also been used as organocatalysts in chemical reactions that require no metals. This chapter provides an outline of the N-Heterocyclic Carbenes in Contemporary Chemistry, including their general properties and highlighting the essential structural and electronic features of different NHCs along with their synthetic procedure.

Keywords: N-heterocyclic carbenes (NHCs), metal-organic framework, precursor, coordination chemistry, organocatalysis

1. Introduction

A carbene is a divalent neutral carbon-bearing six electrons in the valance shell & is considered very reactive to be isolated. Over the last 150 years, chemists have been fascinated about the carbenes and attempted for its isolation but failed [1]. Usually, the carbenes have a brief life span and play the role of very reactive intermediates. However, N-Heterocyclic carbene, in which the carbene center is settled on an N-heterocyclic ring, possesses different traits. It was first investigated in the early 1960s by Wanzlick [2, 3]. Shortly after that, in 1968, Wanzlick and Ofele reported the first application of NHC, where they function as a ligand to make complexes with metal [4, 5]. Later, the first crystalline NHC IAd (**Figure 1**) was first isolated and identified in 1991 by Arduengo et al., who encouraged a plethora of research on the transition metal complexes with NHC [6–19].

A broad range of NHCs is known with different carbene rings, substituting nitrogen atoms or additional heteroatom. The lifetime of NHCs is increased as the carbon is stabilized due to steric shielding. More generally, it can be said that this feature makes it a suitable fit ligand for coordination chemistry [20]. NHCs are also used as organocatalysts in metal-free chemical transformations [21]. This chapter discusses the basic outline of NHCs, including their standard structural features and properties, emphasizing various electronic and steric properties. In addition,

Figure 1.
First isolated NHC IAd (1c).

different synthetic routes leading to N-heterocyclic carbenes, along with their applications, have also conversed.

2. Chemistry of N-heterocyclic carbenes

2.1 Classes of NHCs and related stable carbenes

Many types of carbene compounds were labeled as NHCs in the past, and definitions of NHC based on their constitution are often subject to several interpretations [22]. N-heterocyclic carbenes can be defined as any chemical with a carbene center in a nitrogen-containing heterocyclic ring. A broad array of carbenes depending on substituents, size of the ring, and degree of stabilization of heteroatom are available, out of which a few important selected ones are shown in **Figure 2**. Another important classes of NHCs are imidazolinylidene (1), Tetrahydropyrimidinylidene (2), *N,N*-Diamidocarbene (DAC) (3), Benzimidazolylidene (4). These NHCs trigger small molecules like NH_3 & can go for insertion into alkenes [23]. Out of these Imidazolyliidene-derived NHCs (1) like IPr or IDipp (1a), IMes (1b), and IAd (1c) is the commonest NHCs that are mainly used as ligands with block elements. They function as catalysts in cross-coupling reactions or other significant organic–inorganic transformations [24, 25]. One more category of NHCs was reported by Bertrand et al. [26] where he reported only one nitrogen-containing NHCs like pyrrolidinylidene usually termed as cyclic on the basis of nature of the substituent present neighboring to the carbene center [27, 28].

These compounds are more attracted to the π -electron cloud than other categories of NHCs and help stabilize delicate representative elements and organic free radicals [29]. Another category of NHCs with more than two nitrogen atoms in their heterocyclic framework is also present. Triazolyliidenes (8) are examples of this class, widely used as organocatalysts for many transformations [30]. NHC classes having a different heteroatom like oxygen [oxazolyliidene (6)], sulfur thiazolyliidene (7) are also accessible. Different NHCs moieties can be obtained by developing the carbene center at different positions. In usual NHCs, the carbene center is generally present between the two nitrogen atoms as in imidazolyliidenes 1, generating the carbene center at the 4-position. However, that species is labeled mesoionic or abnormal carbene (MIC or an NHC), which is not neutral, and it is not possible to draw its non-zwitterionic resonance structure (9) [31, 32]. It is termed as “remote” NHC (rNHC) (10) when the carbene center is away from the nitrogen atom [33].

All aforementioned act as NHCs, but some related non-NHCs have also been reported, exhibiting the same characteristics as shown in **Figure 3** [34]. One of these is acyclic diamino carbenes (ADCs) (11) [35–37]. A carbene species 12 stabilized by adjoining silicon & phosphorus substituent was reported by Bertrand in 1988 and after 3 years free NHC was also isolated [38]. Cyclopropenylidene compounds (13) with exocyclic nitrogens were also synthesized by Bertrand [39] while “bent allene” species (14) have themselves been used as ligands [40]. These compounds are considered as NHCs stabilized acyclic carbene.

Figure 2.
 Some examples of important classes of NHC.

Figure 3.
Related classes of stable carbene.

2.2 Common structural features of NHCs

Nitrogen heterocycles are fundamental in defining the characteristics of NHC. Ranging from four-membered heterocycles, NHCs can be poly NHCs also, but the five-membered NHCs are most common (**Figure 4**), and all are based on imidazole and imidazolydiene [41]. Several structural features of imidazolylidene (1) are similar in all variants of NHCs, which helps stabilize the carbenes. Alteration in the structure and substituents of imidazolylidene develops diverse behavior in NHCs.

In the basic structure of imidazolylidene, the carbene carbon is attached to the two nitrogen atoms of the heterocycle. The aliphatic/aromatic substituent on the nitrogen atom (s) is denoted as the N-substituent(s). The remaining positions, i.e., the 4- and 5-positions in imidazolylidenes, are referred to as the NHC backbone. The substituents present on the ring backbone do not contribute any steric effect at the carbene center and affect the electronic environment only. However, substituents present on the nitrogen of the ring greatly influence the steric properties of the carbene center (**Figure 5**).

2.2.1 Stabilization of the carbene center

The steadiness of the carbene center in NHCs can be attributed to kinetic and thermodynamic factors. A carbene is carbon with an incomplete octet formed as an intermediate but does not undergo dimerization to form an alkene. Similarly, NHC bearing bulky aryl or alkyl substituent on nitrogen atom does not dimerize due to steric clashing and is termed the Wanzlick equilibrium. Electronic properties of NHC further contribute toward stability as they bear a singlet ground state despite classical carbene, which carries a triplet ground state. The lone pair of electrons of NHCs (singlet) is confined in sp^2 -hybridized orbital, which exists in the plane of the ring in the highest occupied molecular orbital and an empty p-orbital is lying

Figure 4.
Common five-membered heterocyclic rings.

Figure 5.
 General structural features of NHCs(1c).

Figure 6.
 Stabilization of the carbene by adjacent ring nitrogens.

perpendicular to it in the lowest unoccupied molecular orbital (**Figure 6**). As reported by Goddard et al. [42] singlet carbenes do not undergo dimerization easily, and adjacent nitrogen in NHCs further decreases the energy of HOMO, which causes sizeable singlet-triplet energy gaps. Interrelation among the lone pair of electrons of nitrogen present in p-orbital with empty LUMO (Mesomeric donation) also contributes to stabilizing the structure of the singlet ground-state.

2.3 Attractive features of N-heterocyclic carbenes

NHCs have gained much application as ligands for transition metal catalysis due to their steric and electronic behavior leading toward complex stability.

2.3.1 Electronic character

N-Heterocyclic carbenes belong to the category of very electron-rich ligands, although their degree of π -acceptor power is still doubtful. The electron donation property of NHC depends on the nature/type of metal, the substituents, and the

Ligand	$\nu_{\text{CO}} (\text{A}_1) (\text{cm}^{-1})$	$\nu_{\text{CO}} (\text{E}) (\text{cm}^{-1})$
IMes	2050.7	1969.8
SIMes	2051.5	1970.6
IPr	2051.5	1970.0
SIPr	2052.2	1971.3
Icy	2049.6	1964.6
PCy ₃	2056.4	1973
PPh ₃	2068.9	1990
PtBu ₃	2056.1	1971

Table 1.

IR values for the carbonyl stretching frequencies in $\text{LNi}(\text{CO})_3$ measured in CH_2Cl_2 .

co-ligands present on the NHC ring corresponding to the metal [43–46]. The capability to donate electrons can be calculated by comparing the stretching frequencies of CO ligands of complexes like $\text{LRh}(\text{CO})_2\text{Cl}$, [47], $\text{LIr}(\text{CO})_2\text{Cl}$ [47] with $\text{L} = \text{NHC}$ or $\text{LNi}(\text{CO})_3$ [48]. Hence, it is evident that N-heterocyclic carbenes are electron-rich ligands than the most basic trialkyl phosphines (**Table 1**) [49].

Furthermore, the NHCs have very similar levels of electron-donating ability as compared to the phosphines. The reason for this difference can be explained as the substituents of NHCs are exchanged only on the periphery of the ligand while for phosphines the different substituents are directly attached to the donor atom itself. Therefore, the finest way is to modify the electronic behavior of an NHC is to alter the type of the azole ring. In this way, it is rational to believe that the order of the electron-donating capability is benzimidazole < imidazole < imidazoline. It is easy to understand that components with +I and +M-effects increase the electron density of a NHC making it a better donor, while components with –I and –M-effects show the opposite behavior. However, some substituents have opposing electronic effects and complicate the situation. For example, halo groups (F–, Cl–, Br–, and I–) bound to the carbon atom exhibit the –I-effect due to their increased electronegativity but they also have the +M-effect as a result of three lone pairs for donation that need to be considered as well [50].

This electron-rich property of NHCs impacts many rudimentary levels of the catalytic process, e.g. smoothing the oxidative addition step. Hence, the complex of NHC with metal are suitable for cross-coupling reactions of non-activated aryl chlorides, which encounter the catalyst with a challenging oxidative addition step [51].

2.3.2 Sterics

NHCs are often used as phosphine mimics, but both structures are pretty different (**Figure 7**). Phosphine complexes have a cone-like structure where alkyl/aryl groups are pointed away from phosphorous. So, the steric properties of NHCs can be elucidated using Tolman's ingenious cone angle descriptors [49].

Figure 7.

Shape of phosphines and NHC.

The topology of N-heterocyclic carbene is contrary to phosphene and is more complex to predict factors determining its steric effect. The shape of NHC is defined by the position of the alkyl/aryl group present on the nitrogen(s) of the heterocycle. NHCs have been featured as fence- or fan-like [52]. The side groups are bent toward the metal and wrap it by forming a pocket (**Figure 7**). The steric and electronic properties of NHCs can change via rotation around the metal-carbene bond, hence making it anisotropic.

2.3.3 NHCs as ligands

Most of the metals form a very stable bond with Nitrogen heterocyclic carbene [46, 53]. Whereas quite same bond dissociation energies have been noticed for unsaturated & saturated NHCs with the same steric impacts, phosphines generally form weaker bonds (**Table 2**) [28, 54].

Consequently, the equilibrium between the carbene metal complex and free carbene exists toward the complex compared to phosphines (**Figure 8**). It increases the lifetime of complex but still N-heterocyclic carbenes very sensitive & reactive for many electron-loving moieties. They need careful isolation and storage. The consequential unusual firmness of NHC-metal complexes has been explored in many demanding protocols such as coupling reactions [55, 56], polymerization [57, 58], transfer hydrogenation [59–61], photocatalysis [62, 63], and many other [64–70].

However, escalating publications reveal that the bond between metal and carbene is not unreactive [53, 71–74]. As seen during the migratory insertion of an NHC into the double bond of ruthenium-carbon [75] removal of alkyl imidazolium salts from NHC alkyl complexes via reductive elimination, [76] or the ligand substitution of NHC ligands by phosphines, [77, 78]. Additionally, during applications

Ligand	%V _{Bur} for M-L (2.00 Å)	BDE[kcal/mol] (theoretical) for L in Ni(CO) ₃ L
IMes	26	41.1
SIMes	27	40.2
IAd	37	20.4
ItBu	37	24.0
PPh ₃	27	26.7

Table 2.
 Steric demand and bond strength of some important ligands.

Figure 8.
 Equilibrium of complexation.

of palladium NHC complexes, the generation of palladium black is observed, which points toward the decomposition pathways.

2.3.4 NHC adducts-bonding

The researchers have investigated the bonding between carbene center and metals/non-metals over the past two decades [8, 15]. The main feature of this bonding is the donation of carbene lone pair of electrons into empty sigma orbital of metal/non-metal. It is evident in the graphical representations (**Figure 9**) of NHC-metal complexes (53, 54, and 55) that in spite of a double bond usually a single bond is shown. Therefore, in the deficiency of steric restrictions or chelation, the bond between metal and NHC can rotate easily. The π -orbital in the NHC's complexes and metal is restricted within the NHC ring so indicated by a curved line between the heteroatoms of the ring.

Metal donates its electrons in the carbene's vacant p-orbital (LUMO) of carbene. The carbene can also donate electrons in the vacant π -orbitals of metal. The significance of each factor depends on the nature and geometry of another ligand on the complex and, most importantly nature of carbene itself. Using spectroscopic methods π -accepting ability of different NHCs can be measured and quantified [54, 79].

3. Synthesis of NHCs

As a broad range of N-heterocyclic carbene is based on 5-membered rings, hence the simplest way to prepare them is via removal of a proton from the related azolium salts, such as imidazolium, pyrazolium, triazolium, tetrazolium, benzimidazolium, oxazolium, or thiazolium salts by using appropriate bases. The

Hoveyda-Grubbs II olefin metathesis catalyst (53)

Organ's Pd-PEPPSI-IPr cross-coupling catalyst (54)

Nolan's gold (I) hydroxide catalyst (55)

Figure 9.
NHC-containing transition metal catalysts.

value of dissociation constant (pKa) of benzimidazolium and imidazolium salts was observed between 21 and 24, giving them a place in between the neutral carboxylic acid, acetone, and ethylacetate [9, 15, 80, 81]. Imidazolium salts are synthesized by following two routes. First method involves alkylation of existing imidazoles using appropriate electrophiles resulting in the generation of N-alkyl-substituted imidazolium salts. Whereas in other methods the imidazolium ring is synthesized by condensation reactions (**Figures 10** and **11**). As the attention for the synthesis of

Figure 10.
 Symmetric NHCs Synthesis.

Figure 11.
 Unsymmetrical Synthesis of NHCs.

Figure 12.
Desulfurization of thiones.

NHCs and imidazolium salts is increasing very rapidly, the methodologies related to its synthesis have been improved regularly.

a. **Reductive desulfurization of N-heterocyclic thiones:** a variety of heterocyclic carbene such as saturated, unsaturated, and benzannulated can be prepared by using this method. Imidazole-2-thione gets reduced to carbene by using potassium in boiling THF for 4 h (**Figure 12**). At the same time, benzimidazole-2-thiones undergo a reduction in the presence of Na/K alloy along with toluene within three weeks [82–86].

b. **α -Elimination or dehalogenation:** Imidazolinium salts derivatives bearing bulky *N*, *N'*-substituents **23** undergo α -elimination reaction to form the NHCs **24** under the influence of thermal induction (**Figure 13a**) [30].

Figure 13.
NHCs synthesis (a-e) by α -Elimination or dehalogenation.

Figure 14.
 Unsymmetrical synthesis of imidazolium salts.

The corresponding alcohol elimination from 2-alkoxyimidazolidines **25** to give imidazolin-2-ylidenes of type **26** (Figure 13b) was outlined by Grubbs [87] after early unsuccessful attempts by Wanzlick and Kleiner [88].

Imidazoline-2-ylidenes **26** were also accessible via α -elimination of fluorinated aryls from 2-(fluorophenyl)imidazolidines **27** (Figure 13c) [89, 90]. The α -elimination of acetonitrile from **29** to yield the benzimidazole-2-ylidene **30** has also been described (Figure 13d) [91]. Bertrand reported the dechlorination reaction among tetrahydropyrimidiniumchloride **31** and bis (trimethylsilyl)mercury leading to NHC **32** (Figure 13e) [92].

- c. **Symmetric synthesis:** For symmetric NHCs (**36**), synthesis formaldehyde (**35**) is treated with primary amine (**33**) and glyoxal (**34**) under strongly acidic conditions. Otherwise, the bisimine intermediate (**34a**) is reacted with electrophilic C1-fragments (chloromethyl ethyl ether or chloromethylpivalate) after isolation [81, 93–95]. During few crucial methodologies, the addition of stoichiometric amounts of AgOTf was evidenced to be helpful (Figure 10) [96].
- d. **Unsymmetrical synthesis:** Unsymmetrically, NHCs are prepared by adding alkyls to monosubstitutedimidazoles (Figure 11) [96–103]. The unsymmetrical imidazolium salt (**39**), so obtained is incorporating a counter anion (X^-) to maintain the electric neutrality but careful selection of the counter anion is sensible as it affects the dissolution of the imidazolium salt. It is noteworthy

that non-coordinating counter ions like OTf⁻ or BF₄⁻ increase the solubility of the salts.

In another protocol for synthesizing unsymmetrical NHCs, the α -hydroxy ketone (46) is reacted with the amine (R₄-NH₂) of choice under acidic conditions. Thus, by azeotropic removal of water, the α -aminoketones (47) are obtained, which are then N-formylated (48) before reaction with (CH₃CO)₂O in the presence of aq. HBF₄ or HClO₄. The subsequent cyclization stops at the intermediate acetal stage. Also, the reaction of the oxazolinium adducts 49 with R₂-NH₂ goes on easily, generating hydroxylateimidazolinium salts bromoacetaldehyde diethyl acetal (53) (Figure 14) [104].

4. Conclusions

Since the 1960s, when the initial studies on NHC began, and later (1991) when Arduengo isolated the first NHC, the applications of these compounds are growing across various domains of chemistry. Nature itself has chosen an NHC as a part of vitamin B1 to achieve organocatalytic reactions in vivo. Over the past few years, NHCs have unfolded novel categories of enantioselective organic transformations. This chapter provides a brief outline of the fundamental properties and synthesis of NHCs by analyzing different methods used to quantify their steric & electronic properties.

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Conflict of interest

The authors declare no conflict of interest.

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