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TITLE: On the nature of NO-bonding in *N*-oxide group

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ABSTRACT: The nature of the NO-bond in the N-oxide group was investigated by means of combined theoretical calculations (including QTAIM and NBO approaches) and statistical analysis of the content of Crystal Structure Database. The N→O bond in the N-oxide group should be classified as the NO donating bond with important contribution of ON back-donation (of π-electron

type, when available). Among other things, the visualization of the Laplacian of electron density in the region of oxygen valence sphere suggests the presence of two lone pairs for the imine-N-oxide group (characterized by effective ON back-donation). Detailed bonding analysis performed by means of Natural Resonance Theory indicates that the N→O bond is of order clearly greater than 1. Additionally, the stability of the N→O bond in various N-oxides was estimated. The analysis of hydrogen- and halogen-bonded complexes of the N-oxides reveals strong Lewis basicity of N-oxide group. Formation of H- and X-bonding leads to N→O bond elongation, with all consequences as concerns its structural, topological and spectroscopic characteristics. Moreover, in pyridine-N-oxide the electron-withdrawing -NO_2 group additionally stabilizes the N→O bond, whereas the opposite effect can be seen for the electron-donating -NH_2 substituent. This is due to substituent effect on π-type ON back-donation. As a consequence, the oxygen atom in pyridine-N-oxide may change its availability in intermolecular interaction formation, as revealed in interaction energy changes by about half of the total interaction energy estimated.

TEXT:

INTRODUCTION

Bonds between N and O atoms usually escape the classic description in terms of Lewis structures and the octed rule[1]. They possess a very large spectrum of characteristics, with bond lengths in the span of almost 0.4Å (1.136Å in FNO and 1.515Å in $FONO_2$). The analysis of NO bonds performed in selected model systems by QTAIM[2] and ELF[3] method showed that this type of bonds has large diversity which can be seen as significant differences in ELF-topology[3,4]. In that context the case of the NO bond in the *N*-oxide group is particularly interesting. According to the generally accepted and rooted in Lewis structure model, a classic picture of the N-oxide group bonding is depicted as a type of a donating bond in which the N atom shares its lone pair (LP) with the oxygen atom (see Fig. 1a). As a result, in the generally used notation, the N-oxide bond is represented as the bond with formal charge separation (the formal positive charge located on the N atom and, since the *N*-oxide group itself is neutral, the opposite charge is located on the oxygen atom (see Fig. 1b).). Alternatively the donating character of the bond is symbolically expressed as shown in Fig. 1c. In this paper we consequently use the latter notation.
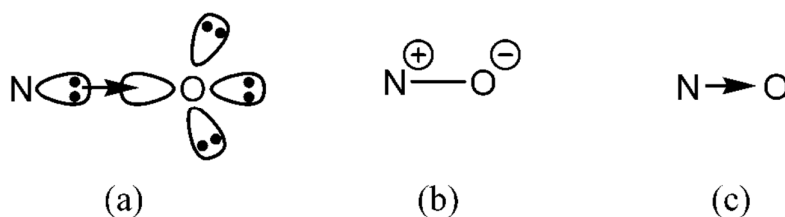

(a)	(b)	(c)

Figure 1. Schematic model of N-oxide bond: The Lewis-type structure as a model of N-oxide bond, (a), chemical notation with formal charge separation, (b), and corresponding notation indicating dative character of that bond, (c).

Following the above model one should consider the N-oxide bond as a formally single donating

bond linking the nitrogen (LP donor) and the oxygen (LP acceptor). The latter should additionally

possess three lone electron pairs, which should correspond to the sp^3 hybridization model, being

most adequate for the description of the electron structure of the oxygen atom in the *N*-oxide group.

In fact, Dobado et al.[5] reported $H_3N\rightarrow O$ and $F_3N\rightarrow O$ molecular systems as those in which the

$N\rightarrow O$ bond exhibits the properties that are typical of a single covalent bond, and in which the

topology of the Laplacian of electron density indicated three local minima (thus, three local

concentrations of electron density) within the oxygen valence sphere, each corresponding to one of

three LPs. An essentially different view on the NO bond in the $F_3N\rightarrow O$ molecule was presented by

Chesnut[6]. According to him LPs formally belonging to the oxygen atom are effectively delocalized

which leads to a triple bond behavior of the NO bond.

Although bonding in amine *N*-oxides seems to be thoroughly characterized (though still with some

discrepancy in final conclusions, as mentioned above) the case of the $N\rightarrow O$ bond in imine *N*-oxide

still requires a deeper and more comprehensive analysis, in particular because such species as *N*-

oxide-pyridines and N-oxide-imidazoles focus the attention of specialists from the field of synthetic

chemistry, biochemistry and pharmacology due to their potential large applications in medicine[7-12].

That is why, in this paper we provide the results of such an analysis in which selected model

systems representing the most important groups of *N*-oxide-imine derivatives were taken into

account. Our aim was thus to study theoretically the nature of the NO bond in relevant molecular

systems. A single NO bond is associated with three electron lone pairs on oxygen. In contrast, a

multiple NO bond is to be associated with just two instead of three LPs. Moreover, they are to be

localized in the plane of a molecule. Our interest was to verify whether this conclusion would be

supported by various theoretical methods such as QTAIM[2] and NBO[13,14]. The QTAIM analysis

gives several descriptors of chemical bonding and as such it allows one to characterize and define

various types of bonds, both of closed-shell and shared character[15-54]. Thus, it is a powerful tool in

bonding analysis, also in the case of the problem here undertaken, as it will be shown in the next sections. As the NBO method refers to the Lewis structure of a molecule, it is thus able to predict the number of electron lone pairs directly. As such, it should also be helpful to perform a deeper study of this issue. Additionally, the ability of the oxygen atom in the *N*-oxide group acting as Lewis base in Lewis-base/Lewis-acid complexation was assessed and a series of hydrogen- and halogen-bonded complexes was investigated by means of theoretical approaches and statistical analysis of the experimental data collected in Crystal Structure Database (CSD)[55].

METHODOLOGY

1. Computational details

DFT calculations were performed with the use of Gaussian09 set of codes[56] at the B3LYP/aug-cc-pVTZ level of theory. Recently it was shown that B3LYP functional in conjunction with large basis set gives satisfactory QTAIM results. In order to improve the accuracy of calculations, the grid used for numerical integrations was additionally increased (Int=UltraFine) and convergence criteria for geometry optimizations were additionally tightened (Opt = Tight option). Frequency calculations were performed at the same level of theory. No imaginary frequencies were found. For optimized geometries the WFX files were produced and used for QTAIM calculations performed with AIMAll software[59]. Since the QTAIM theory was excellently introduced by Richard Bader[2] and his collaborators[35,61], we used its assumptions and specific terminology with no additional explanations, allowing readers with less detailed knowledge on that approach to get inside the original literature. Recently it was shown that B3LYP functional in conjunction with large basis set gives satisfactory QTAIM results.[44,46,51]

In order to have a deeper insight into the N→O bond and since the investigated set of molecules represent highly delocalized character we have used Natural Resonance Theory (NRT) which is based on properties of the first-order reduced density matrix in the natural bond orbital

(NBO[13,14]) representation and was introduced by Glendening and Weinhold[55-56] within NRT formalism the one-particle reduced density matrix $\hat{\Gamma}$ of delocalized molecule is represented in terms of idealized density matrices for resonance structures α, where each $\hat{\Gamma}_\alpha$ is constructed by means of NBOs

$$\hat{\Gamma} = \sum_\alpha w_\alpha \, \hat{\Gamma}_\alpha \qquad (1)$$

and w_α is the weight for the αth resonance structure. As a consequence, e.g. the bond order of the A-B bond (b_{AB}) is obtained as a weigh-averaged number of bonds between A and B

$$b_{AB} = \sum_\alpha w_\alpha \, b_{AB}^{(\alpha)} \qquad (2)$$

Where $b_{AB}^{(\alpha)}$ is the (integer) number of A-B bonds in the idealized Lewis-type structural formula for the αth resonance structure. Summation b_{AB} over all possible atoms B (B $\neq$ A) yields the natural atomic valency of atom A that can be regarded as measure of total bond-making capacity exhibited by atom A in a molecule. Since O in the *N*-oxide group is bonded to the N atom only, its natural atomic valency is equal to the b_{NO} bond order. It is worth mentioning here the impressive agreement between QTAIM and NBO results reported recently.[57]

2. CSD search

The search through Cambridge Structural Database (CSD, release 2014)[58] was done in order to collect geometrical parameters of the *N*-oxide group. The general criteria of the search are shown in Fig. 2 During the search the bonds around the nitrogen atom were specified as single, double, delocalized or π-type (variable type). In order to obtain high-quality results the search criteria were additionally tightened and crystal structures of organometallic compounds, those with *R* factors larger than 0.05, disordered, including numerical errors or obtained from powder studies were
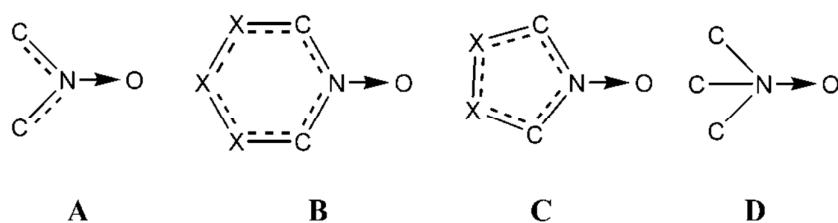
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Figure 2. Molecular motifs used as main criteria of the CSD search: acyclic imine *N*-oxides (**A**), six-membered aromatic *N*-oxides (**B**), five-membered aromatic *N*-oxides (**C**) and aliphatic amine *N*-oxides (**D**). Symbol X corresponds to any element except for metals and hydrogen.

Firstly, CSD was searched for both acyclic and cyclic molecular fragments containing the imine *N*-oxide group. However, a great number and large variety of the observed crystal structures caused that in the case of cyclic *N*-oxides we limited our search to aromatic derivatives only. Moreover, an additional search was performed on aliphatic amine *N*-oxides, which were chosen as a reference group of compounds. Therefore, there are four individual sets of data collected for each of the following chemical species as shown in Fig. 2: acyclic imine *N*-oxides (**A**), six-membered aromatic *N*-oxides (**B**), five-membered aromatic *N*-oxides (**C**) and aliphatic amine *N*-oxides (**D**). Additionally, for each of the **A-D** sets the influence of intermolecular interactions (of H- and X-bond type) on geometrical characteristics of the *N*-oxide group was investigated.

RESULTS AND DISSCUTION

1. *N*-oxide bond

1. 1. QTAIM-based study

As it was mentioned in Introduction, according to classic Lewis model of the bonding the N→O bond should be considered as a formally single donating bond linking the nitrogen (LP donor) and the oxygen (LP acceptor), thus, exhibiting QTAIM characteristics, which will be at least

qualitatively similar to those of, e.g., single N-O or C-O bonds, and perhaps also those of some classic donating bonds, like e.g. in metal complexes (See reference (63) for collection of QTAIM characteristics of various chemical bonds.). Table 1 contains selected QTAIM parameters collected in the N→O bond critical points in molecular systems **1-11** from Chart 1. For comparative purposes the corresponding data was collected for **10** and **11**, in which covalent, formally single and double N-O bonds, respectively, are present. (Note that ΔE_b corresponds to the bond energy estimated from a hypothetic reaction of N→O bond dissociation from Scheme 1 and will be discussed in the further part of the manuscript.)

Table 1. Selected QTAIM and NRT derived characteristics of the N-oxide group. Bond length $d(N\rightarrow O)$ in Å. Values of electron density in BCP (ρ_{BCP}), its Laplacian ($\nabla^2\rho_{BCP}$), total electron energy density (H_{BCP}) and N,O delocalization index given in atomic units. Values of ΔE_b correspond to energy (in kcal/mol) estimated by means of the reaction presented in Scheme 1. Weigth-averaged bond order of the N→O bond (b_{NO}) and number of electron lone pairs on O (nLP_O).

	D(N→O)	ρ_{BCP}	$\nabla^2\rho_{BCP}$	ε_{BCP}	H_{BCP}	DI(N,O)	ΔE_b	b_{NO}	nLP_o
1	1.365	0.343	-0.140	0.000	-0.276	1.385	-100.8	1.0758	2.9242
2	1.152	0.615	-1.852	0.000	-1.002	1.823	135.1	1.8445	2.1553
3	1.164	0.591	-1.797	0.000	-0.955	1.855	133.5	1.7336	2.2662
4	1.164	0.589	-1.840	0.000	-0.966	1.881	137.6	1.7424	2.2575
5	1.266	0.450	-0.759	0.775	-0.512	1.557	133.0	1.0443	2.7627
6	1.284	0.426	-0.585	0.616	-0.450	1.493	118.3	1.2084	2.7442
7	1.276	0.439	-0.677	0.72	-0.482	1.523	127.8	1.2924	2.7049
8	1.288	0.423	-0.580	0.677	-0.444	1.485	124.6	1.2552	2.7420
9	1.264	0.452	-0.767	0.758	-0.517	1.557	129.1	1.3566	2.644
10	1.445	0.282	-0.196	0.143	-0.208	1.238	-	1.0156	1.9886
11	1.198	0.536	-1.614	0.824	-0.833	2.153	-	2.0293	1.9707

Chart 1. A scheme of the investigated molecular systems.
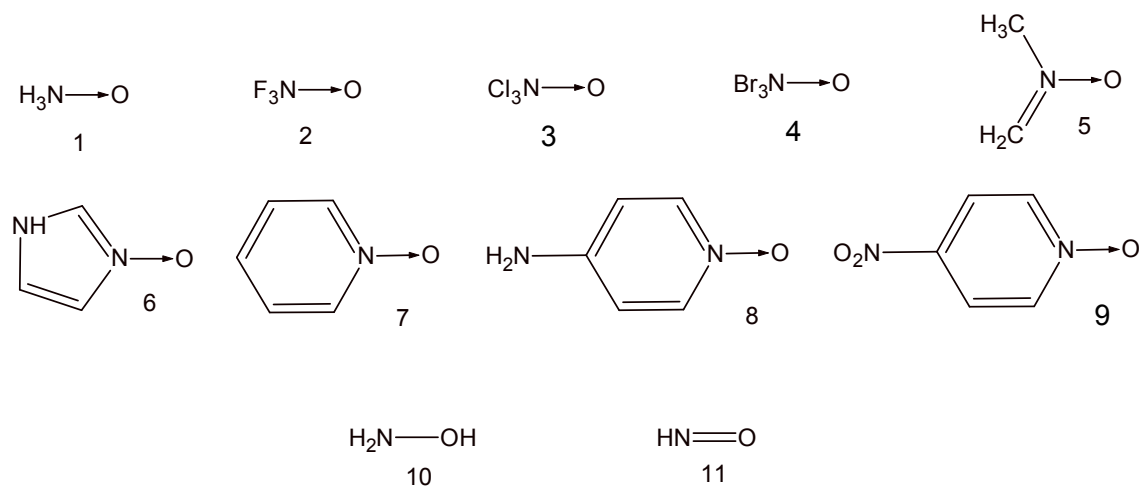
As can be seen, the ρ_{BCP} values are in the range between 0.34 au for $H_3N{\rightarrow}O$ and 0.61au for

$F_3N{\rightarrow}O$, being much higher than it would be expected for the formally single bond. For instance,

the corresponding value found for the formally single N-O bond in H_2NOH (**10**) equals 0.28 au,

whereas for the single C-O bond in dimethyl ether it is about 0.26 au (B3LYP/aug-cc-pVTZ). In

recent studies on the influence of the basis set on QTAIM calculations[44,46] the values of ρ_{BCP} of

single C-O bond were also oscillating around 0.26 au (depending on the basis set) whereas the same

value for the double C=O bond in formaldehyde was about 0.43 au, much closer to the N-oxide

bond investigated here. The ρ_{BCP} of typical N-TM (where TM is the transition metal center)

donating bond is even smaller, being of about 0.05 au.[36]. What is also interesting, the ρ_{BCP} value of

the N-oxide bond is much closer to that in the formally double N=O bond in HNO (see Table 1) or

even in earlier mentioned carbonyl bond in carbonyl group of formaldehyde (ρ_{BCP} =0.42 au,

B3LYP/aug-cc-pVTZ)[46]. The negative sign of $\nabla^2\rho_{BCP}$ and H_{BCP} in N-oxide BCP suggests shared

character of bonding.

As far as ellipticity of the N-oxide bond is concerned, there is a clear difference between **1-4**

systems and the rest of *N*-oxides. In the former the ellipticity is essentially close to zero, whereas in

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the latter it clearly adopts higher values, comparable even with those in the double NO bond in the HNO molecule. Therefore, the values of ellipticity of the N→O bond in systems **5-9** may suggest the contribution from pi-type bonding, whereas in **1-4** the valence of the N atom enforces a specific situation in which π-bonding cannot occur. Note that ellipticity equals zero for bonds with cylindrical cross section, e.g. the single and triple ones, while it adopts large values for bonds with elliptical cross section. The N-oxide bond should be classified somewhere between single and double, depending of the chemical enviroment. In that context two reports are also worth mentioning. One in which ellipticity correlates linearly with bond order of the non-polarized CC bond[62] thus well reflecting the multiplicity of CC bonds, and the other, in which ellipticity of polarized NO bonds in formamide was discussed by Bader and co-workers and the changes of which were used as a measure of charge flow within molecules due to dimerization[65]. Thus, ellipticity can be a useful parameter, assuming that its indications and indications of other QTAIM-based parameters are consistent.

Interestingly, the DI(N,O) values for **2-4** indicate more than just a single N-O bond. Systems **1** and **2** were already investigated[5] and it was stated that in the case of **2** there is a charge flow from the oxygen atom to nitrogen atom. No such effect was observed for **1**. In general, the here analyzed QTAIM parameters of the N→O bonds in **1-4** confirm such an observation. However, due to the electronic structure of the N atom this effect cannot be interpreted directly as the standard π-type back-donation. Thus, the charge flow must in this case occur rather *via* hyperconjugation instead of π-type back-donation (as it was observed for instance for carbonyl ligands in Cr-complexes [36]). When considering the **2-4** systems, it can be seen that DI(N,O) is the largest for **4** and the smallest for **2**. At the same time an opposite trend can be observed for the values of ρ_{BCP}. This likely results from the size of halogen atoms attached to the N atom and the fact that for larger halogens the charge delocalization in general should be more efficient, as indicated e.g. by the X-N→O angle

being about 114°, 115° and 117° for X = Br, Cl and F, respectively. Nevertheless, a more efficient

back-donation should appear for **2**, as compared with **3** and **4**, since strong electronegative character

of the F atoms strengthens the effect. This is reflected by the highest N→O ρ_{BCP} values and the

shortest N→O distances (see Table 1 The values are: 1.365, 1.152, 1.164 and 1.164 Å for **1**, **2**, **3** and

4, respectively.). As already mentioned, in all $X_3N{\to}O$ molecules (where X = H, F, Cl, Br) the

ellipticity of the N-oxide bond is essentially close to zero, which additionally supports the lack of

typical π-type back-donation.

A clearly different picture of the situation can be seen in systems **5-9**. Here the high values of

ellipticity suggest a significant π-type contribution to the N→O bonding, and assuming the back-

donation as an important effect stabilizing the N→O bond, one should consider π-type back-

bonding as an important part of the N→O interaction. This should be reflected in specific electron

structure of the oxygen atom, with two LPs and essentially double NO bond character in the

extreme case corresponding to the double NO bond.

In some reports it was demonstrated that the lone pairs located on some atomic centers can be

visualized with the use of QTAIM analysis[66]. Fig. 3 shows a graphical interpretation of the

Laplacian of electron density for systems **4**,**6**,**7**, and, for comparative purposes, for water and

methanolate anion. Interestingly, it can be observed that, in the case of **6** and **7** (Fig. 3 a and b), in

the region of oxygen valence sphere there are in fact not three, but only two LPs. (Spheres of local

charge concentration, corresponding to atomic core densities of larger atoms and densities of H

atoms, are also visible.) These two LPs are located symmetrically in plane of the molecule. Thus, at

least imidazole-N-oxide (**6**) and its pyridine analog (**7**) should possess a multiple NO bond. This is,

however, not the case of e.g. **4** (Fig. 3 c). Moreover, the electronic structure of the oxygen atom in

the N-oxide group in **6** and **7** is closer to that observed for oxygen atom in the carbonyl group. This

is not what would be expected in the first turn from the (common in organic chemistry) classic view

on the *N*-oxide bond. For comparison, in the case of water molecule (Fig. 3 d) two LPs can be easily located in expected positions. In the case of $H_3C\text{-}O^-$ anion (Fig. 3 e) there is the electron density concentration represented as an envelope in the region of space where three LPs should formally be located. Note that in this case the $\nabla^2\rho$ topology does not show three separate LPs, but rather spherically delocalized charge density in region where LPs were expected to be located. A similar observation can be made for system **4** (see Fig. 3 c). Finally, in methylimine (Fig. 3 f) only one LP is observed in expected position.
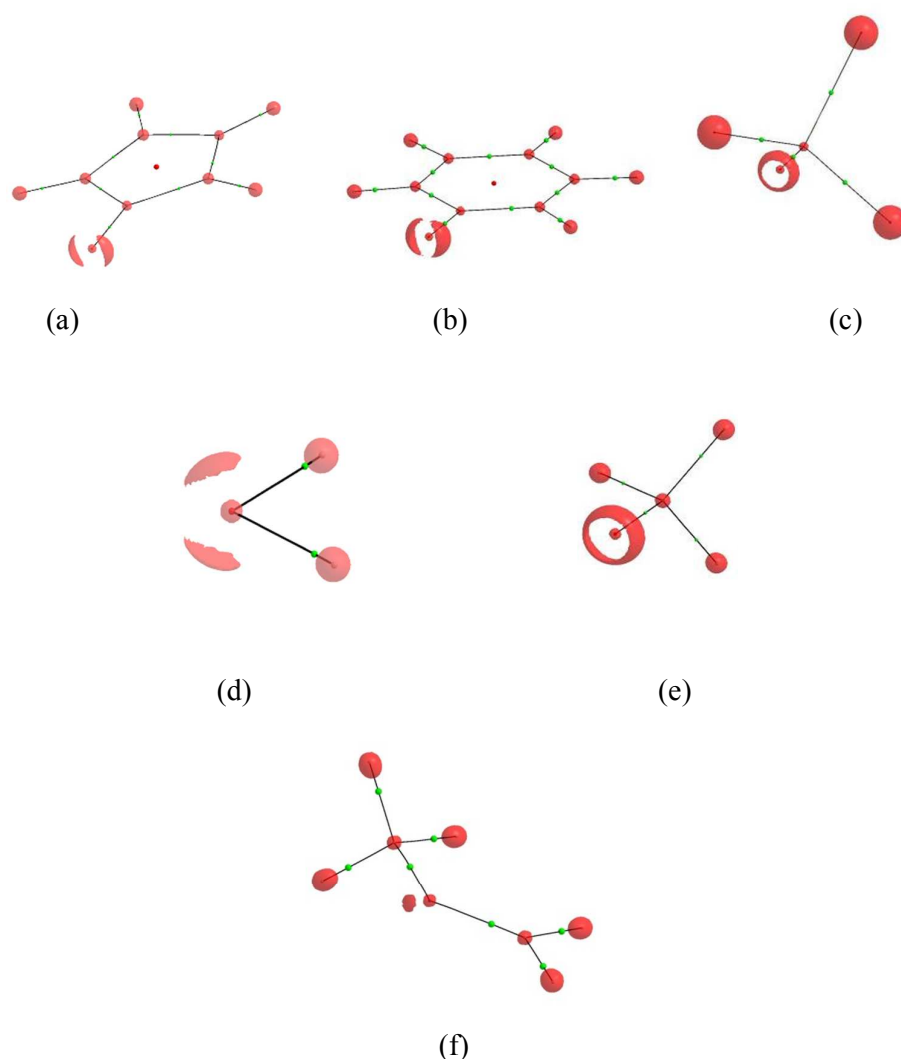

(a)   (b)   (c)

(d)   (e)

(f)

Figure 3. A graphical interpretation of the Laplacian of electron density in imidazole-*N*-oxide (a),

pyridine-N-oxide (b), Br3N→O (c), water molecule (d), and methanolate anion (e), and

methylimine (f). The conditions of calculations were selected in such a way that the $\nabla^2\rho$ valence

topology of oxygen atom indicates positions of LPs.

As concerns three *N*-oxide pyridine derivatives, **7-9**, it can be seen that the presence of a substituent

in the para-position with respect to the N atom clearly influences the N-oxide bond. The electron-

withdrawing -NO$_2$ group additionally stabilizes the N→O bond (as can be seen for instance from

bond shortening, ρ_{BCP} increase, etc.), whereas the opposite effect can be observed for the electron-

donating -NH$_2$ substituent. The trend as concerns the changes indicates that the interaction between

the substituent and the N-oxide group proceeds via resonance effect and an increase of π-back-

bonding in **9** with respect to **7**, and even more so with respect to **8**.

1. 2. The strength of the N→O bond

It would be interesting to estimate the approximate energy of N-oxide bonding. This can be done,

for instance, with the use of a hypothetic reaction of N→O bond dissociation, as shown in Scheme

1. Note that such hypothetic reaction can be considered as the case of isodesmic reaction[67-69].

Isodesmic reactions were shown[50,52,70-75] to be a valuable tool in estimating the energies of various

intramolecular interactions. In order to have a consistent scheme of N→O bond strength estimation,

we used the O atom in its singlet state (calculations were done as restricted in order to avoid

HOMO-LUMO mixing), which corresponds most adequately to oxygen atom electron configuration

in the generally accepted model of N-oxide bonding, with three LPs and one empty orbital (donated

by LP from the N atom in N-oxide). Since the difference between energy of oxygen singlet and

triplet state is constant, the final result of the kind of dissociation limit (singlet or triplet oxygen at

the end) will differ by constant value, that is, 21.5 kcal/mol.[76]

$$R \longrightarrow O \longrightarrow R + O$$
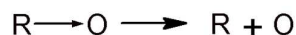
Scheme 1. A scheme of the hypothetical reaction of N→O bond, used for estimation of N-oxide bond energy.

As can be seen in Table 1, all values of ΔE_b are positive, indicating the left-hand position from Scheme 1 as energetically more stable. The span of values is of about 37kcal/mol, with the strongest N→O bond in **4** and the weakest one in **1**. For imine N-oxides this span is within the mentioned values, being of about 15 kcal/mol. For instance, in pyridine *N*-oxide the energy of the dissociation reaction changes by about 4.5 kcal/mol only due to the presence of the π-electron-donating or π-electron-withdrawing substituent in *para* position (with respect to the N-oxide group). What is important, when considering pyridine derivatives **7-9**, the strongest N→O bond exists in **9**, in which *p*-nitro group additionally stabilizes the back-donation in the N-oxo group resonance π-electron withdrawing effect. The opposite effect can be observed in **8**, with the π-electron donating *p*-amino substituent. Such an observation shows an important role of π-type back-donation in systems **5-9**, for which back-bonding may be considered as a component of the N-oxide bond. The importance of π-type back-donation can also be illustrated by a linear relation between the N→O bond ellipticity and ΔE_b (see Fig. 4). Interestingly, for ρ_{BCP} such a good correlation could not be found (cc being of about 0.828). Thus, it should be expected that the changes in ΔE_b parameter mainly result from the changes in π-type contribution to the N-oxide bond. Interestingly, the average bond energies* of covalent, formally single and double bond energies are ~48 and ~145 kcal/mol, respectively[77]. The

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* The energy of i.e. single covalent N-H bond will be different in amine and imine. Thus, the average value in such cases is used as a medium value estimated for chemically various species containing the given considered chemical bond.

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bond energies estimated for N→O fit perfectly in between these values, suggesting that the bond in

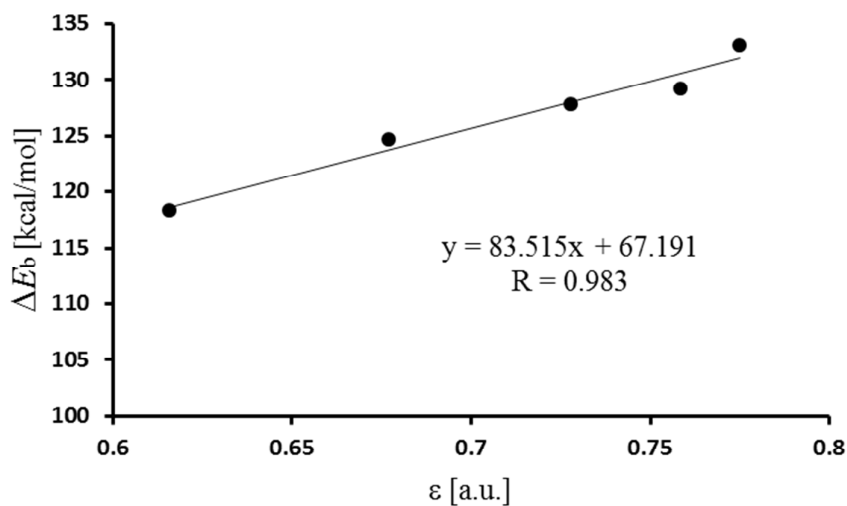N-oxides should be considered as intermediate between the single bond and the double one.

Figure 4. A linear relation between N→O bond ellipticity and N→O bond energy.

1. 3. NBO-based study

As already mentioned, in order to have a deeper insight into the N→O bond and since the

investigated set of molecules represent highly delocalized character we have used Natural

Resonance Theory (NRT) introduced by Glendening and Weinhold[55-57]. Weigthed average bond

order of the N→O bond (b_{NO}) and the number of electron lone pairs on O (nLP_O) are listed in the

last two columns of Table 1.

Similarly as in the case of QTAIM-based analysis, we shall firstly focus on the **1-4** systems.

The N→O bond in $H_3N→O$ (**1**) can clearly be regarded as a single one with a negligible

delocalization of electron density derived from the electron lone pairs on oxygen. The natural bond

order amounts to 1.0758, thus it is close to one and, moreover, comparable to b_{NO} (1.0156) in **10**

(H_2N-OH) with an evident single character of the N-O bond. Both the somewhat greater than just

one value of b_{NO} and the somewhat lesser than three value of nLP_O in **1** results from a negligible (ca. 7.6%) percentage contribution of resonance structures possessing double NO bond and two instead of three electron lone pairs on O. Comparing **1** with **2-4** one can see that the presence of halogen atoms (F in particular) in place of hydrogens leads to a significant increase of the natural bond order that, importantly, is much greater than just one. Its value is 1.8445 in $F_3N \rightarrow O$ (**2**), 1.7336 in $Cl_3N \rightarrow O$ (**3**), and 1.7424 in $Br_3N \rightarrow O$ (**4**). Thus, b_{NO} in **2-4** is only a little lesser than in the HN=O molecule (**11**) possessing a typical N=O double bond (b_{NO} = 2.0293). This indicates a meaningful delocalization of charge within the NO bond. This delocalization certainly results from a hyperconjugative interaction of the $LP_O \rightarrow \sigma^*_{CX}$ (X = halogen) type as nLP_O decreases from 2.9242 in **1** to 2.2662 and 2.2575 in **3** and **4**, respectively, and even more to 2.1553 in **2**. This is further supported by the presence of "double-bond, no-bond" or even of "triple-bond, no-bond" resonance structures in which some of the relevant N-X bonds are broken. The significantly greater value of b_{NO} in **2** (1.8445) in comparision with b_{NO} in **3** and **4** (1.7336 and 1.7424, respectively) results from the considerably lesser weight of the leading Lewis structure possessing three electron lone pairs on X and O atoms and a single N-O bond. Contributions of this Lewis structure, respectively for **2**, **3**, and **4**, amount to 26.26, 40.14, and 40.74%. As a consequence, this result also suggests much greater delocalization of charge in molecule **2** than in either **3** or **4** that, in turn, is in accord with the greatest value of ρ_{BCP} and the shortest NO bond in this molecule (see Table 1). It is worth mentioning that the presence of almost two (nLP_O = 2.2575) electron lone pairs on oxygen in **4** has not been supported by QTAIM-based graphical presentation of the Laplacian of electron density shown in Figure 3c which, instead, has suggested the presence of three electron lone pairs. We would like to stress, however, that, in general, one should not expect the same conclusions regarding the number of lone pairs on oxygen from QTAIM and NRT. This results from the fact that calculations based on the former method relate only to the individual (i.e. single) structure of the studied molecule, whereas the latter one brings about sets of diverse Lewis resonance structures,

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quite often possessing different patterns and orders of bonds, numbers of electron lone pairs, etc. Thus, NRT directly takes strong delocalization of charge into account and thus, as a consequence, seems to be reliable method in counting the number of lone pairs on oxygen in investigated set of molecules.

Now, we will focus on molecules **5-9**. One can see that there is a sizeable difference in values of b_{NO} in **5** and the other molecules. In the former molecule, natural bond order is close to one (1.0414), similarly as in **1** (1.0758) and **10** (1.0156), indicating the (almost) single character of the NO bond. It shows that the NO bond in **5** representing an acyclic N-oxide should rather be considered as a single bond with only negligibly small double character. This, however, does not necessarily has to mean that the NO bond in **5** is weaker than in **6-9** molecules representing aromatic systems possessing either the five-membered imidazole or the six-membered pyridyne ring (see Chart 1). Indeed, the NO bond in **5** turns out to be significantly shorter (1.266Å) and somewhat stronger (133 kcal/mol) than NO bonds in **6-8** (1.276 − 1.288Å and 118.3 − 127.8 kcal/mol, respectively; see Table 1). Also the value of ρ_{BCP} in **5** is greater than in **6-8** (0.450 a.u. vs. 0.423-0.439 a.u.). In molecules **6** and, in particular, **7-9** the partly double character of the NO bond is clearly evident as indicated by values of b_{NO} and nLP_O which are, respectively, greater than 1.2 and lower than 2.75. As a consequence there is clear evidence of a significant π back-bonding in these molecules.

Interestingly, if b_{NO} and nLP_O are both to indicate the magnitude of the charge delocalization within the N→O bond, then it should be significantly larger in systems **2-4**. Hence, the hyperconjugative interaction of the $LP_O \rightarrow \sigma^*_{CX}$ type has a greater impact on N→O than the π back-donation of the $LP_O \rightarrow \pi^*_{CN}$ type. Importantly, in **2-4** and **6-9** values of b_{NO} are clearly higher than 1 characterizing a formal N-O single bond (see $b_{NO} = 1.0156$ for **10**, i.e. H_2N-OH) and the weight-averaged number of electron lone pairs on oxygen is clearly lesser than 3 as would have been expected for the ideal

single N-O bond in these molecules. As a consequence, values of these NRT-based parameters indicate a somewhat double character of the N→O bond in the investigated set of systems (except **1, 5,** and **10**) as resulting from a significant delocalization of electronic charge, being in turn a consequence of a considerable magnitude of either the hyperconjugative interaction of the $LP_O \rightarrow \sigma^*_{CX}$ type or the $LP_O \rightarrow \pi^*_{CN}$ back-bonding. The utmost effect of one of these interactions takes place in molecule **2** ($F_3N \rightarrow O$).

The presence of molecules **7-9** in our set of investigated systems gives the opportunity to study the the influence of the *para*-substituent on a charge delocalization within the N→O bond. The electron-donating -NH$_2$ group in **8** (*p*-amino-N-oxide-pyridine) leads to the decrease of b_{NO} if compared to **7** (1.2552 vs. 1.2924, respectively), thus to the lowering of the N→O bond order. On the contrary, the strongly electron-withdrawing -NO$_2$ group in **9** (*p*-nitro-N-oxide-pyridine) leads to the opposite effect on N→O, namely to the increase of its bond order (from 1.2924 in **7** to 1.3566 in **9**). This results from larger delocalization of oxygen's lone pairs within the N→O bond as indicated by lesser value of nLP_O (2.7049 and 2.6434 in **7** and **9**, respectively).

2. The *N*-oxide group in molecular crystals

X-ray diffraction data are a reliable source of knowledge of both intramolecular bond distances and angles as well as geometric parameters of intermolecular interactions in the solid state. The above-discussed findings about the structure of the *N*-oxide bond, obtained from QTAIM and NBO analysis, turned our attention to experimental data. Hence, we performed the CSD searches to analyze and evaluate the geometry of the title chemical group. For this purpose geometrical parameters of the *N*-oxide group were compared with its intermolecular interactions as observed in the crystalline state. The latter ones are expected to be in relation with the distribution of valence

electron density of the N→O oxygen atom.

2. 1. The *N*-oxide bond

The obtained results concerning N→O bond length are presented in Fig. 5 and in Supplementary

Information (Table S1). For convenience the notation from Fig. 2 is used for discussion, thus, group

A corresponds to the case of acyclic imine *N*-oxides, group **B** to *N*-oxides with the nitrogen atom

belonging to the aromatic six-membered ring, **C** to *N*-oxides with the nitrogen of the aromatic five-

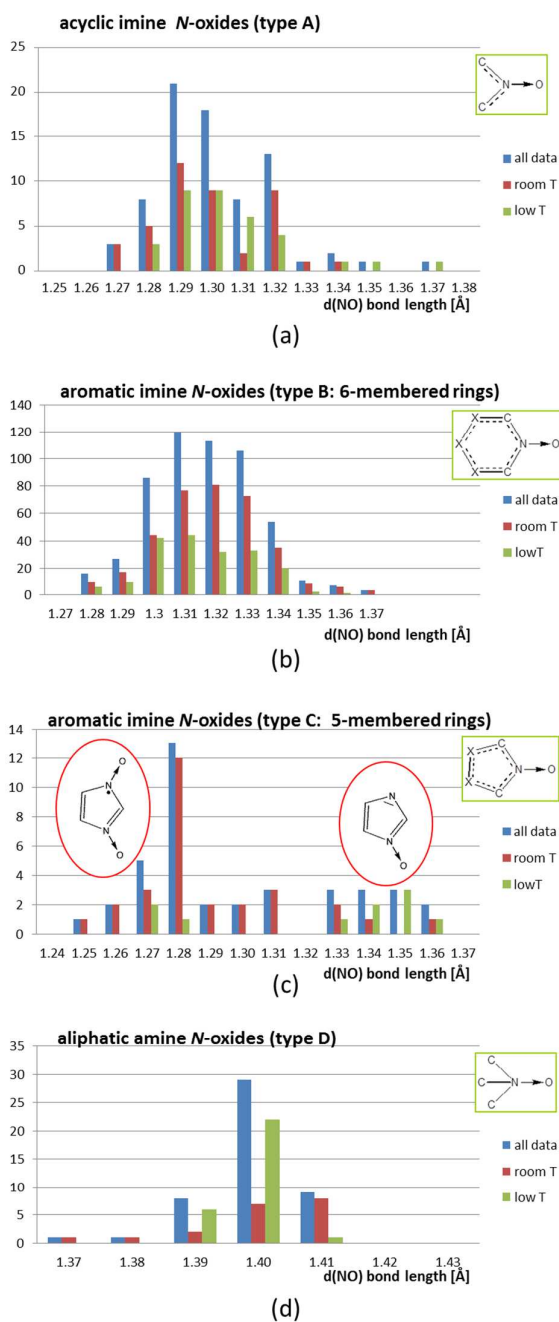membered ring and, finally, **D** aliphatic amine *N*-oxides.

Figure 5. Histograms of d(NO) bond lengths [Å] collected for **A-D** data sets.

At first sight it can be seen that the number of **B** cases (544 observations) is predominant. For **A** and

C this number is much smaller, being 78 and 39, respectively. Finally there are 48 observations for

D. Thus, from the statistical point of view the group **B** is the most representative one.

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The first stage of statistical analysis is concerned with the geometrical structure of the *N*-oxide group. While there are no unexpected results in valence angles, we observed relatively large variations in N→O bond lengths d(N→O). Fig. 5 presents histograms with bond lengths in the analyzed groups of compounds. To take into account temperature-dependent effects, we additionally divided the collected data into two separate samples each of them corresponding to low- and room-temperature diffraction measurements. In general, the low-temperature studies provide more accurate information about bond lengths.[†]

Analyzing N→O bond length (d(NO) parameter) in different groups we can see that in the case of six-membered imine aromatic *N*-oxides (**B**) there is rather normal distribution of data with the mean value about 1.317Å (see Supporting Information, **Table S1**). On the other hand, for the acyclic (**A**) and for the five-membered aromatic (**C**) imine *N*-oxides there is a growing number of crystal structures with a relatively long NO bond (above 1.34Å), especially in the case of low-temperature X-ray data. All these values can be compared with typical N-O single bonds in hydroxylamines (1.45Å) and typical N=O double bonds in nitrosoalkanes (1.27Å).

In the group of acyclic imine *N*-oxides (**A**) d(N→O) bond lengths are relatively short, with the mean value about 1.30Å, but significantly longer than for typical double bonds. On the other hand, for the aromatic imine *N*-oxides N→O bond lengths are increasing up to 1.32Å because of possible involvement of nitrogen atom in ring π-electron resonance. Therefore, for typical aromatic systems (pyridine *N*-oxide derivatives) the observed mean d(N→O) values are equal to 1.314Å or 1.318Å depending on temperature of the measurement (see Supporting Information, **Table S1**).

In the case of five-membered rings (**C**) the two subsets of data can be noticed in the scheme. The

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[†]　　It should be noted that low-temperature X-ray diffraction measurements generally give slightly longer interatomic distances in comparison with room temperature data. This results from the applied in the crystal-structure-solution-procedure mathematical description of atomic thermal movements (usually visualized as displacement ellipsoids) and not from the real temperature-dependent atom-atom distances elongation. In general, the low-temperature studies provide more accurate information about bond lengths. It is also worth mentioning that interatomic distances in crystal state are generally shorter than in gas-phase (theoretical calculations) due to crystal packing effects.

closer view on the related crystal structures allows one to find that, as shown in Fig. 5 c, one of the subsets, with shorter d(N→O) distances corresponds mainly to imidazole-N,N'-dioxide radicals, whereas the other one corresponds to imidazole-N-oxides. For the first group of compounds the octet rule is formally not fulfilled on one of the N atoms. Due to resonance effects there is a deficiency of electron density on both nitrogen atoms and, in consequence, in the structure of imidazole-N,N'-dioxide radicals a more effective back-bonding in the N-oxide group is expected leading to a shortening of bond lengths in comparison with imidazole-N-oxides. For imidazole-N-oxides in turn, d(N→O) bond lengths are slightly longer than for typical aromatic N-oxides (**B**). Finally, the sample of aliphatic N-oxides (**D**) seems to be more homogeneous and N→O bonds are evidently longer (with mean length of about 1.4Å) than for the other groups.

Surprisingly, in each of the **A-D** data sets the mean d(N→O) distances are systematically longer (approximately by about 0.03Å) than those obtained from theoretical calculations (cf. Table 1) performed for isolated molecules in the gas phase. This can be connected with the presence of specific crystal packing effects, e.g. intermolecular interactions which potentially affect the N→O group as revealed by the NO bond elongation.

2. 2. Intermolecular interactions of the *N*-oxide group.

In order to analyze the possible influence of intermolecular interactions on the geometry of the *N*-oxide group in the crystal state, we performed statistical analysis of CSD data. The search was aimed at hydrogen (H-bonds) and halogen (X-bonds) bonding, using a distance between the hydrogen/halogen atom and its acceptor (oxygen in N→O) shorter than the sum of corresponding van der Waals radii as a criterion of interaction. In the group of hydrogen bonds three types were analyzed: O-H…O; N-H…O and C-H…O, all of them with oxygen of the N→O bond as a potential proton acceptor. The search of CSD indicated only a few examples of C-X…O halogen bonds, where X refers to Cl, Br or I atom (details are presented in Supplementary Information **Table S2**).
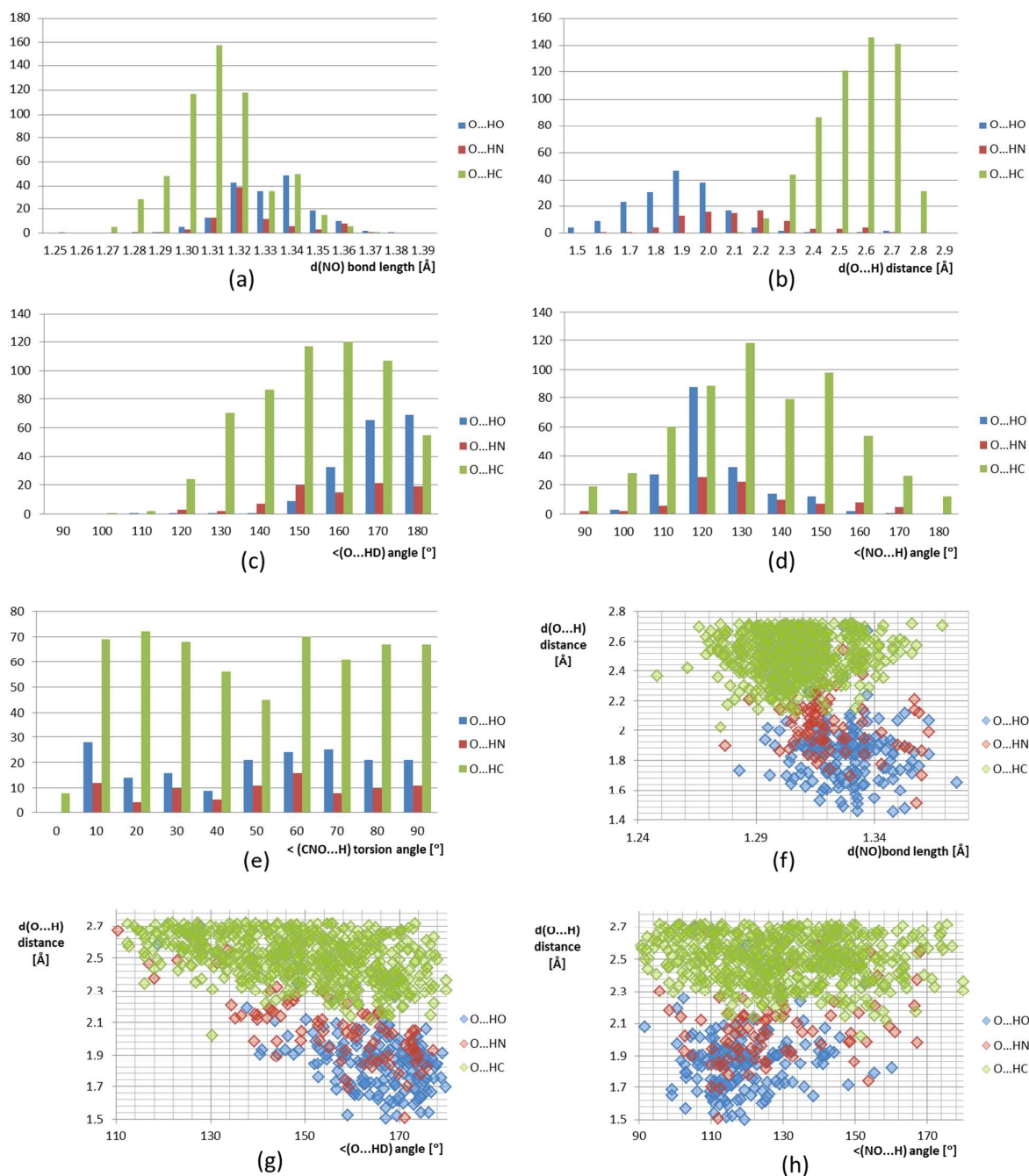
Figure 6. Histograms of selected geometrical parameters of imine *N*-oxides intermolecular

hydrogen bonds summarized for **A-C** data sets.

Firstly, in all the investigated groups (**A**, **B**, **C** and **D**) we noticed (Fig. 6 and **S.3.2.2** in

Supplementary Information) the dominant number of C-H…O intermolecular contacts of relatively

long intermolecular distances (above 2.1 Å).). The other two types of hydrogen bonds are characterized by shorter intermolecular distances in the range of 1.6-2.1Å for a great number of O-H…O interactions and 1.9-2.3 Å for N-H…O, respectively. Interestingly, as can be seen in Fig. 6 **f**, the shorter intermolecular O…H contacts (below 1.6Å) are assisted by the longer N→O bonds (above 1.32Å) which is in agreement with the postulated elongation of *N*-oxide bonds upon intermolecular interactions in the crystal state. The relationships between shortening of the intermolecular O…H contact and the preferred values of the two analyzed angles are well illustrated in the Fig. 6 **g-h**. For short O-H…O and N-H…O hydrogen bonds (with intermolecular distances below 1.7Å) all <(O…H-O/N) angles are close to linearity with the values above 150°, while <(NO…H) angles are below 130°. The latter reflects the direction along which a Lewis acid approaches lone electron pairs of the *N*-oxide oxygen atom. For the longer C-H…O hydrogen bonds there were no similar observations. i.e. the donor of the C-H bond may interact with the oxygen of N→O in many different arrangements, thus leading to wide ranges of <(O…H-C) and <(NO…H) angles (see Fig. 6 **g-h**). All the above-described relationships among geometrical parameters of imine *N*-oxides interactions are similar, as found for aliphatic amine derivatives (for comparison see Supplementary Information Figure S.3.2.2)

It is worth noting that there are no geometrical preferences in the <(CNO…H) torsion angle (see Fig. 6 **e**) which would describe the position of proton (Lewis acid) with respect to the *N*-oxide group (Lewis base), in particular to the plane defined by CN and N→O bonds. On the basis of the quantum theoretical description of the *N*-oxide bond, it is not unequivocally defined how the lone electron pairs of oxygen atom are spatially arranged (see Section 2.1). Here we can see that, probably due to packing effects, also the crystal structure data analysis does not provide information about geometrical preferences of the *N*-oxide group in hydrogen bonds, and indirectly about the arrangement of oxygen lone electron pairs.

The searches of CSD revealed a small number of crystal structures with the *N*-oxide group as a halogen bonding acceptor: 1 with chlorine as a halogen bonding donor, 4 with bromine and 11 with iodine (see Supplementary Information). Most likely this is due to a relatively small number of *N*-oxide derivatives containing halogen atoms in comparison with those containing potential hydrogen donors. In the further part of this work we use quantum chemical methods in order to reveal the nature of intermolecular complexes with the *N*-oxide group involved into H- and X-bonding in small molecular complexes.

3. Modeling N-oxide complexation via H-bonding and X-bonding

As shown in the previous section, the *N*-oxide group often takes part in an intermolecular interaction. Since it possesses negative charge surplus on oxygen atom (LPs), it acts as effective Lewis base fragment, forming H-bonds and X-bonds. Therefore, we analyzed a set of complexes from Chart 2 in which selected *N*-oxides form complexes (*via* H- and X-bonding) with simple model Lewis acid molecules. Table 2 collects basic numerical characteristics of these systems. For the purpose of the discussion we used the notation from Chart 2. Therefore, the system denoted as **7a** corresponds to the H-bonded complex of *N*-oxidepyridine and hydrogen isocyanide, whereas **8b** corresponds to the X-bonded complex of *para*-amino-*N*-oxidepyridine and bromomethane.
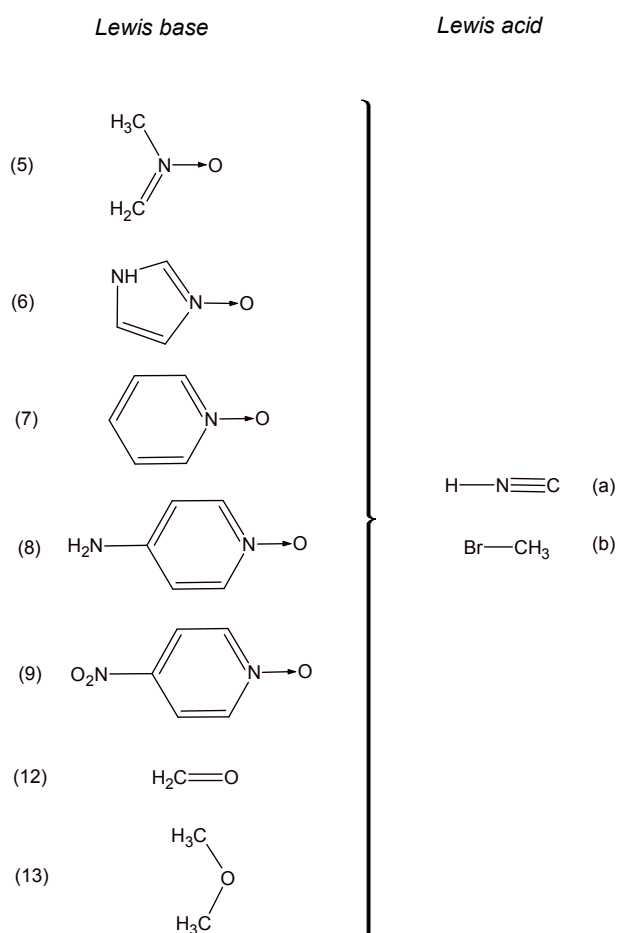
Chart 2. Schematic representation of H- and X-bonded complexes discussed in the text.

Table 2. Selected characteristics of N-oxide complexes formed *via* H- and X-bonding. Note that **9b** was not stable as X-bonded complex and so it is not characterized here.

	$d(H\cdots O)$	$d(N\text{-}H)$	$<(N\text{-}H\cdots O)$	$<(N\to O\cdots H)$	$\Delta d(N\to O)$	$\upsilon(N\to O)_{compl}$	$\Delta\upsilon(N\to O)$	$I(N\to O)_{compl}$	$I_{(compl/mono)}$	ΔE_{int}	E_{def}	$\rho_{BCP}\,(\cdot10^{-2})$	$\nabla^2\rho_{BCP}$	$H_{BCP}(\cdot10^{-2})$	$DI_{(O,H)}$
5a	1.702	1.031	178.20	123.92	0.015	1343.07	-6.25	122.9018	2.10	-11.435	0.531	4.556	0.1006	-0.963	0.1116
6a	1.608	1.050	174.93	112.38	0.021	1272.10	-20.37	191.3993	1.20	-15.738	1.416	5.595	0.0993	-1.843	0.1382
7a	1.673	1.036	175.94	118.87	0.020	1283.00	-36.85	268.6392	1.26	-12.188	0.755	4.952	0.1005	-1.198	0.1194
8a	1.604	1.051	174.67	112.41	0.025	1248.81	-34.75	286.6418	0.93	-15.394	1.604	6.002	0.0990	-1.878	0.1388
9a	1.752	1.024	174.80	123.96	0.017	1313.54	-29.90	504.1304	0.76	-8.716	0.327	4.009	0.0977	-0.657	0.1013
12a	1.837	1.016	174.49	-	-	-	-	-	-	-7.017	-0.103	3.233	0.0893	-0.294	0.0875
13a	1.748	1.022	178.00	-	-	-	-	-	-	-8.820	0.114	3.960	0.1003	-0.632	0.0979

	$d(Br\cdots O)$	$d(C\text{-}Br)$	$<(C\text{-}Br\cdots O)$	$<(N\to O\cdots Br)$	$\Delta d(N\to O)$	$\upsilon(N\to O)_{compl}$	$\Delta\upsilon(N\to O)$	$I(N\to O)_{compl}$	$I_{(compl/mono)}$	ΔE_{int}	E_{def}	$\rho_{BCP}(\cdot10^{-3})$	$\nabla^2\rho_{BCP}$	$H_{BCP}(\cdot10^{-3})$	$DI_{(O,Br)}$
5b	3.294	1.960	172.81	104.76	0.001	1348.77	-0.55	61.6620	1.05	-0.373	0.007	0.694	0.2385	0.110	0.0635
6b	3.186	1.960	178.63	177.14	0.002	1291.50	-0.97	187.9118	1.18	-0.474	0.019	0.877	0.3037	0.134	0.0862
7b	3.320	1.959	177.09	120.13	0.001	1315.08	-4.77	255.8537	1.20	-0.338	-0.000	0.667	0.2297	0.108	0.0645
8b	3.227	1.960	178.54	120.93	0.002	1278.81	-4.75	354.8324	1.16	-0.396	0.016	0.805	0.2788	0.126	0.0786
12b	3.469	1.959	164.76	-	-	-	-	-	-	-0.308	0.008	0.500	0.1753	0.087	0.0464
13b	3.322	1.959	175.96	-	-	-	-	-	-	-0.199	0.010	0.667	0.2300	0.108	0.0597

Since the X-bonds in **5-13b** complexes are significantly weaker than the H-bonds, we will first discuss this type of complexation. As it results from Table 2. the N-oxide group is an effective Lewis base, forming relatively strong H-bonded complexes, clearly stronger than those in **12a** and **13a**. This is reflected in both interaction energy values and in geometrical parameters, such as the H-bond length. Therefore, the oxygen atom in the *N*-oxide group is a strong H-bond accepting center, stronger than the same atom in the carbonyl or ether groups. The geometry of all H-bridges is close to linear, whereas the H-bond itself is directed to the *N*-oxide oxygen in such a way that it forms an angle between 112° and 124° with the N→O bond – a similar result was obtained in the CSD search. This angle parameter indicates spatial localization of LPs on the oxygen atom. Importantly, in almost all complexes the HNC molecule is placed out of plane of the *N*-oxide moiety. This spatial arrangement is shown in Fig. 7 a and b. Only in the case of **9a** the HNC molecule and the *N*-oxide-pyridine ring are co-planar (see Fig. 7 b). This observation would perhaps suggest the presence of 3 LPs on the *N*-oxide oxygen in all but one system, and supports NBO results from section 1.2.

(a)   (b)

Figure 7. Spatial arrangement of molecules in complexes **8a**, (a), and **9a**, (b).

QTAIM characteristics of H-bridges are close to those of strong H-bonds[61,63] with positive values of the Laplacian of electron density, $\nabla^2\rho_{BCP}$, and negative values of total electron energy density, H_{BCP}

- the latter indicating a partially shared character of interaction. Of the set of **5-9** systems, 6 and 8 are the strongest proton-accepting ones. When comparing three pyridine derivatives, **8** forms the strongest H-bonds due to electron-donating properties of the amine substituent, whereas **9** forms the weakest H-bonds due to electron-withdrawing properties of the nitro group. The difference in binding energy between **8a** and **9a** of about 7.5 kcal/mol shows that the substituent situated in *para* position with respect to the *N*-oxide group may efficiently change the Lewis basicity of this group.

When considering X-bonds, it can be noticed that in all complexes the binding energy is very low, with the values smaller than 1 kcal/mol. Such low values of interaction energy result mainly from the relatively weak Lewis acidity of bromomethane[78], but also, to a lesser degree, from the fact that in our calculations the dispersion effects were not included. As it was shown in recent reports, dispersion may contribute significantly to X-bonding (even by about 30%)[78-80]. Nevertheless, even if we assume that dispersion would increase the strength of X-bonding in **5b-13b** by one third of the current result, still the total interaction energy would be very small, much smaller than 1 kcal/mol. Also QTAIM characteristics indicates X-bonds in **5b-13b** as weak interactions, with very small ρ_{BCP}, its positive Laplacian and positive H_{BCP} values[63]. Despite the fact that the interactions in **5b-13b** are weak, the trends concerning the changes of parameters in Table 2 are similar to those found for H-bonded complexes, and similar interrelation between the collected characteristics can be noticed. Only the N→O...Br angle seems to vary more than its counterpart in H-bonded complexes (that is, the N→O...H angle). This results from the fact that in **5b-8b** an additional interaction of C-H...Br type affects final geometry of the complexes (see Fig. 8). Such a situation with halogen atom acting as a center of dual nature, being both the electron-donor and electron-acceptor in the H-bond and X-bond, respectively, was recently reported and thoroughly characterized (among other things it was demonstrated that in such a case there is no cooperative effect accompanying the complexation)[80-81].
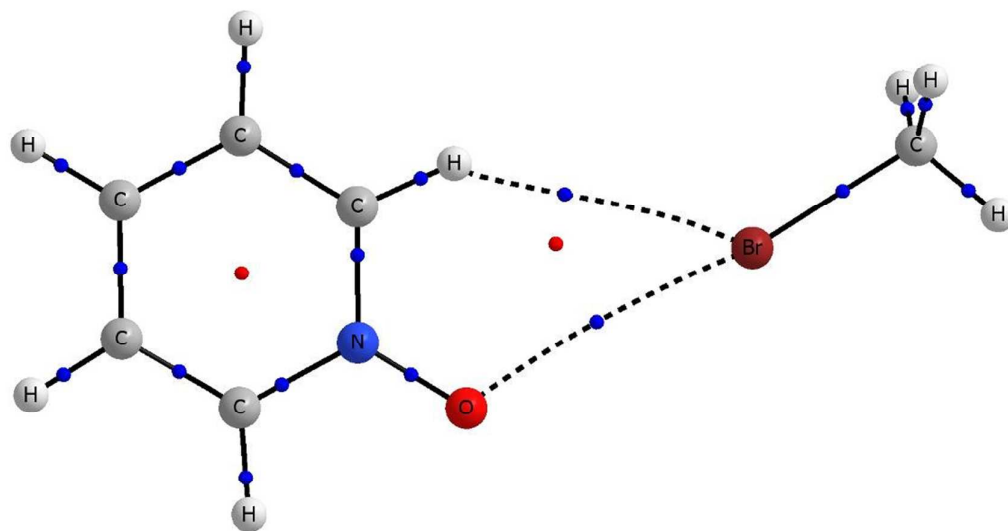
Figure 8. Complex **7b**, with double intermolecular bonding of C-Br...O and C-H...Br type. QTAIM

molecular graph shows (dashed line) bond paths indicating the presence of both interactions. Small

blue spheres are BCPs, small red spheres are RCPs.

The N→O bond elongation due to complexation can be clearly noticed in all complexes (including

both H- and X-bonded systems, see Table 2). The elongation follows the increasing strength of H-

and X-bonding. Such an observation can be easily explained on the basis of conclusions from

section 3.1. The oxygen atom in the *N*-oxide group acts as a back-bonding center (with the charge

transferred in direction from oxygen to nitrogen). When the electron charge is transferred from

oxygen to the adjacent molecule e.g. *via* H-bonding, the tendency of the oxygen atom to back-bond

formation decreases, thus, leading to the N→O bond weakening and d(N→O) elongation. This is

also reflected in stretching vibrations of N→O bond (see Table 2). Complexation leads to a

downfield shift (also called red-shift) of the NO stretching vibration frequency and to a small

increase of the IR intensity of this mode (except for 8a and 9a, for which the value of $I_{(compl/mono)}$ is

very close to but slightly lower than 1). Therefore, in general the length and vibrational properties

of the N→O bond may serve in the experimental assessment of the presence and strength of

intermolecular interactions in which the N-oxide group is involved.

To sum up this section, the *N*-oxide group may act as a Lewis base and it may form strong interactions with Lewis acids, in the form of H-donors in particular. Its Lewis basicity is stronger than that of the oxygen atom in covalently, formally singly and doubly bonded oxygen in the carbonyl and ether groups.

CONCLUSIONS

The N→O bond in amine and imine N-oxides was characterized. It was shown that QTAIM characteristics of the N→O bond in amine- and imine-*N*-oxides clearly differ, indicating a significant π-type back-donation in the case of the latter. For instance, in the amine-*N*-oxides the bond ellipticity is essentially close to zero, whereas in imine-*N*-oxides it clearly adopts higher values, comparable even with the value in double NO bond in the HNO molecule. Also, a linear relation was found between bond ellipticity and the energetic parameter estimated for the proper isodesmic reaction and reflecting the stability of the N→O bond. Moreover, the graphical interpretation of the Laplacian of electron density performed for a selected imine-N-oxide shows only two lone pairs located on the oxygen atom. In the case of *N*-oxide pyridine derivatives the presence of the substituent in the *para* position with respect to the N atom clearly affects the *N*-oxide bond. The electron-withdrawing -NO_2 group additionally stabilizes the N→O bond (as can be seen for instance from bond shortening, ρ_{BCP} increase etc.), whereas the opposite effect can be observed for the electron-donating -NH_2 substituent.

The dissociation reaction was used to estimate the N→O bond. It was found that in all the investigated N-oxides the N→O bond appears to be a stable form of bonding. For imine N-oxides the close to linear relation between ΔE_b and N→O bond ellipticity indicates the importance of π-type back-donation in that species. This is confirmed by the effect of substituents attached in *para*

position in N-oxide pyridines. Importantly, the estimated N→O bond energies adopt values in between those of formally single and formally double covalent NO bond.

Analysis based on Natural Resonance Theory indicates a somewhat double character of the N→O bond in the investigated set of systems. Values of natural bond orders are clearly higher than 1 characterizing a formal N-O single bond and the weight-averaged number of electron lone pairs on oxygen is clearly lesser than 3 as would have been expected for the ideal single N-O bond in these molecules. This partly double character of the N→O bond results from a significant delocalization of electronic charge, being in turn a consequence of a considerable magnitude of either the hyperconjugative interaction of the $LP_O \rightarrow \sigma^*CX$ type or the $LP_O \rightarrow \pi^*CN$ back-bonding. It has been shown that the former interaction has a greater impact on N→O than the π back-donation of the $LP_O \rightarrow \pi^*CN$ type. The utmost effect takes place in $F_3N{\rightarrow}O$.

Statistical analysis of CSD shows that structural parameters of the N-oxide bond may vary within a relatively large range of values, which can be explained by the fact that in crystal state the N-oxide group is usually involved in intermolecular interactions. This in turn, as shown by the calculations on model H- and X-bonded complexes, leads to elongation of the N→O bond. Also, the oxygen atom in the N-oxide group appears to be a more effective Lewis-type base than for instance the covalently-bonded oxygen atom in the carbonyl or ether groups. As a consequence, it readily forms hydrogen bonds that, as we showed, are much stronger than possible halogen bonds.

ASSOCIATED CONTENT

Supporting Information.

Numerical data from CSD search.

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