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Computational characterization of the hydroxylamino (—NH—OH) group

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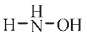
We have examined computationally some properties of the hydroxylamino group, —N(H)—OH, in different molecular environments. Geometries were optimized at the B3LYP/6-31G level and used to calculate B3LYP/6-311G(3df,2p) energy differences and HF/6-31G* electrostatic potentials $V(\mathbf{r})$ and local ionization energies $\bar{I}(\mathbf{r})$. $V(\mathbf{r})$ and $\bar{I}(\mathbf{r})$ were evaluated on the molecular surfaces defined by the 0.001 au contours of the electronic densities. Two important factors in determining the —N(H)—OH structure are lone pair repulsion and possible intramolecular hydrogen bonding involving the remainder of the molecule, which can affect the pyramidal character of the nitrogen. The nitrogen and oxygen lone pairs produce regions of negative potential, those of the oxygen being stronger. These should function as hydrogen bond acceptors, although not as well as NH_3 and H_2O. The nitrogen lone pairs, although less negative, are expected to be the more basic, often roughly similar to pyridine. The amine and hydroxyl hydrogens tend to have quite positive potentials, and should be potent in hydrogen bonding. Depending upon the remainder of the molecule, the hydroxyl and the amine protons can range from essentially no acidity to weak to quite strong. The hydroxylamino group is estimated to have an average polarizability of 2.38 Å^3 and as a substituent on aromatic rings to be activating and *ortho*, *para*-directing, with Hammett $\delta_p = -0.37$. Copyright © 2007 John Wiley & Sons, Ltd.**

Keywords: hydroxylamino group; hydroxamic acids; electrostatic potentials; local ionization energies; noncovalent interactions

INTRODUCTION

The hydroxylamino group, —N(H)—OH, is composed of four reactive atoms in close proximity: two potentially acidic hydrogens attached to two linked basic sites that have high electronegativities and significant lone pairs. It can be anticipated that having these two negative centers bonded to each other will confer some degree of instability, and this is confirmed by the simplest hydroxylamino compound, hydroxylamine H_2N—OH. It is an unstable hygroscopic white solid, m.p. = 33°C, that is decomposed by hot water and detonates when heated with a flame.[1] Hydroxylamines are quite reactive, and are important in a variety of synthetic procedures, for example, converting aldehydes and ketones to oximes, olefins and aromatics to amines, etc.[2]

Our objective in this work has been to computationally characterize the hydroxylamino group and to examine its properties in different molecular environments, as provided by a series of eight representative molecules, R—N(H)—OH, where R = H (**1**), CH_3 (**2**), Cl (**3**), CN (**4**), C_6H_5 (**5**), H_3C—C(O) (**6**), NC—C(O) (**7**), and C_6H_5—C(O) (**8**). The last three, **6**–**8**, are commonly labeled hydroxamic acids, but they can be viewed as derivatives of hydroxylamine; in fact hydroxamic acids can be prepared by the action of hydroxylamine upon esters and acetyl halides.[2]


$H-\overset{H}{N}-OH$

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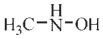
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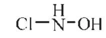
$Cl-\overset{H}{N}-OH$

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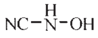
$NC-\overset{H}{N}-OH$

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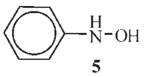

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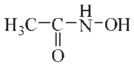
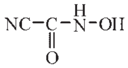

$H_3C-\underset{\underset{O}{\|}}{C}-\overset{H}{N}-OH$

6


$NC-\underset{\underset{O}{\|}}{C}-\overset{H}{N}-OH$

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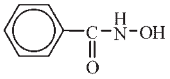

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Our analysis will focus upon two properties: the electrostatic potential $V(\mathbf{r})$ and the local ionization energy $\bar{I}(\mathbf{r})$. These will be defined and briefly discussed in the next section.

PROCEDURES

Electrostatic potential

The electrostatic potential $V(\mathbf{r})$ that is created throughout the space of a molecule by its nuclei and electrons is given by Eqn (1), which is simply a form of Coulomb's Law:

$$V(\mathbf{r}) = \sum_{A} \frac{Z_A}{|\mathbf{R}_A - \mathbf{r}|} - \int \frac{\rho(\mathbf{r}')\mathrm{d}\mathbf{r}'}{|\mathbf{r}' - \mathbf{r}|} \qquad (1)$$

Z_A is the charge on nucleus A, located at $\mathbf{R}_A$, and $\rho(\mathbf{r})$ is the molecular electronic density.

The electrostatic potential $V(\mathbf{r})$ is a physical observable, which can be determined experimentally by diffraction methods[3,4] as well as computationally. It directly reflects the distribution in

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space of the nuclear and electronic charge in a molecule. Thus, $V(\mathbf{r})$ is positive in those regions where the effect of the nuclei is dominant, negative where it is that of the electrons.

Since noncovalent interactions are primarily electrostatic in nature,[5,6] they can be interpreted and predicted via $V(\mathbf{r})$. For this purpose, we evaluate it on the surfaces of the molecules, since these surface potentials, which we label $V_S(\mathbf{r})$, are how the molecules 'see' each other. We define the molecular surface, following Bader *et al.*,[7] as the 0.001 au (electrons/bohr^3) contour of the molecule's electronic density $\rho(\mathbf{r})$; this encompasses about 96% of the electronic charge. Using an outer contour of $\rho(\mathbf{r})$ as the surface has the advantage of reflecting features specific to that molecule, such as lone pairs, pi electrons, and strained bonds. We have confirmed that other outer contours of $\rho(\mathbf{r})$, for example, the 0.002 au, would be equally effective.[8] The computed $V_S(\mathbf{r})$ of H_2N—OH, **1**, is presented in Fig. 1.

In a series of studies, reviewed elsewhere,[9–11] we have demonstrated that a variety of condensed phase physical properties that are governed by noncovalent interactions – heats of phase transitions, solubilities, boiling points and critical constants, viscosities, surface tensions, diffusion constants, etc. – can be expressed analytically in terms of certain statistical quantities that characterize the patterns of positive and negative regions of the surface electrostatic potential $V_S(\mathbf{r})$.

In this paper, our focus shall be primarily upon the most positive and most negative values of $V_S(\mathbf{r})$, the $V_{S,max}$ and the $V_{S,min}$, respectively. There may be several such local and absolute maxima and minima on a given surface, indicating the most positive and negative sites. The former are often associated with hydrogens, especially acidic ones, and the latter with lone pairs, pi electrons of unsaturated molecules, and strained bonds.[12] We have shown that $V_{S,max}$ and $V_{S,min}$ correlate well with empirical measures of hydrogen bond donating and accepting tendencies.[13]

In some instances, we will also refer to the overall most negative potentials (not limited to the molecule's surface), V_{min}, that are associated with nitrogen and oxygen lone pairs. These can be interpreted as indicating the effective 'center' of the lone pair. Such V_{min} are always more negative than the corresponding $V_{S,min}$, and are located within the molecular surface.

As is customary, $V(\mathbf{r})$ and $V_S(\mathbf{r})$ will be given in energy units, kcal/mole. Thus, their values actually represent the interaction energy between the electrostatic potential at any $\mathbf{r}$ and a $+1$ au point charge at that $\mathbf{r}$.

Local ionization energy

The average local ionization energy $\bar{I}(\mathbf{r})$ was introduced as a quantitative measure of the availability of an electron, at any point in the space of a molecule, for charge transfer and/or covalent bond formation. It was originally defined within the framework of Hartree–Fock theory, by Eqn (2),[14]

$$\bar{I}(\mathbf{r}) = \sum_i \frac{\rho_i(\mathbf{r})|\varepsilon_i|}{\rho(\mathbf{r})} \qquad (2)$$

in which $\rho_i(\mathbf{r})$ is the electronic density of orbital i, having energy ε_i. The formalism of Hartree–Fock theory and Koopmans' theorem[15,16] provide justification for interpreting $\bar{I}(\mathbf{r})$ as the local ionization energy, which focuses upon the point in space rather than upon a particular orbital.

For analyzing chemical reactivity, we compute $\bar{I}(\mathbf{r})$ on the $\rho(\mathbf{r}) = 0.001$ au surface of the molecule, just as we do $V(\mathbf{r})$. The lowest values of the resulting $\bar{I}_S(\mathbf{r})$, its local minima $\bar{I}_{S,min}$, show where are the least tightly held, most reactive electrons. The $\bar{I}_{S,min}$ are therefore an effective means for identifying and ranking sites susceptible to electrophilic attack. Although Eqn (2) was introduced within the context of Hartree–Fock theory, we have demonstrated that $\bar{I}_{S,min}$ obtained via Kohn–Sham density functional procedures show the same trends.[17] The computed $\bar{I}_S(\mathbf{r})$ of H_2N—OH, **1**, is in Fig. 2.

It should be noted that $\bar{I}_{S,min}$ are always somewhat larger than the magnitude of the highest occupied orbital energy. This is because $\bar{I}_S(\mathbf{r})$ averages over *all* of the electrons, and thus reflects the probability of inner, more tightly held ones being at the point in question, even on an outer contour of $\rho(\mathbf{r})$.

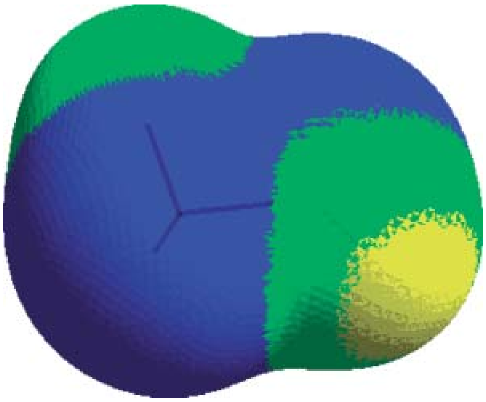


Figure 1. Computed electrostatic potential $V(\mathbf{r})$ on the molecular surface of NH_2OH. Shade (or *color*) ranges, in kcal/mole, are: black (*blue*), negative; gray (*green*), between 0 and 35; white (*yellow*), greater than 35. The amino group is at the left, with its lone pair at the bottom; the hydroxyl is at the right, with its lone pairs at the top. The black (*blue*) region shows the lone pairs of the nitrogen and oxygen to be on opposite sides of the molecule. The white (*yellow*) region corresponds to the hydroxyl hydrogen

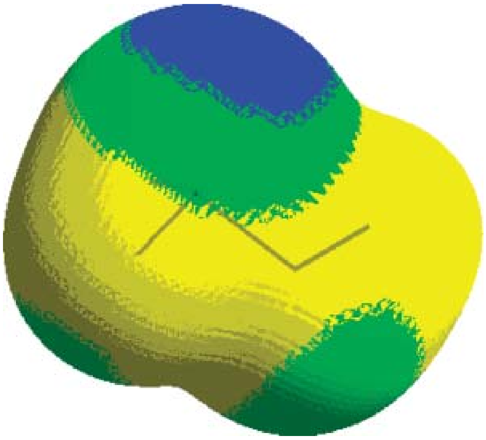


Figure 2. Computed local ionization energy $\bar{I}(\mathbf{r})$ on the molecular surface of NH_2OH. Shade (or *color*) ranges, in eV, are: black (*blue*), less than 14; gray (*green*), between 14 and 17; white (*yellow*), greater than 17. The amino group is at the left, with its lone pair at the top; the hydroxyl is at the right, with its lone pairs at the bottom. The black (*blue*) region at the top shows the lowest ionization energies to be associated with the nitrogen lone pair

In addition to its role as a guide to chemical reactivity, $\bar{I}(\mathbf{r})$ is related to atomic shell structure, electronegativity, local temperature, and local polarizability. It has further been used to characterize radical sites and bond strain. For a recent review, refer Politzer and Murray.[18]

Computational methods

Molecular geometries were optimized with the hybrid density functional B3LYP/6-31G** procedure in the Gaussian 03 code[19] and were then used to find energy differences at the B3LYP/6-311G(3df,2p) level. These ΔE are at 298 K; the zero-point and thermal corrections were taken from the 6-31G** calculations.

The same geometries were utilized, in conjunction with the HF/6-31G* method, to compute the electrostatic potential $V(\mathbf{r})$ and the local ionization energy $\bar{I}(\mathbf{r})$. Hartree–Fock electronic densities and orbital energies are known to be quite satisfactory for these purposes.[12,15,16]

For the most part, we will focus upon the $V_{S,min}$, $V_{S,max}$, and $\bar{I}_{S,min}$ on the surfaces of the molecules, taking these to be the 0.001 au contours of their electronic densities.[7] However, we will also have occasion to refer to the overall most negative potentials, the V_{min}, associated with the nitrogen and oxygen lone pairs.

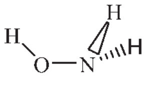
RESULTS AND DISCUSSION

Structures

Our optimized bond lengths and bond angles for **1**–**8** are in Table 1. The values for **1** are in very good agreement with experimental data, and those for **6** and **8** are close to what Remko obtained with a larger basis set;[21] the bond lengths differ by an average 0.004 Å and the angles by 1.1°.

An important determinant of the structure of the —N(H)—OH group is the need to minimize repulsion between the nitrogen and oxygen lone pairs. A good illustration of this is provided by hydroxylamine, $H_2N—OH$ (**1**).

We found two energy minima for **1**, corresponding to the conformers **9** and **10**. In **9**, the effective centers of the nitrogen and oxygen lone pairs, the respective V_{min}, are only 2.40 Å apart. Rotation of the hydroxyl group to give **10** increases this distance to 3.21 Å, while simultaneously lowering the energy by 3.9 kcal/mole [ΔE (298 K), B3LYP/6-311G(3df,2p)]. The separation of the lone pairs can be seen clearly in Fig. 1.



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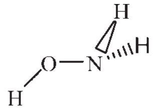

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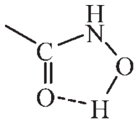
The tendency to maximize the separation of the nitrogen/oxygen lone pairs is pervasive in the hydroxylamines that we have investigated (**1**–**8**). However, in the hydroxamic acids **6**–**8**, a second factor enters the picture: intramolecular hydrogen bonding between the hydroxyl hydrogen and the acetyl oxygen, as shown in **11**. These H—O separations in **6**–**8** are, respectively, 1.95, 2.05, and 1.92 Å; all three are considerably less than the sum of the hydrogen and oxygen van der Waals radii, 2.69 Å.[22] (Such intramolecular hydrogen bonding in hydroxamic acids has also been noted by Remko[21,23] and by García *et al.*[24])



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There are some significant structural differences between the —N(H)—OH groups in **1**–**5** and those in **6**–**8**, which can be attributed at least in part to the intramolecular hydrogen bonding in the latter. The nitrogens in **1**–**5** are essentially pyramidal, as can be seen from their bond angles in Table 1; these average 106.5° (compared to 106.7° in NH_3[25]). In **6**–**8**, however, the nitrogen bond angles average 116.6°, approaching the 120.0° that would correspond to planarity. Furthermore, the R—N bond lengths in **6**–**8**, 1.354–1.377 Å (Table 1), are much closer to the typical $C(sp^2)—N(sp^2)$, 1.355 Å, than to the $C(sp^2)—N(sp^3)$, 1.416 Å.[26] Similarly, the N—O distances in **6**–**8**, 1.390–1.404 Å, are what would be expected for $N(sp^2)—O(2)$, 1.397 Å, rather than for $N(sp^3)—O(2)$, 1.463 Å.

To confirm that the intramolecular hydrogen bonding is partially responsible for these effects, we disrupted it in **6** by rotating the hydroxyl group away from the acetyl oxygen. Another energy minimum, 1.9 kcal/mole higher [ΔE(298 K),

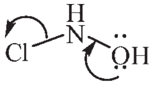
Table 1. Computed geometries (B3LYP/6-31G**) for —N(H)—OH portions of R—N(H)—OH, where R = H (**1**), CH_3 (**2**), Cl (**3**), CN (**4**), C_6H_5 (**5**), $H_3C—C(O)$ (**6**), NC—C(O) (**7**), and $C_6H_5—C(O)$ (**8**)[a]

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Bond length, Å								
R—N	1.022 (1.016)	1.461	1.864	1.356	1.417	1.368	1.354	1.377
N—H	1.022 (1.016)	1.021	1.024	1.017	1.018	1.012	1.011	1.013
N—O	1.448 (1.453)	1.449	1.392	1.433	1.429	1.403	1.390	1.404
O—H	0.966 (0.962)	0.967	0.971	0.970	0.968	0.984	0.981	0.984
Bond angle, degree								
R—N—H	104.8 (107.1)	107.9	98.2	112.6	111.0	121.0	124.2	118.7
R—N—O	103.4 (103.2)	107.0	109.1	111.6	112.7	115.3	116.8	114.3
H—N—O	103.4 (103.2)	102.7	101.2	107.1	105.6	110.6	112.6	115.6
N—O—H	101.7 (101.37)	101.4	103.2	102.4	102.6	100.2	101.7	100.6

[a] Experimental data for **1** are in parentheses, and are taken from reference [25].

B3LYP/6-311G(3df,2p)], was obtained with an O—C—N—O dihedral angle of 156.7° (*vs.* 11.9° in **6**). The nitrogen bond angles now average 1.6° less than in **6**, while the C—N and N—O distances are 0.026 and 0.011 Å longer; all of this indicates that the nitrogen has more sp^3 (pyramidal) character in the non-hydrogen-bonded conformer.

An interesting feature of **3**, Cl—N(H)—OH, is that the Cl—N distance of 1.864 Å (Table 1) is about 0.1 Å greater than is normally observed for this bond.[25,26] The N—O, on the other hand, is shorter than in any of the other molecules **1**–**5**. A possible interpretation is that the electronegative chlorine is inducing some charge delocalization such as is indicated in **12**.



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In **4**, NC—N(H)—OH, it is notable that the NC—N distance, 1.356 Å, is about 0.1 Å less than what is typical for a C—N single bond.[25] An analogous shortening is observed for the NC—C bond in **7**, which has a length of 1.465 Å. In both instances, this can be attributed largely to the presence of the adjacent triple bond.[27,28] However, the CN group does also exert its anticipated strongly electron-withdrawing inductive effect,[29] as will be seen in the next section.

Electrostatic potentials; hydrogen bonding

The electrostatic potential $V_S(\mathbf{r})$ on a molecular surface is effective as an indicator of the overall charge distribution in the molecule and also as a guide to its noncovalent interactions, such as hydrogen bonding. The most positive and negative values of $V_S(\mathbf{r})$, the $V_{S,max}$ and the $V_{S,min}$, are known to correlate with empirical measures of hydrogen bond donating and accepting abilities.[13]

In Table 2 are listed the computed $V_{S,max}$ and $V_{S,min}$ of molecules **1**–**8**. In order to provide perspective, the same data are included for two reference molecules, NH_3 and H_2O.

The $V_{S,min}$ in Table 2 are, for the most part, due to the lone pairs of the nitrogens and oxygens, the latter being the more negative. Oxygen formally has two lone pairs, and so it might be expected to have two $V_{S,min}$, as indeed it often does. However, extensive overlapping of its lone pair negative regions, or some other factor, can result in only one $V_{S,min}$ being obtained. This is so for all of the oxygens in Table 2, and also for the chlorine in **3**.

Some $V_{S,min}$ that are not related to lone pairs are found above and/or below the central portions of the aromatic rings in **5** and **8**. They are produced by the pi electrons. (In benzene, there are $V_{S,min}$ of −20.1 kcal/mole above and below the center of the ring.[30]) Only one such $V_{S,min}$ is observed in **8** because the negative potential on the other side of the ring has merged with that of the acetyl oxygen.

Chlorine and the cyano group, which also have lone pair negative regions (Table 2), are both strongly electron attracting, and the effects of this can readily be seen in the $V_{S,min}$ and $V_{S,max}$ of **3**, **4**, and **7**. The $V_{S,max}$ of the amine and hydroxyl hydrogens become more positive and the $V_{S,min}$ of the oxygens and amine nitrogens less negative; the $V_{S,min}$ of the amine nitrogen lone pair in **4**, NC—N(H)—OH, is only −6.6 kcal/mole.

As pointed out in the last section, the pyramidal characters of the amine nitrogens in **6**–**8** are greatly reduced. Thus, their lone pairs become more 2*p*-like and less localized, with the consequence that no $V_{S,min}$ are found.

The nitrogen and oxygen $V_{S,min}$ in NH_3 and H_2O are more negative than any in **1**–**8**. This can be understood from the fact that the amine nitrogens and the hydroxyl oxygens in the latter molecules are linked to each other, diminishing their opportunities to attract electronic charge. Accordingly, the nitrogen and

Table 2. Computed electrostatic potentials, in kcal/mole (HF/6-31G*//B3LYP/6-31G**), on molecular surfaces of R—N(H)—OH, where R = H (**1**), CH_3 (**2**), Cl (**3**), CN (**4**), C_6H_5 (**5**), H_3C—C(O) (**6**), NC—C(O) (**7**), and C_6H_5—C(O) (**8**)

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
$V_{S,min}$								
Amine N	−31.7	−30.2	−20.7	−6.6	−24.9	—	—	—
Cyano N	—	—	—	−39.8	—	—	−25.6	—
Hydroxyl O	−33.6	−34.4	−22.3	−20.1	−31.4	−33.0	−18.4	−35.0
Acetyl O	—	—	—	—	—	−39.7	−28.9	−38.0
Ring	—	—	—	—	−21.4, −21.4	—	—	−6.2
Cl	—	—	−17.3	—	—	—	—	—
$V_{S,max}$								
Amine H	32.3	30.8	48.1	58.4	37.8	54.9	67.6	49.7
Hydroxyl H	44.5	44.1	61.2	65.6	50.4	30.7	50.7	29.2
Methyl H	—	8.2, 9.5	—	—	—	21.0, 22.9	—	
Acetyl C	—	—	—	—	—	16.3	31.1	7.1
Ring H	—	—	—	—	11.6–15.2	—	—	21.9–24.1
Cl	—	—	5.7	—	—	—	—	—

Reference molecules

NH_3: $V_{S,min}$ (N) = −48.1; $V_{S,max}$ (H) = 27.6, 27.6, 27.6

H_2O: $V_{S,min}$ (O) = −42.1; $V_{S,max}$ (H) = 49.0, 49.0

oxygen in NH_3 and H_2O should be the best hydrogen bond acceptors in Table 2, although the $V_{S,min}$ of many of the others indicate that they can also function in this manner. We have already seen this for the acetyl oxygens in **6**–**8**.

The $V_{S,max}$ of the amine and hydroxyl hydrogens in **1**–**8** show that these molecules, for the most part, should be at least as effective hydrogen bond donors as H_2O and better than NH_3. The only low hydroxyl hydrogen $V_{S,max}$ are in **6** and **8**; this is due to the intramolecular hydrogen bonding in these molecules. It is known that decreases in the magnitudes of the donor $V_{S,max}$ and the acceptor $V_{S,min}$ are associated with hydrogen bonding.[31,32] This decrease in the hydroxyl $V_{S,max}$ is not observed in **7** because it is countered by the electron withdrawal of the CN group. However, the intramolecular hydrogen bonding probably accounts for the hydroxyl $V_{S,max}$ being less positive than the amine $V_{S,max}$ in **6**–**8**, whereas the former are more positive in **1**–**5**.

There are also $V_{S,max}$ associated with the acetyl carbons in **6**–**8**. These are consistent with their known reactivities toward nucleophiles.[2]

Finally, we want to mention a particularly interesting feature of Table 2: a small positive region on the outer portion (the tip) of the chlorine in **3**. It has a $V_{S,max}$ of 5.7 kcal/mole at the point where the extension of the N—Cl bond intersects the chlorine surface. While this $V_{S,max}$ is quite weak, stronger ones are found on the outer surfaces of many covalently bonded halogens, especially bromines and iodines. The remainder of the surface may be negative. These positive potentials can interact electrostatically with the lone pairs of Lewis bases, forming weak, highly directional noncovalent 'halogen bonds.'[33–37] The origins of these positive regions can be explained in terms of the 'σ-hole' concept,[38] which can also account for analogous local positive centers and directional interactions involving covalently bonded atoms of Group V[39] and Group VI.[40]

Local ionization energy; acidity/basicity

While the electrostatic potentials discussed in the last section are very useful for analyzing and predicting noncovalent interactions, such as hydrogen and σ-hole bonding, the local surface ionization energy, $\bar{I}_S(\mathbf{r})$, is more appropriate when there is significant charge transfer, as in acid/base or electrophilic processes. The lowest values of $\bar{I}_S(\mathbf{r})$, the $\bar{I}_{S,min}$, indicate the sites of the most reactive, most available electrons. Accordingly, the magnitudes of the $\bar{I}_{S,min}$ can serve to rank the basicities of these sites. A quantitative correlation has in fact been found between the experimental aqueous basicities of a group of nitrogen heterocycles and the $\bar{I}_{S,min}$ of the nitrogens.[41]

Acidities can also be ranked, by looking at the $\bar{I}_{S,min}$ of the conjugate base sites. The lower is the $\bar{I}_{S,min}$ of the conjugate base, the more strongly can it interact with the proton and the weaker is therefore the corresponding acid. Good correlations have been shown to exist between pK_a and conjugate base $\bar{I}_{S,min}$;[42] the larger is the $\bar{I}_{S,min}$, the smaller is the pK_a.

Literature tabulations sometimes list only pK_a values, for bases as well as for acids, since the pK_b for the former can readily be determined: $pK_b = 14.00 - pK_a$ (at 25°C). There can, however, be some ambiguity. For example, H_2N—OH (**1**) has a reported pK_a of 5.94.[25] Does this correspond to the loss of an amine or hydroxyl proton, or does it mean that the basicity of the nitrogen or the oxygen is $pK_b = 14.00 - 5.94 = 8.06$? Computed $\bar{I}_{S,min}$ can help to resolve such questions.

Table 3 presents the computed $\bar{I}_{S,min}$ of the —N(H)—OH portions of molecules **1**–**8** and also the $\bar{I}_{S,min}$ for the conjugate base sites corresponding to the loss of the potentially acidic amine and hydroxyl protons. For H_2N—OH, for example, these latter would be the $\bar{I}_{S,min}$ at the nitrogen in HN^-—OH and at the oxygen in H_2N—O^-. Also in Table 3, for reference purposes, are the nitrogen $\bar{I}_{S,min}$ for the bases NH_3 and pyridine, and the conjugate base $\bar{I}_{S,min}$ for acetic acid, that is, at either oxygen in $[H_3C—C(O)—O]^-$. Experimental pK_a values are included in the table when available; for NH_3 and pyridine, these are converted to pK_b.

Even though both $V_{S,min}$ and $\bar{I}_{S,min}$ are characteristic of lone pairs, there is not a close correlation between their magnitudes in Tables 2 and 3. For example, the amine nitrogens in **6**–**8** do not have $V_{S,min}$ but do have $\bar{I}_{S,min}$. Each of the hydroxyl oxygens in **1**–**8**

Table 3. Computed local ionization energy minima, $\bar{I}_{S,min}$, in eV (HF/6-31G*//B3LYP/6-31G**), on molecular surfaces of —N(H)—OH portions of R—N(H)—OH and its conjugate bases, where R = H (**1**), CH_3 (**2**), Cl (**3**), CN (**4**), C_6H_5 (**5**), H_3C—C(O) (**6**), NC—C(O) (**7**), and C_6H_5—C(O) (**8**)

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
pK_a[a]	5.94	—	—	—	—	8.70	—	—
pK_b[a]	8.06	—	—	—	—	—	—	—
Basic sites								
Amine N	12.8	12.5	14.3	14.7	12.8	13.5	14.7	13.4
Hydroxyl O	15.2, 15.2	15.1, 15.2	16.6	16.9	15.7	15.4	16.5, 16.5	15.3, 15.4
Acidic sites (conj base)[b]								
Amine H	2.3	3.2, 3.4	6.5, 6.9	5.9, 6.2	5.7, 5.7	5.9	7.3, 7.3	6.4, 6.4
Hydroxyl H	3.9	4.3, 4.4	11.6	6.1, 6.2	6.1, 6.1	6.3	7.1, 7.1	6.2, 6.3
Reference molecules[a]								
NH_3, $pK_a = 9.25$, $pK_b = 4.75$				$\bar{I}_{S,min}$ (N) = 11.9				
Pyridine, $pK_a = 5.23$, $pK_b = 8.77$				$\bar{I}_{S,min}$ (N) = 12.7				
H_3C—C(O)—OH, $pK_a = 4.756$				$\bar{I}_{S,min}$ $[H_3C—C(O)—O^-] = 7.0, 7.1$				

[a] Experimental pK_a (aqueous) from Reference [25]. For bases, pK_b obtained from $pK_b = 14.00 - pK_a$.

[b] For acid sites, $\bar{I}_{S,min}$ are for conjugate bases, that is, after removal of proton.

has only one $V_{S,min}$, but four of them have two $\bar{I}_{S,min}$. Particularly significant is that even though the hydroxyl oxygens in each instance have more negative $V_{S,min}$ than do the amine nitrogens, it is the latter that have the lower $\bar{I}_{S,min}$ and are therefore the more basic. This is seen in Fig. 2 for H$_2$N—OH, **1**.

The nitrogen $\bar{I}_{S,min}$ is 0.8 eV higher in pyridine than in NH$_3$, and its pK_b is correspondingly greater by four units. The amine nitrogens in **1**, **2**, and **5** have $\bar{I}_{S,min}$ similar to that of pyridine, and this can be expected to be true as well of their pK_b. Thus, it can be inferred that the reported pK_a of **1**, 5.94, should be interpreted as a pK_b of $14.00 - 5.94 = 8.06$, reasonably close to pyridine's 8.77 (Table 3). The amine nitrogens in **3**, **4**, and **6**–**8** all have $\bar{I}_{S,min}$ significantly above that of pyridine, and are therefore expected to have very low basicities. The highest of these $\bar{I}_{S,min}$, in **3**, **4**, and **7**, can be attributed to the electron-withdrawing effects of the chlorine and the cyano group.

The reported pK_a of the hydroxamic acid **6** is 8.70 (Table 3). Since its nitrogen and oxygen $\bar{I}_{S,min}$ are too high for any meaningful basicity (compare to the $\bar{I}_{S,min}$ of pyridine), it can be concluded that the pK_a does represent its acidity, presumably primarily that of the hydroxyl proton rather than the amine, since the conjugate base of the former has a somewhat greater $\bar{I}_{S,min}$. Its value, 6.3 eV, is 0.8 eV less than that of acetic acid, and its pK_a is four units larger. Thus, the ratio $\Delta pK_a/\Delta\bar{I}_{S,min}$ is essentially the same in magnitude (but opposite in sign) to $\Delta pK_b/\Delta\bar{I}_{S,min}$ (as described above) and to the analogous ratios observed earlier.[41,42]

For **1** and **2**, the conjugate base $\bar{I}_{S,min}$ are very low, confirming that these are amine bases and that the literature pK_a of **1** is actually indicative of its pK_b. The molecules **4**, **5**, and **8** should have acidities roughly comparable to **6**; both the amine and the hydroxyl protons may be involved, especially in the cases of **4** and **8**. This is so for **7** as well, which is, however, expected to have a pK_a approximating that of acetic acid. However, the most acidic proton in Table 3, by far, is that of the hydroxyl group in **3**, evidently due to the electron-withdrawing power of the chlorine.

It should be noted that there has been considerable disagreement as to whether the amine or the hydroxyl proton is the more acidic in various hydroxamic acids, or whether they are approximately the same in this respect. A good summary, with numerous references, has been given by García *et al.*[24] In the case of benzohydroxamic acid, **8**, there is experimental evidence that the two possible conjugate bases are found in similar concentrations in aqueous solutions,[24,43] which is consistent with our results in Table 3.

Overall, the $\bar{I}_{S,min}$ in Table 3 do allow a qualitative characterization of the relative strengths of the acidic and basic sites on the hydroxylamino group in the different molecular environments represented by **1**–**8**. Neither the $V_{S,min}$ of the nitrogen and oxygen lone pairs nor the $V_{S,max}$ of the amine and hydroxyl hydrogens are reliable guides in this respect.

Effects on aromatic substitution

An early successful use of local ionization energies on molecular surfaces was in predicting how substituents will affect the reactivity of an aromatic ring toward electrophiles,[14,17] that is, do they activate or deactivate it, and what will be their directing properties. The first question can be answered by comparing the magnitudes of the $\bar{I}_{S,min}$ to those of unsubstituted benzene, the second by noting their positions on the ring. It has in fact been shown that both Hartree–Fock and Kohn–Sham density functional $\bar{I}_{S,min}$ correlate very well with Hammett's empirical substituent parameters.[14,17]

The $\bar{I}_{S,min}$ of the aromatic rings in **5**, C$_6$H$_5$N(H)—OH, and **8**, C$_6$H$_5$—C(O)—N(H)—OH, can accordingly be used to quantify the substituent effects of the hydroxylamino group, —N(H)—OH, and its extended form —C(O)—N(H)—OH that is characteristic of hydroxamic acids. In **5**, the ring has $\bar{I}_{S,min}$ of 11.5–11.6 eV above and below the *ortho* and *para* carbons, showing that these are the sites to which the —N(H)—OH group directs electrophiles. Since these $\bar{I}_{S,min}$ are less than those of the carbons in benzene, 11.9 eV,[30] the group activates the ring to electrophilic substitution. The aromatic ring in **8**, on the other hand, has $\bar{I}_{S,min}$ of 12.4–12.5 eV above and below the *meta* carbons. It is to these that the —C(O)—N(H)—OH group directs electrophiles, and the ring is deactivated, the $\bar{I}_{S,min}$ being greater than those of benzene. It should be noted that aromatic $\bar{I}_{S,min}$ are associated with specific carbons, whereas the $V_{S,min}$ are above and below the central portions of the rings (Subsection 'Electrostatic Potentials; Hydrogen Bonding').

We can also estimate the relevant Hammett parameters of the —N(H)—OH and —C(O)—N(H)—OH groups, in the same manner as was done earlier.[14,17] Taking Hammett *meta* and *para* parameters, δ_m and δ_p, from Exner[44] and $\bar{I}_{S,min}$ for a series of substituted benzenes from Politzer *et al.*,[30] we obtain a linear correlation,

$$\delta = 0.8315\,\bar{I}_{S,min} - 9.9441 \qquad (3)$$

with $R^2 = 0.991$. Inserting the appropriate $\bar{I}_{S,min}$ (11.51 and 12.42 eV) yields $\delta_p = -0.37$ for —N(H)—OH and $\delta_m = 0.38$ for —C(O)—N(H)—OH. Thus, the —N(H)—OH group is an *ortho, para* director and activates the aromatic ring toward electrophilic attack, although not as strongly as does —NH$_2$ ($\delta_p = -0.57$) due to the presence of the OH. The —C(O)—N(H)—OH, on the other hand, deactivates the ring and is a *meta* director, similarly to the —C(O)H group ($\delta_m = 0.41$).

Polarizability

The polarizability $\boldsymbol{\alpha}$ of an atom or molecule is an indicator of the extent to which its charge distribution is affected by an electric field in its surroundings, perhaps due to another molecule. It is thus a key factor in both covalent and noncovalent interactions; Pearson's terms 'hard' and 'soft' really refer to low and high polarizability.[45]

Polarizability is defined by

$$\boldsymbol{\Delta\mu}(\varepsilon) = \boldsymbol{\alpha}\cdot\varepsilon \qquad (4)$$

in which $\boldsymbol{\Delta\mu}(\varepsilon)$ is the first-order change in the dipole moment $\boldsymbol{\mu}$ that is produced by the electric field $\boldsymbol{\varepsilon}$.[46] $\boldsymbol{\alpha}$ is a nine-component tensor which can be represented by a symmetric 3 × 3 matrix; what is commonly tabulated and invoked, however, is the average, or scalar, polarizability α,

$$\alpha = \frac{1}{3}(\alpha_{xx} + \alpha_{yy} + \alpha_{zz}) \qquad (5)$$

where α_{xx}, α_{yy}, and α_{zz} are the diagonal elements of the matrix.

It is well known that α can be approximated as a sum of atom, group, and/or bond contributions:[47–49]

$$\alpha \approx \sum_i \alpha_i \qquad (6)$$

In Eqn (6), the α_i are the average polarizabilities of the molecule's components. Various approaches for determining the

α_i have been proposed; one of these, due to Miller,[48] reproduces experimental molecular α with an average error of only 2.8%. Using Miller's empirical polarizabilties for the —NH— and —OH components of the hydroxylamino group, 1.351 and 1.024 Å^3, respectively, the predicted average polarizability of —N(H)—OH is 2.38 Å^3. If the group is expanded by attaching —C(O)—, for which α_i is 1.921 Å^3, then the estimated average polarizability of —C(O)—N(H)—OH is 4.30 Å^3. In the same fashion, the total molecular polarizabilities can be approximated for all of the molecules **1**–**8**.

SUMMARY

A key factor in determining the geometry of the hydroxylamino group, whatever may be the remainder of the molecule, is the repulsion between its nitrogen and oxygen lone pairs, which must be minimized. Superposed upon this, when the hydroxylamino group is part of a hydroxamic acid, is intramolecular hydrogen bonding between the hydroxyl hydrogen and the acetyl oxygen.

The primary analytical tools that have been used in this work are the electrostatic potential and the local ionization energy, both computed on the molecular surfaces. The $V_{S,max}$ show that the hydroxylamino group should be, in general, a potent hydrogen bond donor, involving both the amine and the hydroxyl hydrogens. It should also be a reasonably good hydrogen bond acceptor, especially through the oxygen lone pairs.

With regard to basicity, it is the nitrogen lone pairs that are dominant, their pK_a estimated to be roughly similar to that of pyridine, except when the R part of the molecule is strongly electron-withdrawing or intramolecular hydrogen bonding reduces the pyramidal character of the nitrogen and somewhat delocalizes its lone pair, as in **6**–**8**. As for acidity, except for **1** (R = H) and **2** (R = CH_3), the hydroxyl and the amine protons are weakly acidic, usually considerably less than acetic acid. In the case of **3** (R = Cl), however, the hydroxyl proton is actually much more acidic than that of acetic acid.

Both the basicity and the acidity of the hydroxylamino group are quite dependent upon the remainder of the molecule. However, if it can be assumed that **1** and **2** come closest to reflecting the intrinsic nature of the group, then it can be described as weakly basic and not significantly acidic.

As substituents on aromatic rings, the effects of —N(H)—OH and its extended form —C(O)—N(H)—OH are dominated by the portion of the group directly adjacent to the ring. Thus, —N(H)—OH is an *ortho*, *para*-directing, ring-activating electron donor, but less so than —NH_2, and —C(O)—N(H)—OH is a *meta*-directing, ring-deactivating electron withdrawer, quite similar to —C(O)H.

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