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A DFT AND MP2 STUDY OF TRENDS IN *PARA*-SUBSTITUTED ARYLDIAZENIUM-DIOLATE (CUPFERRON) DERIVATIVES

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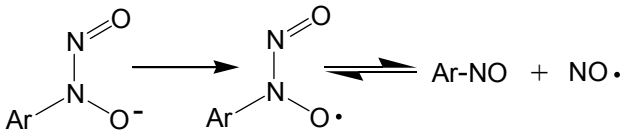
In the 1970s the reversble spin-trapping of the biologically active nitric oxide (NO) by nitrosobenzene was discovered, and it allowed devising new NO donors from cupferron derivatives. In the present study, two *ab-initio* methods (Density Functional Theory and Møller-Plesset-2) were used for computing electronic properties (ground state and HOMO-LUMO energies, Mulliken charges and spin densities) as well as reaction parameters involving neutral, anionic and free-radical derivatives of aryldiazenium-diolates, where the aryl is a phenyl group or a *para*-substituted phenyl with an electron-donor or electron-acceptor substituent. The present theoretical computations allow a comparison between experimental and theoretical data such as interatomic bond lengths and spin densities of N-nitroso-N-aryl-nitroxides. They also confirm that electron-donor substituents lower the activation barrier for delivering NO.



INTRODUCTION

Electrically neutral N-aryl-N-nitroso-hydroxylamines (**1**) are tautomeric with aryl-diazohydroxide-N-oxides (**2**); both tautomers afford a single N-aryldiazeniumdiolate anion (older name N-aryl-NONO-ate anion, **3**) and a single N-aryl-N-nitroso-nitroxide free radical (**4**). However, each of these four molecules can exist in two different rotational diastereomers with a *cisoid* or a *transoid* geometry denoted by *Z* and *E*, respectively.

Previous experimental studies by Balaban and coworkers reported that oxidation of cupferron (the ammonium salt of N-nitroso-phenylhydroxylamine, or ammonium phenyldiazen-1-ium-1,2-diolate) afforded a stable free radical, N-nitroso-N-phenyl-nitroxide (**4**, Ar = Ph) with a complicated but well-resolved ESR spectrum.[1] The 3,5-di-*tert*-butylphenyl analog had a simpler ESR spectrum[2] because it no longer had small *meta*-hydrogen hyperfine couplings (Fig. 2). With various other aryl groups, these studies arrived at a satisfactory determination of all hyperfine coupling constants (HFCs).[3,4] It was also observed that analogous N-aryl-N-nitroso-nitroxide free radicals could be obtained from the decomposition of N-arenesulphonyl-N-aryl-nitroxides,[5] and on trapping nitric oxide (NO) by nitrosoarenes in a reversible reaction.[3-6]

Positions of nitrogen and oxygen atoms in free radicals **4** are denoted by numbers 1 and 2 (see structure **4*Z*** in Fig. 1). The relative weight of resonance structure **4*Z*c** is larger than for **4*Z*d**, explaining thereby the relative values of the corresponding nitrogen HFCs shown in Fig. 2. The

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last resonance structure (**4*Z*e**), using single-electron opposite spin notations (α and β) according to Linnett's double quartet theory,[7-9] explains the stability of nitroxides in terms of heteroatoms having full octet electronic shells if the N^1–O^1 bond has a bond order of 1.5 (Fig. 3). An experimental proof for the Linnett structure of analogous stable hydrazyls was provided by the high rotation barrier around the N–N bond in 1-benzoyl-2,2-bis-(3,5-di-t-butyl-phenyl)-hydrazyl.[10] Even the stability of push-pull (capto-dative) N-alkoxy-N-aryl-aminyls can be explained similarly.[11]

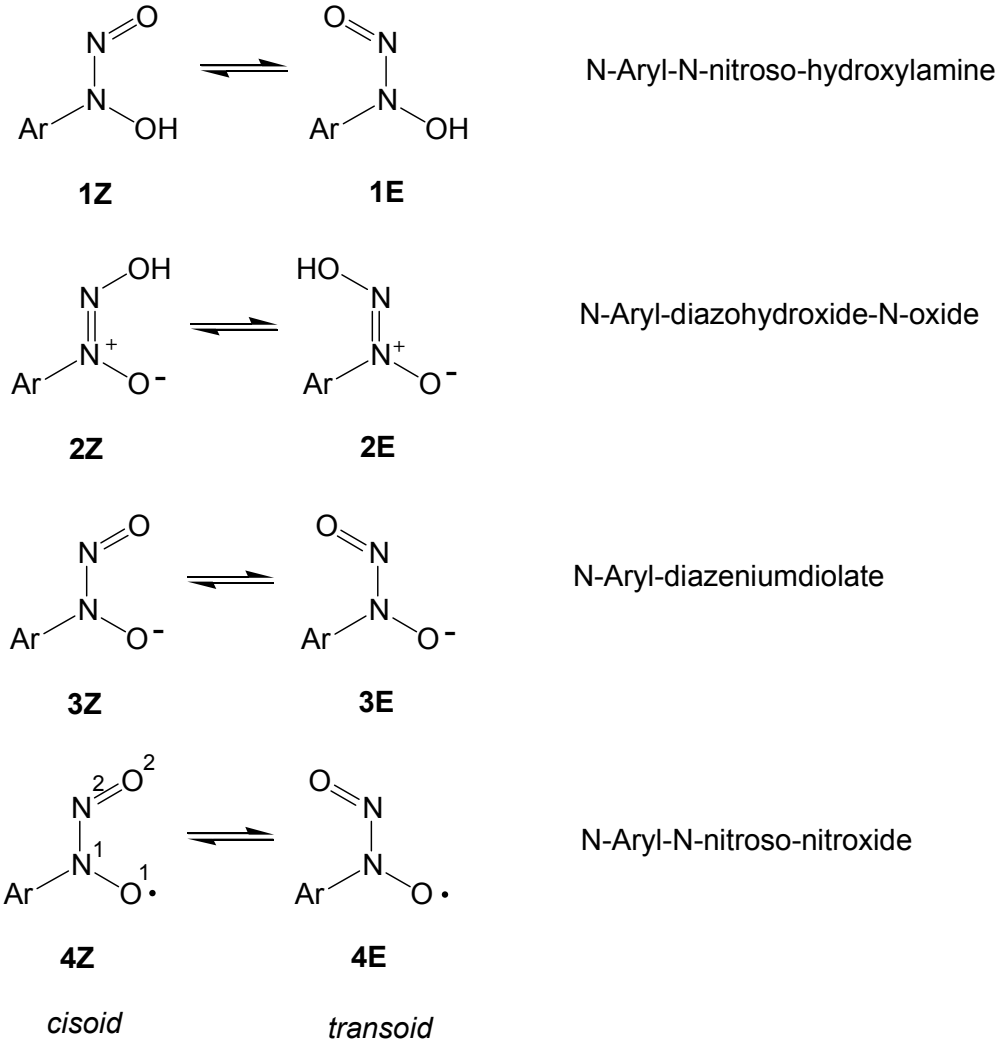

Fig. 1 – Rotational diastereomers (*E* and *Z*) of N-aryl-N-nitroso-hydroxylamines (**1**), their tautomeris aryl-diazohydroxide-N-oxides (**2**); the corresponding N-aryldiazeniumdiolate anion **3** and N-aryl-N-nitroso-nitroxide free radical (**4**). Numberings of N and O atoms are indicated in structure **4*Z***.

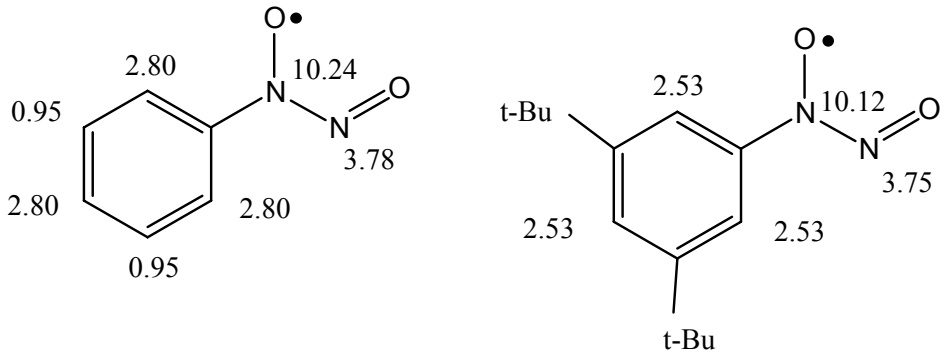

Fig. 2 – Hyperfine coupling constants (mT) for N-phenyl- and N-3,5-di-*tert*-butylphenyl-N-nitroso-nitroxude. [1,2]

An interesting difference between N-aryl-N-nitroso-nitroxides **4** and N-acyl-N-aryl-nitroxides **5** (oxidation products of hydroxamic acids)[12] is that the latter ones are more stable in the *transoid* form **5E**; the *cisoid* form **5Z** is the only possible one with 5- or 6-membered rings (k = 3 or 4, respectively) and presents lower nitrogen spin coupling constants than acyclic *transoid* radicals **5E** (Fig. 4). Reasoning from observed nitrogen HFCs for N-aryl-N-nitroso-nitroxides, it was hypothesized that they exist in the *cisoid* form **4Z**; an unrestricted Hartree-Fock[13] and an NMDO theoretical study confirmed this hypothesis.[14]

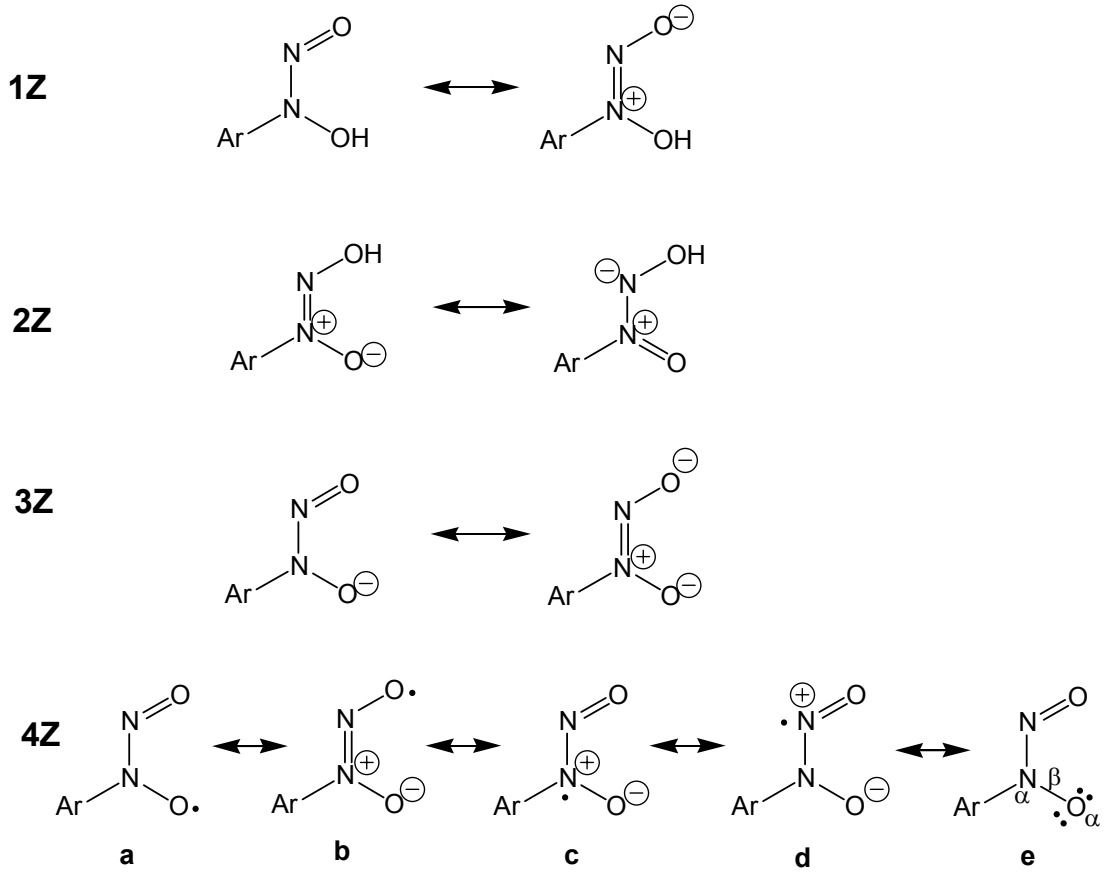

Fig. 3 – Resonance structures of *cisoid* N-aryl-N-nitroso-nitroxides and their congeners; the last structure (**4*Z*e**) illustrates Linnett's theory with all atoms having electronic octets from four pairs of electrons with opposite spins α and β.

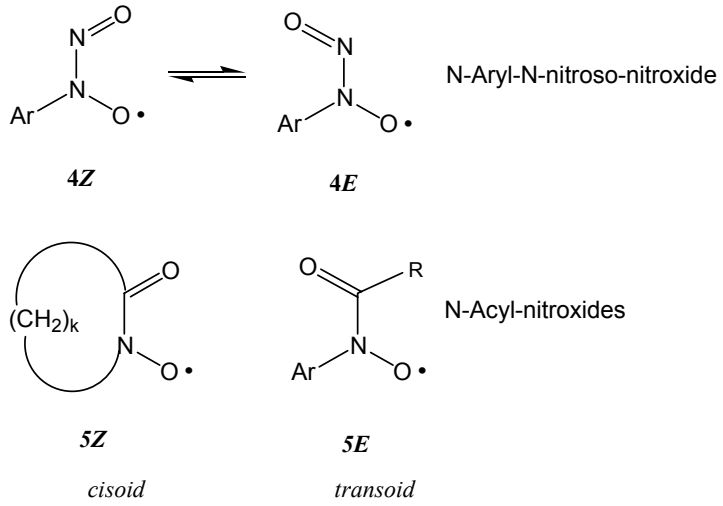

Fig. 4 – Analogous *cisoid* (Z, left column structures) and *transoid* (E, right column) N-aryl-N-nitroso-nitroxides and N-acyl N-aryl –nitroxides.

In 1992, the journal *Science* designated nitric oxide (NO) as the "Molecule of the Year" in recognition of its many biological roles. The three main ones are (i) as indicated by the name 'endothelium-derived relaxing factor', which preceded its identification as NO, due to a constitutive NO synthase, produced by blood vessels for vasodilation; (ii) a second constitutive NO synthase (neuronal-tissue-produced) for cell communication, and (iii) an inducible-synthase-produced NO for immune defense against pathogens. Additionally, NO is also produced via recycling of nitrate and nitrite anions in living cells. The 1998 Nobel Prize for Medicine or Physiology was awarded to Furchgott, Ignarro, and Murad for the discovery of the biological functions of nitric oxide.[15] A few among the many books dedicated to NO are cited here, with a special mention to books published by Murad, by Moncada, and by Packer.[16]

Salts which contain the aryldiazen-1-ium-1,2 diolate (Ar-N(O)NO$^-$) anion have been targeted extensively as potential pharmacological agents for *in situ* delivery of nitric oxide. Derivatives of alkyl-diazenium-diolates decompose in physiological solution either spontaneously or upon acidification to yield nitric oxide. Unlike these compounds that have only two connected nitrogen atoms, related amino-diazenium-diolates with three connected nitrogen atoms were first obtained by Drago and coworkers.[17] Keefer and associates have synthesized and tested a wide variety of such amino-diazenium diolate derivatives as NO-donor agents whose rates of NO release are affected by variations in side chain structure and other factors.[17-21] *para*-Aminophenyl-diazenium-diolates may be considered to be phenylogs of Drago's and Keefer's structures.

An aryldiazenium-diolate, cupferron (the ammonium salt of phenyldiazen-1-ium-1,2-diolate) is stable in neutral or moderately basic solution, but undergoes NO-releasing decomposition in acidic solution. Cupferron owes its name to the fact that the anion (**3**) formed by deprotonation of N-nitroso-N-phenylhydroxylamine (**1**) or its tautomer (**2**) strongly chelates copper(II) cations. It can also be prepared by reduction of the radical (**4**) formed by a spin-trapping reaction between nitrosobenzene and NO.[1-3] Aryldiazenium-diolates or *cupferrates* (**3**) offer potential control of differential NO release rates. Identification of nitrosobenzene as one of the decomposition products indicates that the NO-release reaction involves cleavage of the N–N bond with production of one equivalent of nitric oxide. By contrast, dialkylamino- or alkyl-diazeniumdiolates decompose in acid solution with first-order kinetics releasing the unstable dimer of NO, which then fragments into two NO molecules.[22-25]

Experimental data demonstrated that cupferrate derivatives prepared with single substituent groups on the phenyl moiety produce NO-related physiological activity at rates which depend both on substitution site and on the nature of the substituent group.[4,24] McGill and coworkers have shown for several single substituents at *para* that the experimental oxidation potential leading to electrochemical NO release correlates well with Hammett *sigma* constants and with gas phase oxidation energies computed by density functional theory.[22] Solutions of cupferrate salts with electron-releasing substituents in *ortho* positions generally are more reactive and some are even unstable to atmospheric decomposition.[4,24] Because aryl byproducts of this decomposition may not degrade to potentially carcinogenic nitrosamines, substituted cupferrates may join the list of candidates for drugs designed for specific rates of *in situ* delivery of NO.

Various species may be involved in mechanisms of nitric oxide release. Rate dependence on pH for NO-releasing reactions has been noted in a number of studies. This implicates protonated intermediates as suggested in a recent theoretical study of amino and alkyl diazenium-diolates. For cupferrate dissociation, a mechanism of NO release could involve oxidation of the anion to the free radical **4**, followed by dissociative cleavage of the N–N bond. This reaction seems plausible as a "microscopic reversal" of previously observed spin-trapping reactions. Thus the neutral nitroso-hydroxylamine or its diazo-hydroxide-N-oxide tautomer, the corresponding anion and free radical (**1** – **4**) may all be involved in NO release, and yields may be influenced by factors that affect these chemical species.

Experimentally determined hyperfine coupling constants from ESR spectra have led to the conclusion that N-aryl-N-nitroso-nitroxides adopt a *cisoid* conformation, which is lower in energy than the *transoid* one.[3] This contrasts with the cyclic N-acyl-N-aryl-nitroxides which are forced sterically to adopt a *transoid* conformation. The study included semiempirical calculations which

agreed with experiment.[14] A *cisoid* NONO conformation is also indicated in X-ray crystallographic investigations of the cupferrate anion.[24] Ample X-ray structural data provided by Keefer and his coworkers are cited in Section III.F.2 of his review.[21]

A recent *ab-initio* quantum chemical study of protonated ([*R*-NONO]H) and nonprotonated non-aryl substituted diazenium-diolates considered both *cisoid* (**Z**) and *transoid* (**E**) planar conformers of similar energy for nonarene diazenium-diolate anionic derivatives. In this study Taylor *et al.* found a tetrahedral NONO moiety for *cisoid* N-nitroso-hydroxylamine derivatives, but they found a planar NONO, stabilized by hydrogen bonding, for hydroxydiazenium nitroxide tautomers (analogues of **1E** and **2E**, respectively, with nonaromatic residues).[23]

PRESENT STUDY

The present study employs density functional and *ab initio* second order perturbation theories to examine the influence of substitution at the 4 or *para* location of phenyldiazen-1-ium-1,2-diolate and related chemical species on electronic properties (see below), on structure, and on the gas phase energies of reactions which result in NO loss. Both computational approaches identify trends, which for most properties vary regularly with substituent group in the order: **A**, *electron-donating* (R = NH_2), **B**, *none* (R = H), to **C**, *electron-withdrawing* (R = NO_2) for **1E**, **1Z**, **2Z**, **3Z**, and **4Z**.

METHODS

The Gaussian series of programs[28] was employed in the (U)B3LYP//6-31G(d,p) calculations (for **1 – 4**) and MP2//6-31G(d,p) (for **1 – 3**) model chemistries. Vibrational analyses were performed on select species to ensure that optimizations had identified true minima; MP2 computations retained a high degree of spin contamination for **4** after annihilation of the first spin contaminant. Semiempirical AM1 and SCF computations (performed earlier by Professor D. G. Bonchev and not reported here) revealed trends similar to those reported in the present study.

RESULTS

Results of calculations are displayed in tables including both *E* and *Z* geometries for **1**, and for the remaining structures (**2 – 4**), only the real-world *Z*-geometry. In Tables 1a and 1b we present results of computed bond lengths for the free anions **3Z** or its salts.[21,22] It may be seen that the longest bond is that between the aromatic ring and the NONO-ate moiety, whereas in most computations the shortest bond appears to be that of the terminal N2–O2 bond, indicating a more pronounced nitroso-double-bond character and predominance of higher electron density on the O1 oxygen atom.

Table 1a

Bond distances (in Å) for *cisoid* cupferrate anion ***3Z***

						with Na^+
	[a]B3LYP 6-31G(d)	**[b]B3LYP 6-31G(d,p)**	**[b]B3LYP 6-311++G(d,p)**	**[b]MP2 6-31G(d,p)**	**[b]MP2 6-311++G(d,p)**	**[a]B3LYP 6-31G(d)**
$C–N^1$	1.417	1.411	1.422	1.416	1.427	1.436
N–N	1.324	1.354	1.357	1.363	1.356	1.306
$N^1–O^1$	1.303	1.297	1.275	1.285	1.275	1.318
$N^2–O^2$	1.256	1.252	1.268	1.278	1.268	1.281

Table 1b

Experimental X-ray diffraction data (in Å) for *cisoid* cupferrate **3Z** with various cations

Bond	Ref. 22	Data from ref. 24	Ref. 21	Ref. 21
Cation	NH_4^+	Na^+	NH_4^+	K^+
$C–N^1$	1.410	1.432	1.432(6)	1.512(7)
N–N	1.355	1.287	1.288(7)	1.297(3)
$N^1–O^1$	1.288	1.309	1.301(7)	1.297(5)
`$N^2–O^2$	1.271	1.284	1.260(7)	1.290(5)

In Tables 2 and 3 we present, for each set of structures, results on three rows denoted virtually by A, B, and C for the *para*-substituent with increasing electronegativity (NH_2, H, and NO_2). For each set of families, we summarize, on the last line of each set of compounds, the observed trend with increasing electron-withdrawing effects (from **A** to **B** to **C**). Structural parameters, namely again the four bond lengths as in Table 1, the corresponding four bond angles, and the dihedral bond angle between the aromatic ring and the NONOate moiety, are displayed in Tables 2a (Hartree-Fock/6-31G**), 2b (B3LYP/6-31G**), and 2c (MP2/6-31G**). One can observe that except for the sterically hindered **1E**, the dihedral angle shows that all the other whole molecules in the *Z* conformation are practically planar. The trends indicated for the effect on bond lengths of increasing electron-attraction of the *para*-substituent show a consistent decrease for the N^1–O^1 and the terminal N^2–O^2 bond lengths in all compounds **1 – 4**. A decreasing trend is also computed for the C–N^1 bond length.

Table 2a

Structural parameters optimized by Density Functional Theory (B3LYP/6-31G**) [a,b,c]

Compound [d,e]	N^1–N^2	N^1–O^1	N^2–O^2	C–N	<CCN^1	<CNO^1	<CNN	<NNO^2	*d*CCNO^1
1E -NH_2	1.355	1.392	1.225	1.427	121.1	116.4	129.2	114.9	-161.2
-H	1.364	1.392	1.220	1.427	120.7	116.3	129.0	115.2	-164.7
-NO_2	1.377	1.390	1.215	1.420	120.9	116.2	129.0	115.3	-169.7
Trend A → C	*In.*	*Dc.*	*Dc.*	*Dc.*	*Dc*	*Dc.*	*In.*	*In.*	*In.*
1Z -NH_2	1.314	1.372	1.257	1.438	120.1	118.9	124.5	111.8	179.9
-H	1.318	1.372	1.251	1.413	119.7	118.5	124.2	111.9	-180.1
-NO_2	1.326	1.372	1.243	1.405	119.7	118.5	123.8	111.9	180.0
Trend A → C	*In.*		*Dc.*	*Dc.*	*Dc.*	*Dc.*	*Dc.*	*sIn.*	
2Z -NH_2	1.289	1.281	1.352	1.438	121.4	120.2	118.2	112.4	180.0
-H	1.288	1.279	1.346	1.446	120.8	120.3	117.9	112.4	-180.1
-NO_2	1.290	1.278	1.340	1.443	120.8	120.8	117.6	112.5	-180.0
Trend A → C	*sIn_B*	*Dc_B*	*Dc.*	*In_ B*	*Dc.*	*In.*	*Dc.*	*sIn.*	
3Z -NH_2	1.348	1.299	1.256	1.416	124.0	119.6	114.7	114.3	179.8
-H	1.354	1.297	1.252	1.411	123.8	120.1	114.6	114.1	180.0
-NO_2	1.388	1.282	1.235	1.393	123.8	120.0	115.3	112.9	180.0
Trend A → C	*In.*	*Dc.*	*Dc.*	*Dc.*	*Dc.*	*In.*	*Dc.*	*Dc.*	
4Z -NH_2	1.476	1.245	1.205	1.414	121.8	123.0	116.4	111.6	-180.0
-H	1.493	1.243	1.197	1.423	121.0	123.0	116.9	110.4	-180.0
-NO_2	1.527	1.242	1.187	1.417	120.8	123.3	117.3	109.7	-180.0
Trend A → C	*In.*	*Dc.*	*Dc.*	*In_B*	*Dc*	*In.*	*Dc.*	*Dc_B*	

a. Bond distances in Å;
b. <WXY specifies the WXY bond angle in degrees;
c. *d*WXYZ specifies the dihedral angle between the WXY and XYZ planes in degrees;
d. Atom numbering: *Ar*-$N^1(O^1)N^2O^2$;
e. Abbrev.: *In* "increase"; *sIn* "slight increase; *In_B* "increase with B anomalous", *Dc* "decrease"

Taking into account that in Fig. 3 the left-hand resonance formulas of **1Z**, **3Z**, and **4Z** allow delocalization of the lone-pair electrons of N^1 by conjugation with the aromatic ring, the above observed trend finds a simple rationalization. Electron-attracting substituents should therefore favor such delocalization, leading to shorter C–N^1 and N^2–O^2 bond lengths.

Table 2b

Structural parameters optimized by MP2/6-31G**) [a,b,c]

Compound [d,e]	N–N	N–O^1	N–O^2	C–N	<CCN	<CNO^1	<CNN	<NNO^2	*d*CCNO^1
1Z -NH_2	1.326	1.368	1.272	1.408	119.4	118.6	124.4	110.7	178.4
-H	1.325	1.369	1.268	1.411	119.0	118.5	124.1	110.9	181.2
-NO_2	1.327	1.371	1.264	1.408	119.2	118.3	123.9	111.1	179.2
Trend A → C	*In.*	*In.*	*Dc.*		*sDc.*	*In.*	*Dc.*	*sDc.*	
2Z -NH_2	1.327	1.272	1.357	1.434	120.6	121.1	117.0	107.8	179.3
-H	1.329	1.268	1.355	1.439	120.0	121.0	116.7	107.7	-180.6
-NO_2	1.332	1.265	1.354	1.438	120.2	120.9	116.4	107.8	180.5
Trend A → C	*In.*	*Dc.*	*Dc.*	*In_B*	*Dc.*	*sIn.*	*Dc.*		
3Z -NH_2	1.364	1.286	1.279	1.417	123.6	119.6	114.1	112.7	-179.8
-H	1.363	1.285	1.278	1.416	123.5	119.9	114.1	112.6	180.0
-NO_2	1.376	1.277	1.270	1.402	123.8	121.1	113.6	112.0	180.0
Trend A → C	*In.*	*sDc.*	*Dc.*	*Dc.*		*In.*	*Dc.*	*Dc.*	

a. Bond distances in Å
b. <WXY specifies the WXY bond angle in *degrees*
c. *d*WXYZ specifies the dihedral angle between the WXY and XYZ planes in *degrees*
d. **.** atom numbering: *Ar*-N1(O1)N2O2
e. *In* "increase"; *sIn* "slight increase; *In_B* "increase with B anomalous", *Dc* "decrease"

Table 3a

Electronic properties of derivatives: B3LYP//6-31G** optimization

					Mulliken Charges			
R	**ΔE[a]**	**HOMO[a]**	**LUMO[a]**	**Dipole Moment[b]**	**N^1**	**O^1**	**N^2**	**O^2**
1E -NH_2	13.28	-127.6	-29.7	4.70	-0.14	-0.39	0.16	-0.36
-H	12.68	-147.9	-36.6	3.72	-0.14	-0.39	0.17	-0.34
-NO_2	10.18	-163.3	-65.4	4.37	-0.16	-0.39	0.19	-0.32
Trend A → C	*Dc.*	*Dc.*	*Dc.*	*Dc_2.*	*sDc.*		*sIn.*	*sIn.*
1Z -NH_2	2.28	-127.7	-33.1	5.05	-0.07	-0.44	0.14	-0.44
-H	1.56	-147.3	-42.1	3.19	-0.07	-0.43	0.16	-0.43
-NO_2	0.34	-163.4	-69.0	2.48	-0.08	-0.42	0.17	-0.40
Trend A → C	*Dc.*	*Dc.*	*Dc.*	*Dc.*	*sDc*	*sDc.*	*sIn.*	*In.*
2Z -NH_2	0.00	-130.6	-33.7	6.18	0.08	-0.54	0.05	-0.40
-H	0.00	-151.3	-45.5	3.29	0.08	-0.53	0.06	-0.39
-NO_2	0.00	-164.6	-73.2	1.65	0.08	-0.52	0.08	-0.38
Trend A → C		*Dc.*	*Dc.*	*Dc.*		*sInc.*	*In.*	*In.*

Table 3a (continued)

3Z -NH_2	367.09	9.4	82.7	11.05	0.02	-0.62	0.01	-0.49
-H	359.74	5.4	78.8	7.92	0.02	-0.61	0.02	-0.47
-NO_2	340.06	-21.5	24.9	3.77	0.01	-0.57	0.06	-0.40
Trend A → C	*Dc.*	*Dc.*	*Dc.*	*Dc.*	*sDc.*	*In*	*sIn.*	*In.*
4Z -NH_2	400.29	-121.8	-70.8	7.86	0.02	-0.38	0.13	-0.27
-H	398.94	-141.1	-81.9	4.29	0.01	-0.35	0.16	-0.24
-NO_2	398.76	-154.8	-96.2	1.16	-0.01	-0.34	0.18	-0.21
Trend A → C	*Dc.*	*Dc.*	*Dc.*	*Dc.*	*sDc*	*In*	*In_2*	*sDc_2*

[a] kcal/mol
[b] Debye

Table 3b

Electronic properties of derivatives: MP2//6-31G** optimization

					Mulliken Charges			
R	**ΔE[a]**	**HOMO[a]**	**LUMO[a]**	**Dipole[b] Moment**	**N^1**	**O^1**	**N^2**	**O^2**
1Z -NH_2	4.28	-183.5	53.8	4.93	-0.14	-0.50	0.30	-0.55
-H	5.44	-203.7	47.2	3.45	-0.15	-0.49	0.31	-0.53
-NO_2	5.38	-225.4	13.1	2.69	-0.17	-0.48	0.32	-0.51
Trend A → C		*Dc.*	*Dc.*	*Dc.*	*Dc.*	*SDc.*	*sIn.*	*In.*
2Z -NH_2	0.00	-188.1	46.9	6.39	0.08.	-0.61	0.11	-0.50
-H	0.00	-214.8	35.9	4.07	0.08	-0.61	0.13	-0.49
-NO_2	0.00	-233.5	2.5	1.63	0.07	-0.60	0.15	-0.48
Trend A → C		*Dc.*	*Dc.*	*Dc.*	*sDc.*	*SInc.*	*In.*	*In.*
3Z -NH_2	367.2	-53.3	162.5	12.42	-0.02	-0.71	0.13	-0.57
-H	365.4	-57.8	158.9	5.00	-0.03	-0.71	0.14	-0.56
-NO_2	351.3	-77.6	96.6	6.68	-0.04	-0.69	0.17	-0.50
Trend A → C	*Dc.*	*Dc.*	*Dc.*	*Dc.*	*Dc.*	*In_2*	*sIn.*	*In.*

[a] kcal/mol, relative to corresponding sructures **2Z**
[b] Debye

Table 3a and 3b modeled after the preceding table presents electronic properties: (i) relative energies calculated by two *ab-initio* theoretical methods, with **2Z** as reference compound; (ii) highest occupied and lowest unoccupied molecular orbital energies (HOMO and LUMO, respectively); (iii) dipole moments; and (iv) Mulliken charges for the four atoms in the NONO moiety. Again, as expected, a reasonable agreement between all methods is apparent. The trend in calculated dipole moments for anionic **3Z** is again explained by the large dipole moment when the electron-donating X substituent is the positive end and the NONO moiety is the negative end of the dipole; however, when X is electron-accepting, the molecule has two antagonistic dipoles playing a tug-of-war game at the C–N^1 bond, resulting in a small molecular dipole moment. The parallel trends for HOMO and LUMO leave a HOMO-LUMO gap that has a low variation. Interestingly, the partial negative charge on O^1 is calculated to be higher than on O^2, both in

the anion **3Z** (so that O^2 is closer to being part of a nitroso group) and in the free radical **4Z.** Because of spin contamination, no Møller-Plesset results for **4Z** are included in Tables 2 and 3.

The resonance structures of the free radical **4** obtained by oxidation of the N-aryl-diazenium-diolate anion were presented in Fig. 2. The unequal spin density on the four atoms forming the NONO-ate moiety can be explored experimentally by the hyperfine coupling constants a_H due to protons (with nuclear spin ½) and a_N for ^{14}N atoms (with nuclear spin 1). In the absence of ^{17}O-labeling, spin densities on oxygen atoms are not available. As seen in Fig. 2, the spin density on N^1 is about three times higher than on N^2. A significant spin density (approximately equal to that for N^2) is observed on the *ortho*-protons, and a smaller one on *meta*-protons.

In Table 4a we show hyperfine coupling constants determined experimentally and in Table 4b the Mulliken spin densities calculated by the B3LYP/6-31G** method for several N-aryl-N-nitroso-nitroxide radicals **4Z**. From Table 5a it is apparent that the relative magnitudes of hyperfine coupling constants agree with calculated Mulliken spin densities. However, one observes that a nitro electron-acceptor substituent lowers a_N values, whereas electron-donor substituents (methyl, methoxy) increase a_N values, but this trend is unsatisfactorily accounted for by Mulliken spin densities.

In Table 5 one may see an energetic balance for the decomposition of cupferrate salts (**3Z**) in acid medium leading to the formation of nitric oxide (NO) via a mechanism involving **1Z** that is the reverse of the experimentally proved spin trapping of NO by nitrosobenzene derivatives.

Table 4a

Hyperfine coupling constants (in G) for *para*-substituted ArNONO radicals (**4Z**) in dioxane at 28ºC

R	N^1	N^2	*o*-H av[b]	*m*-H av[c]	Hammett *para*-σ
OCH_3	10.30	3.43	3.43	-	–0.27
CH_3	10.20	3.70	2.80	0.90	–0.17
H	10.00	3.50	2.75	0.90	0.00
Cl	9.85	3.28	3.28	-	0.23
NO_2	9.00	2.45	0.81	-	0.78

[a] ref. 3; values for R = H are slightly different from those reported in Fig. 2
[b] averaged over *ortho* hydrogens
[c] averaged over *meta* hydrogens

Table 4b

Mulliken spin densities for *para*-substituted ArNONO radicals (**4Z)** by B3LYP/6-31G**

R	N^1	O^1	N^2	O^2	*o*-H av[a]	*m*-H av[b]
NH_2	0.19	0.38	0.04	0.26	0.0089	0.0033
H	0.21	0.45	0.03	0.23	-0.0038	0.0015
NO_2	0.22	0.47	0.02	0.19	0.0060	-0.0010

[a] averaged over *ortho* hydrogens
[b] averaged over *meta* hydrogens

Table 5

DFT Energies (ΔE)[a,b] of gas phase reactions

Reaction	R		
	$-NH_2$	-H	$-NO_2$
(i) Proton affinity of **3Z** *vs* NH_4^+/NH_3	-144.07	-139.75	-121.28
(ii) Oxidation of **1Z** *vs* $HOO^•/HOOH$	-4.69	-3.03	-1.99
(ii) Bond dissociation (N–N) of **4Z**	7.36	8.93	9.73
(iv) NET REACTION	-141.4	-133.8	-113.5

[a] B3LYP//6-31G(d,p) electronic energies
[b] kcal/mol

Gas phase reactions:

3Z + NH_4^+ → **1Z** + NH_3 (i)

1Z + $HOO^•$ → **4Z** + HOOH (ii)

4Z → $NO^•$ + *p*-R-*Ar*-NO (iii)

p-R-*Ar*-$NONO^-$ (**3Z**) + NH_4^+ + $HOO^•$ → NO^- + *p*-R-*Ar*-NO + NH_3 + H_2O_2 (iv)

CONCLUSIONS

The present study was focused on effects of donor or acceptor *para*-substituents in N-nitroso-N-phenyl-hydroxyalmine and its derivatives. Calculations for the two possible tautomers ArN(OH)–N=O (**1**), ArN(O)=N–OH (**2**) and the unique corresponding anion (**3**) and free radical (**4**) were performed using DFT, with model electron-donor and electron-acceptor *para*-substituents of the benzene ring (Ar).

The results of these computations provide a theoretical basis for the observed trends concerning the ease with which cupferron derivatives release NO under physiological conditions. Till now, such structures have not been tested clinically. Two other patents for topical delivery of NO deserve to be mentioned. Instead of chemical processes for NO administration, one can use the higher solubility of gases such as NO in perfluorinated solvents.[29] On applying to the skin a gel containing sodium nitrite and on top of it another gel containing ascorbic acid and an organic acid with a convenient pK_a such as maleic acid, one obtains a topical delivery of NO that is used cosmetically at present in China and Taiwan.[30]

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