Hydrogen bond acceptor properties of two radicals: nitric oxide molecule and hydrogen atom

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Dedicated to our friend Professor Branko Stanovnik on his 65th anniversary

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Abstract

Two very significant, although for different reasons, radicals $NO^{\cdot}$ and $H^{\cdot}$ have been examined theoretically as hydrogen bond acceptors (HBA). Two acids have been studied as hydrogen bond donors (HBD), hydrogen fluoride and ammonium. Nitrogen oxide should be a nitrogen base towards both neutral and cationic acids as HBD. Atomic hydrogen, although a much weaker hydrogen-bonded base, should form stable complexes with the ammonium cation. A conclusion of this work is that DFT methods only work acceptably well for relatively strong HBs.

Keywords: Hydrogen bond donor, hydrogen bond acceptor, nitric oxide, hydrogen

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Introduction

We have been interested these last years in non-conventional hydrogen-bonds [1-11] including carbon radicals as hydrogen bond acceptors [12]. Now we have turned our attention to two very simple radicals: first to nitric oxide and the possibility that its physiological properties, occurring by interaction with the receptor, could be mediated by hydrogen bonds, as usually happens in non-irreversible drug-receptor interactions [13,14]. Then we have studied the most simple of all radicals, the hydrogen atom.

Results and Disussion

Nitric oxide

Although one of the simplest biological molecules in nature, nitric oxide has found its way into nearly every phase of biology and medicine ranging from its role as a critical endogenous regulator of blood flow and thrombosis to a principal neurotransmitter mediating erectile function and to a major pathophysiological mediator of inflammation and host defense. These major discoveries have stimulated intensive and extensive research into a vast array of fields including chemistry, molecular biology, and gene therapy.

The formation of hydrogen bonds between some aminoacids and nitric oxide is of paramount importance in biochemistry. Thus nitric oxide binding to ferric and ferrous myoglobin takes place between a protonated distal histidine hydrogen bond to the NO ligand [15]. Specifically, the N_e nitrogen atom of $histidine_{64}$ is located 2.8 Å away from the nitrogen atom of the bound ligand [16]. Abraham *et al*. have measured the hydrogen-bond basicity of nitric oxide (B = 0.086) [17] but they did not indicate which extremity is the more basic.

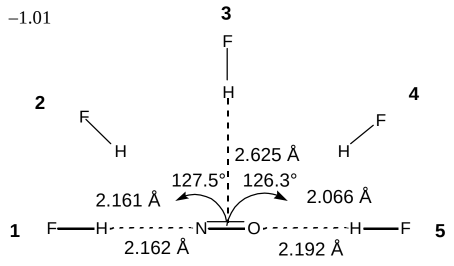
We have started carrying out UB3LYP/6-31+G(d,p) calculations of the complex $NO^{\cdot}/HF$. As a neutral hydrogen bond donor (HBD), we have chosen hydrogen fluoride, for its simplicity. We have calculated five different situations (Scheme 1 and Table 1):

Table 1. $NO^{\cdot}/HF$ complex

Situation	Number of imaginary frequencies N_{im}	E_i (kcal mol^{-1})
1	1	–1.63
2	0	–2.39
3	1	–0.28
4	0	–1.61
5	1	–1.01

N_{im}, the number of imaginary frequencies, should be 0 for a minimum and 1 for a transition state. Although there are two minima, the most stable is that bound to the nitrogen extremity (the angle of 127.5º corresponds loosely to the location of the lone pairs). In the case of the TS (**3**), the F–H is not exactly perpendicular to the middle of the N=O bond, but the angles are close to 90º (84.3º towards the oxygen and 95.7º towards the nitrogen). To go from **2** to **4** there is a barrier of 2.11 kcal mol^{-1} through **3**.

Increasing the level of the calculations up to UB3LYP/6-311++G(2d,2p) yields for the minima **2** and **4** –2.58 (2.068 Å) and –1.50 kcal mol^{-1} (2.024 Å) respectively, close to those found at the lower level. Since other authors [18] have reported that the O-complex is more stable than the N-complex, we carried out a UMP2/6-311++G(d,p) obtaining for **2** and **4** –2.87 (2.092 Å) and –1.44 kcal mol^{-1} (2.176 Å) respectively. Therefore, the HB basicity of the N extremity is larger than that of the O extremity in nitric oxide. Note that the F–H···N and F–H···O angles obtained for **2** and **4** are close to 180º.



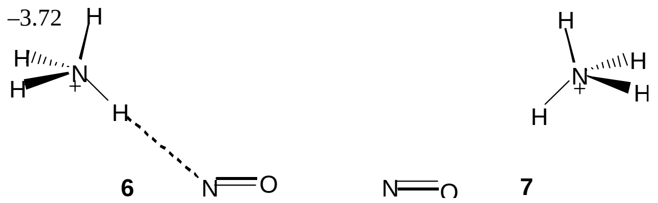
Scheme 1

The Ar matrix complex of HF and $NO^{\cdot}$ seems to have the H atom of HF bound to the O atom of the base, according to the infrared spectra and UHF 6-31G**//6-31G calculations (E_i = –6.67 kcal mol^{-1}) [18]. On the other hand, an UMP2 study of the water-nitric oxide complex reports that the global minimum is the N-bonded [19]. The relative low level of the calculations reported in ref. 18, led us to suggest that our UMP2 calculations should be preferred.

As a model of protonated histidine, we decided to study the ammonium/$NO^{\cdot}$ complex at the same three levels, but only for the two minima (corresponding to the **2** and **4** structures of Scheme 1): $H_3N^+–H\cdots NO^{\cdot}$ (**6**) and $H_3N^+–H\cdots ON^{\cdot}$ (**7**). The results are gathered in Table 2 and the complexes represented in Scheme 2.

Table 2. Geometries (angles °, distances Å) and energies (kcal mol^{-1}) of ammonium/nitric oxide complexes

Complex	Method	Angle H-NO/H-ON	H X distance	E_i
(**6**)	UB3LYP/6-31+G(d,p)	136.1	2.041	–5.76
(**6**)	UB3LYP/6-311++G(2d,2p)	135.5	2.005	–6.19
(**6**)	UMP2/6-311++G(d,p)	135.4	2.024	–6.31
(**7**)	UB3LYP/6-31+G(d,p)	137.0	1.994	–4.21
(**7**)	UB3LYP/6-311++G(2d,2p)	133.5	1.992	–4.00
(**7**)	UMP2/6-311++G(d,p)	148.8	2.034	–3.72



Scheme 2

Therefore, in this case also, the HB basicity of the N extremity is larger than that of the O extremity: this corresponds to the $N^+–H\cdots NO^{\cdot}$ situation reported for myoglobin [16]. The N···N distances in complex **6** are 3.07, 3.04 and 3.05 Å, depending on the method of calculation. These distances could be compared with the 2.8 Å distance measured between nitrogen atoms in the protonated histidine/nitric oxide complex [16].

Hydrogen radical

This is the simplest chemical entity (if one excludes the electron, present in electrides [20] and in hydrated electrons [21], and the proton), its energy being 0.5 hartree. Concerning its hydrogen-bond basicity, it is known that $H^{\cdot}$ forms very weak hydrogen bonds [22-24].

Again, we have studied one neutral acid, hydrogen fluoride (complex **8**), and one cationic acid, ammonium (complex **9**), with the same three bases previously used. The results are reported in

Table 3 (they are linear, either $C_{\infty v}$ or C_{3v}).

Table 3. Geometries (distances Å) and energies (kcal mol^{-1}) of hydrogen fluoride/hydrogen atom and ammonium/hydrogen atom complexes

Complex	Method	H···H Distance	E_i
(**8**)	UB3LYP/6-31+G(d,p)	1.979	–0.82
(**8**)	UB3LYP/6-311++G(2d,2p)	1.941	–0.74
(**8**)	UMP2/6-311++G(d,p)	2.662	–0.58
(**9**)	UB3LYP/6-31+G(d,p)	1.937	–2.17
(**9**)	UB3LYP/6-311++G(2d,2p)	1.923	–1.89
(**9**)	UMP2/6-311++G(d,p)	2.191	–1.35

The eighteen values of the energies of complexes (E_i in kcal mol^{-1}) can be examined statistically. The three bases yield proportional results, compared with the smaller one:

$$E_i\ [\text{UB3LYP/6-311++G(2d,2p)}] = (0.24\pm0.20) + (1.08\pm0.06)\ E_i\ [\text{UB3LYP/6-31+G(d,p)}],$$
$$n = 6,\ r^2 = 0.987 \qquad (1)$$

$$E_i\ [\text{UMP2/6-311++G(d,p)}] = (0.45\pm0.44) + (1.12\pm0.14)\ E_i\ [\text{UB3LYP/6-31+G(d,p)}],$$
$$n = 6,\ r^2 = 0.944 \qquad (2)$$

Since the intercept is almost not significant, the comparison of eqs. (1) and (2) indicates that E_i slightly increases with the quality of the base.

We can use now an average of the three bases and calculate with regard to the $H_3N^+–H\cdots H^\cdot$ (**9**) and the $F–H\cdots H^\cdot$ (**8**) complexes, the relative E_i energies of the five other complexes (Table 4).

Table 4. Relative energies of complexes **8**, **6**, **7**, **2** and **4** with regard to **9** and of complexes **2** and **4** with regard to **8**

$F–H\cdots H^\cdot$ (**8**)/ $H_3N^+–H\cdots H^\cdot$ (**9**) = 0.40
$H_3N^+–H\cdots NO^\cdot$ (**6**)/ $H_3N^+–H\cdots H^\cdot$ (**9**) = 3.53
$H_3N^+–H\cdots ON^\cdot$ (**7**)/ $H_3N^+–H\cdots H^\cdot$ (**9**) = 2.27
$F–H\cdots NO^\cdot$ (**2**)/ $H_3N^+–H\cdots H^\cdot$ (**9**) = 1.53
$F–H\cdots ON^\cdot$ (**4**)/ $H_3N^+–H\cdots H^\cdot$ (**9**) = 0.87
$F–H\cdots NO^\cdot$ (**2**)/ $F–H\cdots H^\cdot$ (**8**) = 3.78
$F–H\cdots ON^\cdot$ (**4**)/ $F–H\cdots H^\cdot$ (**8**) = 2.16

Conclusions

According to the calculations and independently of the method used (B3LYP or MP2), the

following conclusions can be drawn:
– H_3N^+–H is a stronger HBD than F–H (about 2.5 times greater).
– $NO^{\cdot}$ is a stronger HBA than $H^{\cdot}$ (about 3.6 times greater by its most basic extremity).
– $NO^{\cdot}$ is a stronger HBA by its N extremity than by its O one (about 1.6 times greater).

There is a fundamental question about the reliability of DFT calculations (for instance, B3LYP) to study hydrogen bonded systems (energies and geometries). If we compare the differences (▤) of the hydrogen bond distance between UB3LYP/6-31+G(d,p) and UMP2/6-311++G(d,p) for four complexes with the calculated interaction energies at UMP2/6-311++G(d,p), we obtain the values of Table 5.

Table 5. Comparison between distances and energies in complexes **6-8**

Complex	▤(HB distance Å)	E_i kcal mol^{-1} (UMP2)
(6)	–0.017	6.31
(7)	0.040	3.72
(9)	0.254	1.35
(8)	0.683	0.58

Computational details

The geometries of the monomers and complexes have been optimized at the UB3LYP/6-31+G(d,p) [25-27] computational level within the Gaussian-98 package [28]. The minimum or transition state nature of the structures has been confirmed by frequency calculation at the same computational level. Further geometry optimizations have been carried out at the UB3LYP/6-311++G(2d,2p)[29] and UMP2/6-311++G(d,p) levels [30].

Acknowledgments

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References and Notes

1. Alkorta, I.; Elguero, J.; Foces-Foces, C. *Chem. Commun*. **1996**, 1633.
2. Alkorta, I.; Elguero, J. *J. Phys. Chem*. **1996**, *100*, 19367.
3. Rozas, I.; Alkorta, I.; Elguero, J. *J. Phys. Chem. A* **1997**, *101*, 4236.
4. Rozas, I.; Alkorta, I.; Elguero, J. *J. Phys. Chem. A* **1997**, *101*, 9457.
5. Ramos, M.; Alkorta, I.; Elguero, J.; Golubev, N. S.; Denisov, G. S.; Benedict, Limbach, HH. *J. Phys. Chem. A* **1997**, *101*, 9791.
6. Alkorta, I.; Rozas, I.; Elguero, J. *Chem. Soc. Rev*. **1998**, *27*, 163.

7. Alkorta, I.; Rozas, I.; Elguero, J. *J. Phys. Chem. A* **1998**, *102*, 9925.
8. Alkorta, I.; Rozas, I.; Elguero, J. *Theor. Chem. Acc*. **1998**, *99*, 116.
9. Prieto, P.; de la Hoz, A.; Alkorta, I.; Rozas, I.; Elguero, J. *Chem. Phys. Lett*. **2001**, *350*, 325.
10. Alkorta, I.; Rozas, I.; Elguero, J. *THEOCHEM* **2001**, *537*, 139.
11. Alkorta, I.; Rozas, I.; Elguero, J. *Int. J. Quantum Chem*. **2002**, *86*, 122.
12. Alkorta, I.; Rozas, I.; Elguero, J. *Ber. Bunsenges Phys. Chem*. **1998**, *102*, 429.
13. Jeffrey, G.A. *An Introduction to Hydrogen Bonding*; Oxford University Press: Oxford, 1997.
14. Desiraju, G.R.; Steiner, T. *The Weak Hydrogen Bond*, International Union of Crystallography, Oxford University Press, Oxford, 1999.
15. Miller, L.M.; Pedraza, A.J.; Chance, M.R. *Biochemistry* **1997**, *36*, 12199.
16. Brucker, E.A.; Olson, J.S.; Ikeda-Saito, M.; Phillips, G.N. *Proteins: Struct., Funct., Genet*. **1998**, *30*, 352.
17. Abraham, M.H.; Gola, J.M.R.; Cometto-Muñiz, J.E.; Cain, W.S. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2067.
18. Davis, S.R.; Andrews, L.; Trindle, C.O. *J. Chem. Phys*. **1987**, *86*, 6027.
19. Myszkiewicz, G.; Sadlej, J. *Chem. Phys. Lett*. **2000**, *318*, 232.
20. Dye, J.L. *Science* **1990**, *247*, 663. Singh, D.J.; Krakauer, H.; Haas, C.; Pickett, W.E. *Nature* **1993**, *365*, 39. Wagner, M.J.; Huang, R.H.; Eglin, J.L.; Dye, J.L. *Nature* **1994**, *368*, 726. Huang, R.H.; Wagner, M.J.; Gilbert, D.J.; Reidy-Cedergren, K.A.; Ward, D.L.; Faber, M.K.; Dye, J.L. *J. Am. Chem. Soc*. **1997**, *119*, 3765.
21. Thomsen, C.L.; Madsen, D.; Keiding, S.R.; Thogersen, J.; Christiansen, O. *J. Chem. Phys*. **1999**, *110*, 3453.
22. Symons, M.C.R.; Rhodes, C.J; ReId, I.D. *Magn. Res. Chem*. **2000**, *38*, 823.
23. Goldschleger, A.U.; Misochko, E.Ya.; Akimov, A.V.; Goldschleger, I.U.; Benderskii, V.A. *Chem. Phys. Lett*. **1997**, *267*, 288.
24. Stark, K.; Werner, H.J. *J. Chem. Phys*. **1996**, *104*, 6515.
25. Becke, A.D. *J. Chem. Phys*. **1993**, *98*, 5648.
26. Lee, C.; Yang, W.; Parr, R.G. *Phys. Rev. B* **1988**, *37*, 785.
27. Hariharan, P. A.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213.
28. Gaussian 98. Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Zakrzewski, V.G.; Montgomery, J.A.; Stratmann, R.E.; Burant, J.C.; Dapprich, S.; Millam, J.M.; Daniels, A.D.; Kudin, K.N.; Strain, M.C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G.A.; Ayala, P.Y.; Cui, Q.; Morokuma, K.; Malick, D.K.; Rabuck, A.D.; Raghavachari, K.; Foresman, J.B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B.B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R.L.; Fox, D.J.; Keith, T.; Al-Laham, M.A.; Peng, C.Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P.M.W.; Johnson, B.G.; Chen, W.; Wong, M.W.; Andres, J.L.; Head-Gordon, M.; Replogle, E.S.; Pople, J.A. Gaussian, Inc., Pittsburgh, PA, 1998.
29. Frisch, M.J.; Pople, J.A.; Krishnam, R.; Binkley, J.S. *J. Chem. Phys*. **1984**, *80*, 3265.
30. Møller, C.; Plesset, M.S. *Phys. Rev*. **1934**, *46*, 618.