NHC Ligated Oximes: Exploring the Electronic Structure and Properties

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Abstract

Compounds with (NHC)-E coordination bond are being generated and their chemistry is being explored over the past 15 years (NHC= N-heterocyclic carbenes, E = main group elements). Many examples of species with N-heterocyclic olefins (NHOs) are known, which exhibit umpolung chemistry. Increasing number of chemical species, which carry NHC as a functional unit, are being reported. There is a need to understand their electronic structure. Alkylated imidazole oximes (cationic, found useful in medicinal chemistry) ((NHC)-C(H)=N-OH(+)) carry NHC unit as a functional group. Similarly, the corresponding nitroso-N-heterocyclic olefins ((NHC)=C(R)-N=O) also carry NHC as a functional unit. It is important to establish the interaction between the NHC unit and the rest part of the molecule in these species. Density functional (DFT) study has been carried out to explore the electronic structure details of a few oximes and nitroso NHOs. The results indicate that a structure with NHC-C coordination interaction can be considered as one of the resonance structures of these species.

Introduction

N-heterocyclic carbenes (NHCs) are well known species with many unique properties. High nucleophilicity is one of the distinctive properties of these species, which help them in coordinating with transition metals as well as main group elements [1-5]. Especially, compounds with ()-C bond are quite intriguing and lots of research is in progress to understand the unique properties of these species [6,7]. For example, carbones (**A** and **B**, Figure 1) are species which were shown to carry the ()-C coordination interaction [8-10]. Recent work reports the importance of ligand exchange reactions due to carbones [11]. There are many reports which do not specifically mention about the bonding characteristics but consider the unit as a well-defined functional unit in the organic molecules, either in the cationic state, radical or in neutral state. For example, the recently reported radical species (**C**, **D** and **E**) [12-15] were considered to carry the unit in its cationic state, whereas in N-heterocyclic olefins (NHOs) (**F**, **G)**, the unit is considered to carry ()-C umpolung character [16-18]. Exploring the characteristic features of ()-C bond has been of current interest. In this context, it was realized that species with the imidazolium-2-aldoximes (**H**, Figure 2) and related species offer a unique opportunity to explore the chemical bond between the ring and the oximic carbon center.

Fig. 1 Examples of carbones (**A**, **B**),N-heterocyclic carbene radical cations (**B**, **C, D**), N-heterocyclic Olefin (**F**) and Breslow intermediate (**G**).

Imidazolium-2-aldoxime (**H**) and pyridinium oxime (**I**) are cationic species, which exhibit organophosphate detoxification property [19-24]. The pralidoxime (**I**), obidoxime (**L**), HI-6 (**M**), etc. are drugs/leads, being used as antidotes in the poisoning due to nerve agents (tabun, sarin, soman, etc.) [25-29]. TAB2OH (**N**), a cationic nonpyridinium aldoxime is a lead molecule and considered as an efficient acetylcholineesterase reactivator [30]. The drug action of these species is expected to involve the participation of the zwitterionic nitroso compound (**O**) [31], which may be considered as the nitroso-N-heterocyclic olefins (NNHOs), the chemistry of which has not been explored in detail. The crystal structure of pralidoxime (**I**) has been

reported, the (ring) C-C (oxime) bond length has been found to be 1.46 Å [32,33]. Grosev *et al* . reported the vibrational analysis of **I** and its isomer **K** . They concluded that the N-O stretching frequencies for **I** and**K** are 1082 cm^{-1} and 1074 cm^{-1}, respectively and C=N stretching frequencies are 1649 cm^{-1} and 1611 cm^{-1}, respectively for **I** and **K** . These wavenumbers indicate**I** can behave as a strong acid when compared to **K**[34].

Fig. 2 Representative examples of cationic oximes reported in medicinal chemistry literature.

The chemistry of **I** involves the reaction as shown in Scheme 1, in which the drug pralidoxime (**I**) is the starting material and the phosphorylated pralidoxime (**J**) is the product. Castro and Figueroa-Villar reported quantum chemical studies on the molecular structure and the conformations of **I** using B3LYP/6-31G(d) level. The NHC-C rotational barrier was estimated to be 6 kcal/mol and the corresponding NNHO has been shown to carry largely increased rotational barrier (~30 kcal/mol) [35]. Quantum chemical studies on the chemistry of the reaction shown in Scheme 1 confirmed the participation of NNHO as the causative agent in the reactivation of OP-inhibited human acetylcholinesterase [31,36]. Quantum chemical studies have also been performed on the reactivity profiles of phosphyloximes (**J**) [37]. Wong *et al* . studied the oxime reactivation reaction by exploring the influence of chirality and mutagenesis (experimental and theoretical analysis) [38]. Delfino and Figueroa-Villar proposed that the oximates participate in the reaction in a three-step mechanistic path, in comparison to other nucleophiles, which may require four-step processes [39], in an extended work, this group concluded that the neutral oximes have greater potential to act as antidotes [40]. Franca and co-workers performed molecular modelling studies, estimated the free energy change values using molecular dynamics simulations and suggested that the blood brain barrier (BBB) related limitations of the cationic oximes can be overcome [41]. Further, similar study using QM/MM analysis was reported to explore the reactivation by pralidoxime [42].

Scheme 1 Representation of reactivation mechanism of VX-Inhibited Human Acetylcholineesterase triggered by zwitterionic nitroso compounds.

In this work, quantum chemical analysis has been carried out to explore the electronic structure of a series of cationic oximes (**O-1** to**O-15**) and the corresponding NNHOs (**O'-1** to**O'-15**) using density functional methods. This work is in continuation of our efforts in exploring the L-N coordination bond in nitrone class of compounds [43-52]. The chemical bond between the ring systems and the carbon center was explored; the bond dissociation energy of the NHC in these species has been estimated.

Computational Details

Density functional theory (DFT) calculations were carried out using Gaussian09 suite of programs [53-55]. Geometry optimization was carried out using the density functional B3LYP and M06 methods and using two different basis sets 6-31+G(d) and 6-311++G(d,p) [56]. The results (relative energy values) obtained using M06/6-311++G(d,p) level of quantum chemical methods are provided in Tables 1 and 2, the results obtained using other three levels (as well as the corresponding absolute energy values) are given in supporting information. All the minima are characterized by zero negative frequencies and the transition states are characterized by one negative frequency. The Gibb's free energy values are employed in the analysis. The bond dissociation energy values are estimated by breaking the L-C bond in which the L is a fully characterizable carbene unit.

Results and Discussion

NHCs are highly nucleophilic, they can donate electron density to main group elements like carbon, nitrogen etc. and examples are carbones and nitreones [43-52]. In the series of oximes studied in this work, the oxime center is electron deficient because the C=N-OH center carries a proton. Hence, the chances are very high to consider the electron donation from NHC to the oxime center. This distribution of electron density would be reflected in the interaction between the NHC unit and the oxime unit in these compounds. Consequently, the C1-C2 bond lengths, their bond dissociation characteristics are expected to be significantly different from the standard values. The C1-C2 double bond character is supposed to become much weaker and hence the

rotational barriers are expected to be low. These factors are reflected in the quantum chemically estimated bond characteristics in the cationic oximes (**O-1** to **O-15** , Figure 3). Similarly, in the corresponding neutral species (**O'-1** to **O'-15,** Figure 4), the C1-C2 bond characteristics are expected to be significantly influenced. Traditionally, **O-14** was considered as a system carrying positively charged ring and neutral oxime center, as in**I** (Figure 2). However, the positive charge does not get localized at the site of alkylation; hence, it is more appropriate to consider **O-14** as the right representation of **I** . In fact, **I** and **I'** may be in resonance equilibrium and it is better to write **I** with overall positive charge as in**O-14** as the right representation, rather than localized positive charge. The same was emphasized by Van Havere *et al* . who reported the crystal structure of pralidoxime [32]. This argument is applicable to all structures in Figure 3.

Fig. 3 The cationic oxime species explored in this work.**O-5** , **O-6** , **O-13** to **O-15** were experimentally explored earlier. All other species are the designed analogs.

Fig. 4 Nitroso *N* -heterocyclic olefins **O'-1** to**O'-15** are designed species and none are known experimentally.**O'-14** was earlier studied using quantum chemical methods.

O-1 carries a 3-membered cyclic system and this compound has been designed based on the carbocyclic carbene (CCC) which was isolated in the past [57]. **O-2** , **O-3** and **O-4** have been designed inspired from the carbodicyclopropenylidene system [58], the experimentally known 4π electron 4-membered*N* -heterocyclic carbene [59] and the reported 6π electron 4–membered cyclic carbene [58], respectively. **O-5** to**O-8** carry well-known NHC systems based on imidazoles and thiazoles [60]. **O-9** contains CAAC type NHC [61].**O-10** and **O-11** carry the mesoionic carbene systems [4]. **O-12** is similar to **O-5** except for the fact that the oxime center carries aromatic ring substitution. **O-13**and **O-14** carry the N-alkyl pyridine ring systems, which were experimentally explored [25]. **O-15** carries a quaternary N-center and considering this as a carbene using this kind of substituent is not an easy proposition. This is a known compound, which was tested for its therapeutic applications [30].

Table 1 shows the geometric, energetic and electronic characteristic features of the oximes (**O-1** to **O-15**). The C1-C2 bond length values in **O-1** to **O-15** are in the range of 1.42 Å to 1.46 Å. These values are much smaller than the standard C-C single bond length (1.54 Å) and much longer than the standard C=C double bond length (1.34 Å). All these molecules adopt co-planarity of the fragments across C1-C2 bond (except **O-12**). This establishes that there is some additional interaction between C1 and C2 in these molecules in comparison to the single bond but not sufficiently strong to consider it as a double bond. The Wiberg bond index is only marginally larger than one. The C1-C2 rotational barrier values in **O-1** to**O-15** are in the range of 2.5-11 kcal/mol, (much smaller than that in alkenes) implying that the C-C interaction does not carry double bond character. The bond dissociation energy (BDE) values of**O-1** to **O-15** are in the range of 95-154 kcal/mol (slightly high than C-C single bond dissociation in ethane that is ˜73 kcal/mol and also smaller than the C=C BDE in ethylene 183 kcal/mol using the same basis set). These values are facilitated by the fact that upon the heterolytic dissociation, the two fragments can be shown to be independent species that is NHC and the protonated fulminic acid. **O-12** is a ketoxime, its bond dissociation energy (BDE) value is very small because it carries non-coplanar arrangement between NHC and an oxime unit. The weaker is the C1-C2 BDE, the stronger is the opportunity to consider L-C interaction in these species. It is intriguing to note that in**O-7** and **O-8,** the BDE values are small and quite comparable (95.50 and 95.90 kcal/mol, respectively). This implies that the carbenes containing sulfur in a heterocyclic ring carry stronger L-C character. All the data presented in Table 1 support the hypothesis that the NHC character for the heterocyclic ring in **O-1** to**O-15** is significantly high. The NHC being nucleophilic, it is donating electron density towards the electron deficient protonated fulminic acid component of this series of compounds. Hence, the L-C interaction is strongly supportable in the cationic oximes.

Table 1 Geometric and energy parameters of designed compounds**O-1** to **O-15** obtained at M06/6-311++G (d,p) level of theory. The bond lengths are in A units and the energy values are in kcal/mol.

Compound	L-C_1 bond length	C_1-N bond length	WBI (L-C_1)	L-C_1 Rotational barrier	L-C_1 Rotational barrier	L-C_1 BDE[a]
O-1	1.43	1.28	1.10	6.49	113.33	113.33
O-2	1.42	1.28	1.12	8.92	104.99	104.99
O-3	1.43	1.28	1.12	9.08	9.08	107.02
O-4	1.44	1.27	1.09	4.92	4.92	106.76
O-5	1.44	1.27	1.11	4.64	4.64	106.72
O-6	1.44	1.27	1.11	3.48	3.48	106.27
O-7	1.44	1.28	1.14	4.70	4.70	96.17
O-8	1.44	1.27	1.13	3.78	3.78	95.90
O-9	1.44	1.28	1.12	4.84	4.84	111.80
O-10	1.44	1.25	1.10	2.46	2.46	127.86
O-11	1.44	1.27	1.09	3.89	3.89	113.57
O-12	1.46	1.28	1.02	**	**	80.35
O-13	1.45	1.27	1.11	10.92	10.92	134.10
O-14	1.45	1.27	1.10	4.49	4.49	113.87
O-15	1.45	1.27	1.10	3.17	3.17	119.68

** The rotational barrier could not be estimated owing to the fact that the fragments across C1-C2 bond are already orthogonal to each other.

The most representative of all the cationic oximes considered in this study is **O-5** . It shows BDE of the order of 106.72 kcal/mol. The C1-C2 rotational barrier is 4.64 kcal/mol. The discussion on all other species in Table 1 can be done in comparison to that of **O-5** . The cationic oximes containing 3-membered carbenes (**O-1**) exhibits relatively larger BDE, however, **O-2** exhibit comparable BDE and also both **O-1** & **O-2** exhibit larger C1-C2 rotational barrier in comparison to that of **O-5** . On the other hand, the cationic oximes with 4-membered carbenes (**O-3** and **O-4**) exhibit relatively comparable BDE and relatively large C1-C2 rotational barriers. The cationic oximes with 5-membered carbene are all quite comparable in terms of rotational barrier as well as BDE. The system **O-10** containing a mesoionic carbene is exhibiting slightly different characteristic features in comparison to other 5-membered ring containing systems. It exhibits relatively large BDE value and very small C1-C2 rotational barrier. It is important to note that **O-13** shows maximum C1-C2 rotational barrier and the greater bond dissociation energy among all the species considered in Figure 3. Also, the rotational barrier and bond dissociation energy values are significantly different from that of **O-14** . This can be attributed to the fact that carbene like character is weak in N-4 alkyl pyridyl-2-ylidene in comparison to the same in N-2 alkyl pyridyl-2-ylidene [35]. The molecule **O-12** is slightly different from all others as it is a ketoxime (an aryl derivative of **O-5** at C2 position). This molecule adopts a torsional angle of N-C1-C2-N up to 47⁰. Because of this reason, it is not possible to estimate the rotational barrier. Also the bond dissociation energy value has been estimated to be very small in comparison to other species in Figure 3.

Table 2 lists the important geometric, electronic and energy parameters of the NNHOs **O'-1** to **O'-15** . The C1-C2 bond length values in **O'-1** to **O'-15** are in the range of 1.35 A to 1.44 A. The rotational barrier values around C1 and C2 in **O'-1** to **O'-15** are in the range of 8-35 kcal/mol. The Bond dissociation energy (BDE) values of **O'-1** to **O'-15** are in the range of 20-50 kcal/mol (very low), thus making these species highly unstable.

Table 2 Geometric and energy parameters designed compounds **O'-1** to **O'-15** obtained at M06/6-311++G(d,p) level of theory. The bond lengths are in A units and the energy values are in kcal/mol.

Compound	L-C$_1$ bond length	C$_1$-N bond length	WBI (L-C$_1$)	L-C$_1$ rotational barrier	L-C$_1$ BDE[a]	PA at O center
O'-1	1.38	1.35	1.32	24.34	30.51	-261.25
O'-2	1.36	1.37	1.45	35.04	34.63	-248.80
O'-3	1.35	1.37	1.49	33.71	48.57	-236.88
O'-4	1.37	1.36	1.40	19.64	36.39	-248.80
O'-5	1.39	1.34	1.32	14.11	30.25	-254.90
O'-6	1.38	1.35	1.36	16.85	32.65	-252.05
O'-7	1.38	1.36	1.41	20.97	28.60	-246.00
O'-8	1.38	1.36	1.43	22.56	29.09	-245.23
O'-9	1.37	1.36	1.44	25.95	43.45	-246.78
O'-10	1.41	1.32	1.22	8.12	32.28	-274.02
O'-11	1.40	1.34	1.27	12.46	29.71	-262.29
O'-12	1.41	1.36	1.22	**	19.65	-260.73
O'-13	1.38	1.36	1.41	21.52	55.71	-256.82
O'-14	1.38	1.36	1.39	24.09	41.46	-250.85
O'-15	1.44	1.32	1.18	9.33	32.07	-266.04

** The rotational barrier could not be estimated owing to the fact that the fragments across C1-C2 bond are already orthogonal to each other.

The major difference between oximes (Table 1) and NNHOs (Table 2) is that the C1-N bond length and C1-C2 bond length values became relatively smaller after deprotonation. Another significant observation is that the C1-C2 rotational barrier increased by at least 10-20 kcal/mol. The BDE values are significantly smaller in the neutral species. This reduction is due to the fact that C1-C2 bond strength is significantly reduced upon deprotonation in **O-1** to **O-15** . Also, the two fragments upon dissociation exists independently (Figure 5). These observations imply that the L-C coordination character is quite justifiable in NNHOs. This also implies that these NNHOs are very unstable and they may get dissociated to the NHC and the fulminic acid species easily. Bond dissociation in **O-12** gives rise to NHC and aryl cyanide oxide which is a stable species. This could be the reason why no information is available on the nitroso NHO's in the chemistry of NHO's. The above study indicates that it is possible to consider the carbene-Fulminic acid coordination interaction in these species as shown in Figure 5 as one of the resonating structures.

Fig 5 . Possible NHC-C interaction in Pralidoxime and its deprotonated form.

Conclusions

Quantum chemical analysis has been carried out on a set of cationic oximes which are analogous to the drug, Pralidoxime, known as a detoxification agent in organophosphate poisoning. The geometrical, electronic, energy parameters associated with these species indicate that the NHC-C interaction can be considered to carry a dative bond rather than a single bond. This observation is significant considering the fact that many species containing NHC functional moiety are being generated, a few of them are therapeutically important. Because of this interaction, the NHC unit can easily dissociate away from the rest of the molecule. Quantum chemical calculations have been performed on NNHOs also. The results clearly indicate the possible dative bond between the NHC unit and the fulminic acid. The BDE values in the neutral species are significantly less than that of corresponding cationic oximes, explaining the options of nitroso NHOs in the chemistry of NHOs.

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