Substituent Effects on the Reaction of 2-(Substituted phenyl)-4,5-dihydro-4,4,5,5-tetramethylimidazol-1-oxyl 3-Oxides with Nitric Oxide: an Experimental and MNDO Study

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The relative rate constants of the oxygen transfer reaction of 2-(substituted phenyl)-4,5-dihydro-4,4,5,5-tetramethylimidazol-1-oxyl 3-oxides with nitric oxide have been measured by using liquid chromatography (h.p.l.c.). The Hammett ρ value (−0.37) indicates that electron-donating substituents favour the reaction. This can be explained by a mechanism which includes electron transfer to nitric oxide and can be rationalised by frontier orbital energies and electron densities on the nitroxyl oxygen calculated by semiempirical MNDO methods.

The radical reagent 4,5-dihydro-4,4,5,5-tetramethyl-2-phenylimidazol-1-oxyl 3-oxide (**1**) reacts specifically with nitric oxide (NO) to yield the imino nitroxyl radical (**2**).[1] In view of this specific reactivity, the nitroxyl radical (**1**) has been used as an efficient free radical reagent for the direct analysis of NO in the atmosphere.[2,3] This method has the advantage of allowing measurements of the time-averaged concentration of NO over a long period (1 day to 1 week) at various places simultaneously without use of delicate instruments. The e.s.r. spectra of 2-alkyl and -aryl derivatives of (**1**) have been studied by Ullman and Boocock's groups.[4] However it remains uncertain whether electronic or steric factors play the major role in this radical reaction. Therefore, we have determined the relative rate constants (k_X/k_H) of the reactions of a series of 2-(substituted phenyl)-4,5-dihydro-4,4,5,5-tetramethylimidazol-1-oxyl 3-oxides, X-(**1**), by means of h.p.l.c. The observed substituent effects and the reaction mechanism are discussed on the basis of semiempirical MO (MNDO)[5] calculations.

Polar substituent effects on radical reactions have been investigated extensively. Thus, Hammett ρ values have been reported for additions of aryl radicals to olefins[6–8] and for the abstraction of benzylic protons from substituted toluenes.[9–12] Ingold's group have determined the rate constants of spin-trapping reactions between nitrone or nitroso spin traps and primary alkyl radicals, and have reported Hammett ρ values.[13] We have further investigated the effect of substituents on the reactions of substituted aryl radicals towards substituted phenyl t-butyl nitrones, and have inferred the intermediate formation of a charge-transfer complex during addition.[14] Reported Hammett ρ values for these radical reactions are small (−0.1 to +0.1) and substituent effects have been ascribed chiefly to charge-transfer stabilisation of the transition states. In the reactions of X-(**1**) with NO, both reactants are paramagnetic. There are few previous reports of substituent effects on reactions between free radical species.

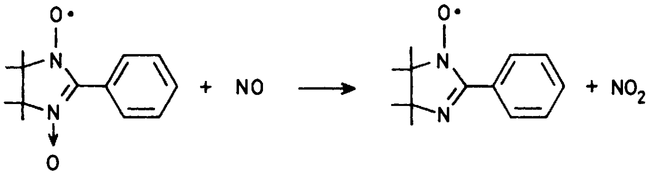
Results and Discussion

Kinetic Study.—The reaction of the nitroxyl (**1**) with NO to yield the imino nitroxyl (**2**) is assumed to be first order with respect to both (**1**) and NO [equation (i), the integrated form of which is equation (ii), where the subscript zero denotes an initial concentration].

$$(\mathbf{1}) + \mathrm{NO} \xrightarrow{k_H} (\mathbf{2})$$

$$-\mathrm{d}[(\mathbf{1})]/\mathrm{d}t = \mathrm{d}[(\mathbf{2})]/\mathrm{d}t = k_H[(\mathbf{1})][\mathrm{NO}] \quad \text{(i)}$$

$$\ln\{[(\mathbf{1})][\mathrm{NO}]_0/[(\mathbf{1})]_0[\mathrm{NO}]\}/[(\mathbf{1})]_0 - [\mathrm{NO}]_0 = k_H t \quad \text{(ii)}$$



(**1**) (**2**)

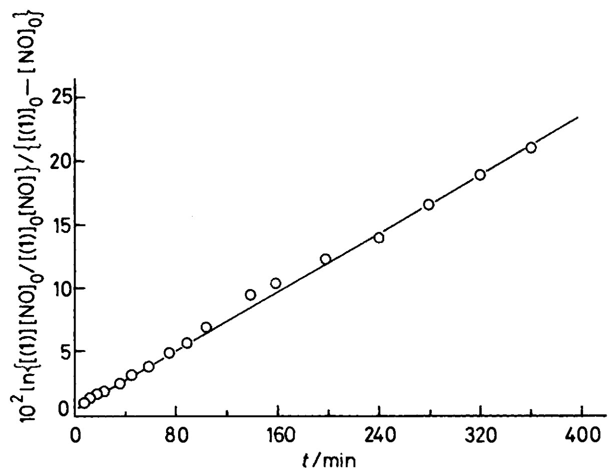


Figure 1. A plot of $\ln\{[(\mathbf{1})][\mathrm{NO}]_0/[(\mathbf{1})]_0[\mathrm{NO}]\}/\{[(\mathbf{1})]_0 - [\mathrm{NO}]_0\}$ as a function of *t* (min) for determining the rate constant k_H of the reaction between (**1**) and NO

A plot of the left-hand side of equation (ii) as a function of *t* (min) gives a good straight line (Figure 1) $\{[(\mathbf{1})]_0 = 1.25 \times 10^{-3}$ mol l^{-1}, $[\mathrm{NO}]_0 = 0.40 \times 10^{-3}$ mol l^{-1} at 15 °C$\}$. From the slope, $k_H = 1.04 \times 10^{-4}$ l mol^{-1} s^{-1}.

If we assume that X-(**1**) reacts with NO with the same kinetics as (**1**), we can determine relative rate constants (k_X/k_H) from competitive reactions of (**1**) and X-(**1**) with NO. When the initial concentrations of (**1**) and X-(**1**) are adjusted to be equal, the rate equation (iii) can be derived. Since the concentrations of (**1**) and X-(**1**) may be assumed to be equal in the early stages of the reaction, equation (iii) leads to equation (iv). Therefore the relative rate constant (k_X/k_H) can be determined from the slope of the time–conversion curves which monitor X-(**1**) and the reference (**1**) species. The absolute values of the rate constants (k_X) could be obtained easily by multiplying k_H by the experimental value of the ratio. High-performance liquid

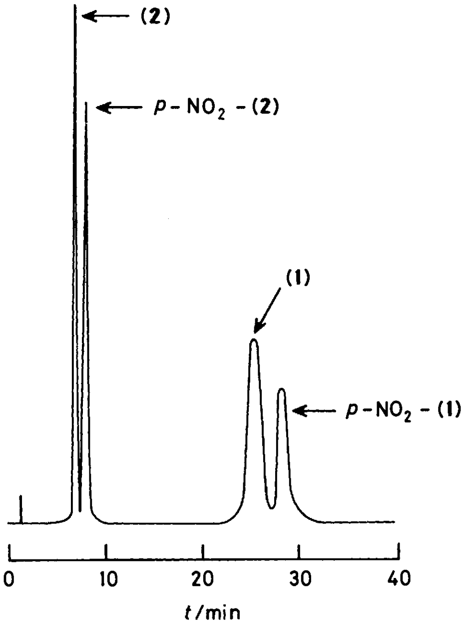


Figure 2. H.p.l.c. of the system of (**1**)/p-NO$_2$-(**1**) [spherisorb silica (5μ), eluant n-hexane–chloroform (4:1 v/v); detection wavelength 254 nm; flow rate 2.5 ml min^{-1}]

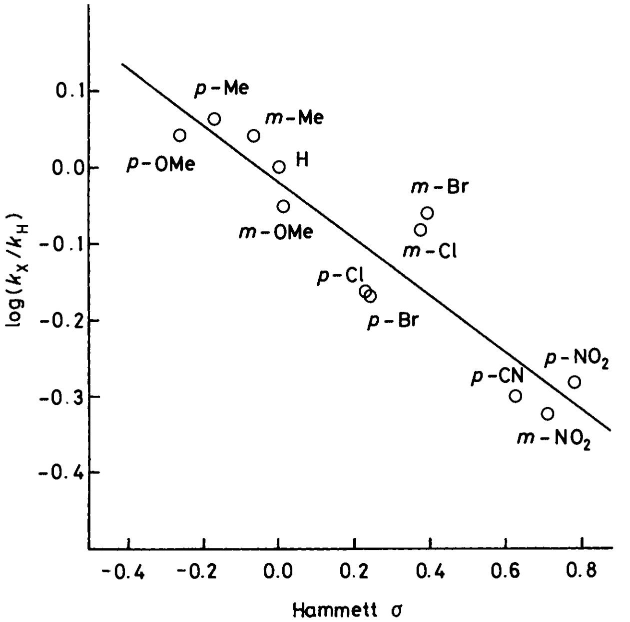


Figure 3. Hammett plot [log(k_X/k_H) *vs.* σ] in the series of *para*- or *meta*-substituted nitroxyls X-(**1**)

$$\frac{-d[X\text{-}(1)]/dt}{-d[(1)]/dt} = \frac{d[X\text{-}(2)]/dt}{d[(2)]/dt} = \frac{k_X[X\text{-}(1)][NO]}{k_H[(1)][NO]} = \frac{k_X[X\text{-}(1)]}{k_H[(1)]} \qquad \text{(iii)}$$

$$\frac{-d[X\text{-}(1)]/dt}{-d[(1)]/dt} = \frac{d[X\text{-}(2)]/dt}{d[(2)]/dt} = \frac{k_X}{k_H} \qquad \text{(iv)}$$

chromatography (h.p.l.c.) is a convenient tool for separating compounds (**1**), (**2**), X-(**1**), and X-(**2**) and for determining the concentrations of these species. Figure 2 shows a chromatogram [column of spherisorb silica (5μ), eluant n-hexane–chloroform 4:1 (v/v)] of the system (**1**)/p-NO$_2$-(**1**). In general, (**2**) has a longer retention time than (**1**) and X-(**1**) is eluted more slowly than (**1**).

Table. Relative rate constants (k_X/k_H) of reactions of nitroxyls X-(**1**) with NO at 15 °C, energies of electron transfer (E_{tr}), and electron densities on nitroxyl oxygen (Q_0)

Substituent X	k_X/k_H	10^4k_X/ l mol^{-1} s^{-1}	E_{tr}/eV[a]	Q_0[b]
o-OMe	0.0	0.0	9.776	6.2572
m-OMe	0.89	0.926	9.977	6.2513
p-OMe	1.1	1.14	9.929	6.2530
o-Me	0.27	0.281	9.915	6.2525
m-Me	1.1	1.14	9.918	6.2528
p-Me	1.2	1.25	9.916	6.2527
o-Cl	0.37	0.385	9.915	6.2510
m-Cl	0.83	0.863	10.033	6.2489
p-Cl	0.69	0.718	10.047	6.2503
o-Br	0.20	0.208	9.902	6.2509
m-Br	0.87	0.905	10.022	6.2499
p-Br	0.68	0.707	10.039	6.2502
o-NO$_2$	0.25	0.260	9.928	6.2620
m-NO$_2$	0.47	0.489	10.232	6.2474
p-NO$_2$	0.52	0.541	10.288	6.2464
p-CN	0.50	0.520	10.125	6.2496
2,6-Cl$_2$	0.0	0.0	9.915	6.2492
H	1.0	1.04	9.916	6.2529

[a] Energy for electron transfer from the HOMO of X-(**1**) to the LUMO of NO. [b] Electron density (Mulliken population) in nitroxyl oxygen.

The relative rate constants (k_X/k_H) are summarised in the Table. A Hammett plot [log(k_H/k_H) *vs.* σ] for the series of *para*- or *meta*-substituted (**1**) (Figure 3)[15] showed a good linear relationship (correlation coefficient 0.92). The ρ value (−0.37) suggests that electron-donating substituents favour the reaction. In the case of *ortho*-substituted (**1**), reactivity towards NO is lower, regardless of the electronic nature of the *ortho*-substituent. 2,6-Dichloro-(**1**) reacted extremely slowly with NO (k_X/k_H = 0.0). The lower reactivity of *ortho*-substituted (**1**) may, at least partially, be ascribed to a steric effect.

MNDO Study.—MNDO Calculations[16] for X-(**1**) were applied to elucidate the reaction mechanism on the basis of frontier orbital theory. The structure of the dihydroimidazole ring was estimated from structural data from the Cambridge Crystallographic Database by using the TOOL-IR library programme system of the Computer Centre of the University of Tokyo. The torsion angle (ω) between the imidazole and aryl rings and the bond length (r) between the atoms connecting these rings are important geometrical parameters for determining the stable conformations of X-(**1**); therefore these parameters were optimised.

We considered the direction of electron transfer in this reaction on the basis of the results. The interacting orbitals may be the HOMO of X-(**1**) and the LUMO of NO, or the LUMO of X-(**1**) and the HOMO of NO. In general, electron transfer is favourable when the energy difference between the interacting orbitals is small if the overlap between interacting orbitals is similar. By inspection of the calculated frontier orbitals of X-(**1**), the HOMO and LUMO of X-(**1**) are found to be the p_z-type orbitals (π orbital) of the N–O bonds. A frontier orbital energy diagram of (**1**) and NO, calculated by UHF-MNDO, is shown in Figure 4. Electron transfer from the HOMO of (**1**) to the LUMO of NO is estimated to be energetically more favoured than electron transfer from the HOMO of NO to the LUMO of (**1**). The same trend was shown for electron transfer between

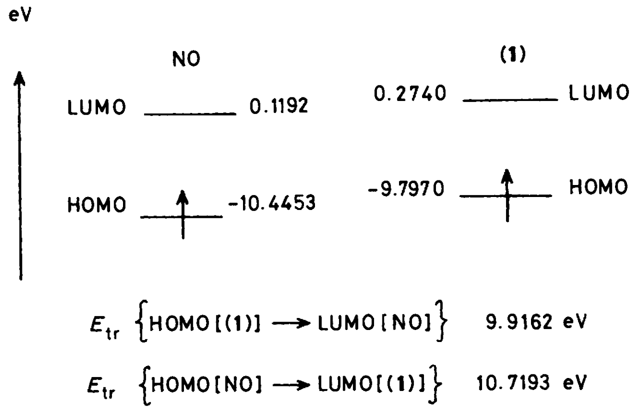


Figure 4. The frontier orbital energy diagram of (**1**) and NO

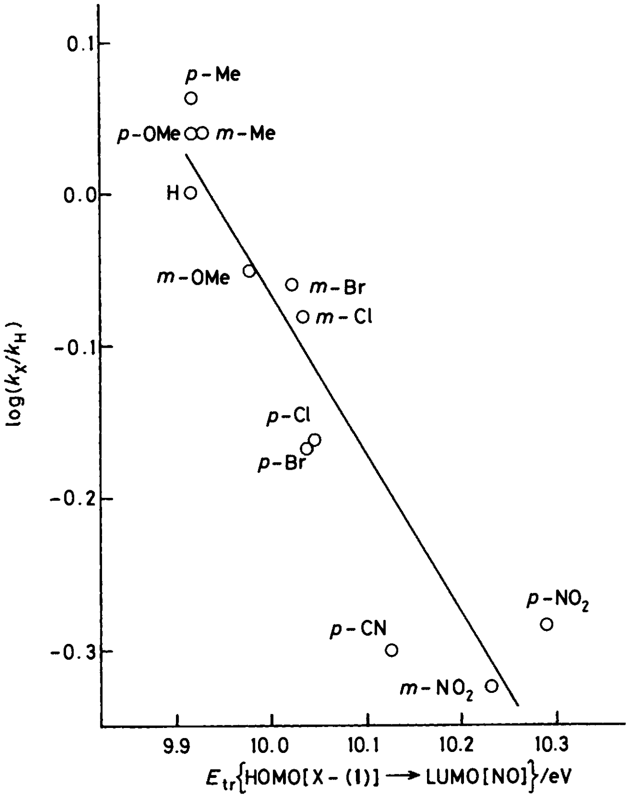
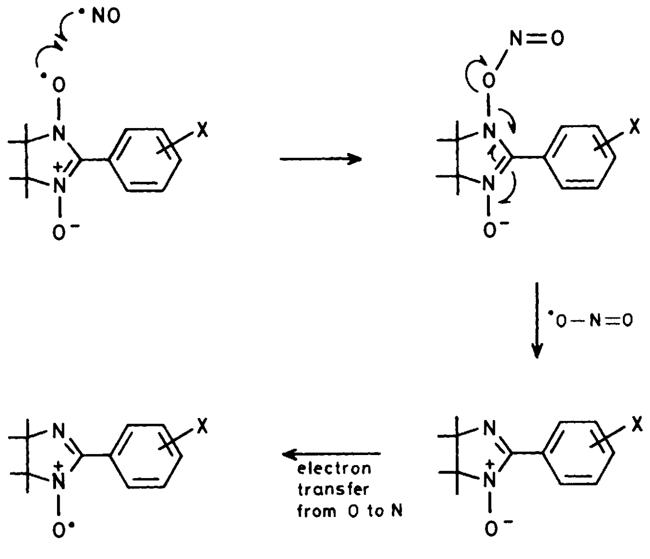


Figure 5. Plot of logarithms of the relative rate constants (k_X/k_H) of the reactions between X-(**1**) and NO *vs.* the energy for electron transfer from the HOMO of X-(**1**) to the LUMO of NO



Scheme.

X-(**1**) and NO. If the calculations are correct, electron transfer from the HOMO of X-(**1**) to the LUMO of NO should play a more important role in this radical reaction than electron transfer in the reverse direction. The energies for electron transfer from the HOMOs of X-(**1**) to the LUMO of NO in the series of *para*- and *meta*-substituted X-(**1**) are compiled together with the relative rate constants (k_X/k_H) in the Table. The smaller the energy for the electron transfer from the HOMO of X-(**1**) to the LUMO of NO, the higher is the reactivity of X-(**1**) towards NO which can be attained, in accord with the results of the calculations. Similarly, log(k_X/k_H) could be correlated linearly with E_{tr}{HOMO[X-(**1**) ⟶ LUMO[NO]} [the energy for electron transfer from the HOMO of X-(**1**) to the LUMO of NO] (correlation coefficient −0.93) (Figure 5). Thus the MNDO calculations could reproduce the electronic features of the reaction at least qualitatively.

From these experimental and theoretical results, we suggest the mechanism for the reaction between X-(**1**) and NO shown in the Scheme. The nitroxyl oxygen atom of X-(**1**) nucleophilically attacks the nitrogen atom of NO, and then N–O bond fission in X-(**1**) takes place, yielding X-(**2**) and NO$_2$. The sites of attack on NO and X-(**1**) molecule can be estimated from the spin density distributions in the molecules. As the spin densities on the nitrogen atom in NO and the nitroxyl oxygen atom in X-(**1**) are the largest in the respective molecules, this free radical reaction is predicted to occur smoothly at these atoms. If the proposed scheme is correct, there should exist a correlation between the electron density on this oxygen atom of the nitroxyl group and log(k_X/k_H). As shown in Figure 6, the plot of log(k_X/k_H) against electron density on the nitroxyl oxygen† is linear (correlation coefficient 0.90). The plot shows that the reactions become fast as the electron density on the nitroxyl oxygen increases. This supports the mechanism involving electron transfer from the X-(**1**) to NO.

Comparison of the electronic natures of *ortho*-substituted and *para*-substituted nitroxyls (**1**) gives an interesting result. *ortho*-Substituted nitroxyls X-(**1**) have values of E_{tr}{HOMO[X-(**1**)] ⟶ LUMO[NO]} almost equal or smaller values than the *para*-substituted derivatives, and their electron densities are very similar. Thus the *ortho*-substituted should be as reactive as the corresponding *para*-substituted derivatives X-(**1**). However, the *ortho*-substituted derivatives do not react as smoothly with NO as the corresponding *para*-substituted derivatives, even if the *ortho*-substituent is electron-donating. This result indicates the importance of steric factors in this reaction. An *ortho*-substituent may hinder the attack of NO on the nitroxyl group. This steric hindrance is confirmed by the relative rate constants for 2,6-dichloro-(**1**) (k_X/k_H = 0.0). However, the steric effect could not be correlated with steric substituent constants and other parameters used in evaluating the bulk of substituents.

In summary, the effects of substitution on the reaction of (**1**) can be explained by electronic and steric effects. Both the energy

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† In X-(**1**) molecules, there are two oxygen atoms (nitroxyl oxygen and *N*-oxide oxygen). However, both can behave as either nitroxyl or *N*-oxide. Therefore the electron density on the nitroxyl oxygen is taken to be the arithmetic mean of the Mulliken populations on nitroxyl and *N*-oxide oxygens.

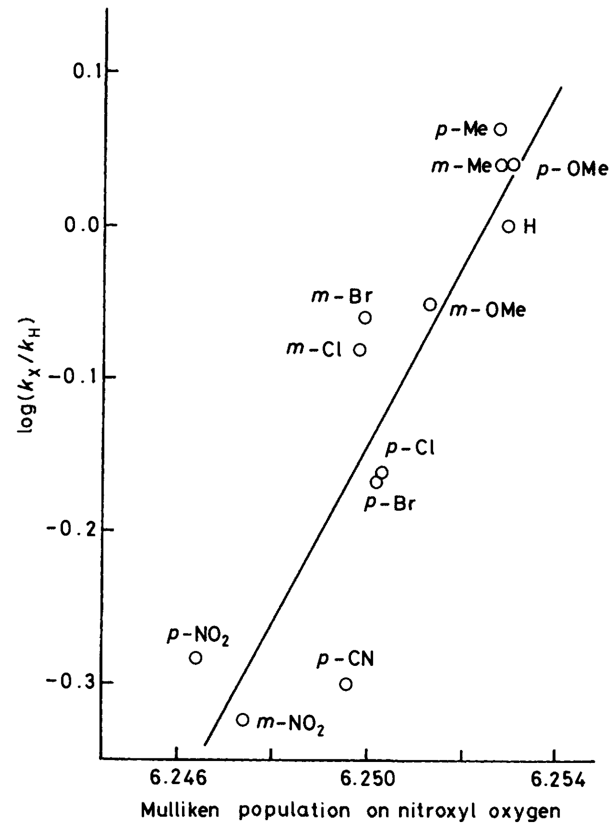

Figure 6. Plot of logarithms of the relative rate constants (k_X/k_H) of the reactions between X-(**1**) and NO *vs.* electron density on the nitroxyl oxygen of X-(**1**)

of electron transfer and the electron density on the nitroxyl oxygen (from MNDO) supported a reaction mechanism deduced from experiments. In the case of *ortho*-substituted nitroxyls (**1**), steric effects overpower electronic effects and lead to a decrease in reactivity towards NO.

Experimental

Materials.—Substituted nitroxyls X-(**1**) were synthesised *via* condensation of the sulphate salt of 2,3-bis(hydroxyamino)-2,3-dimethylbutane with the corresponding substituted benzaldehyde, and oxidation of the condensation product with sodium periodate.[2] The bis(hydroxylamine) was prepared from 2,3-dimethyl-2,3-dinitrobutane, which was synthesised from the lithium salt of 2-nitropropane,[17] by reduction with zinc powder below 20 °C.[18] The synthesised nitroxyls X-(**1**) were purified by column chromatography on silica gel with ether or n-hexane as eluant and recrystallisation from n-hexane, and were identified by their m.p.s and e.s.r. and mass spectra.

Measurement of Rates of Reactions.—The rate constant for the reaction of (**1**) with NO (k_H) in n-hexane–chloroform (1:1 v/v) was measured at 288 K by monitoring the decrease in the intensity of the u.v. absorption of (**1**) at 618 nm. The absorption band of the product (**2**) does not affect the intensity at 618 nm. From the concentration of (**1**) at time t calculated from the absorption intensity at 618 nm, and the concentration of NO at time t assumed equal to $[NO]_0 - ([(\mathbf{1})]_0 - [(\mathbf{1})])$, the rate constant ($k_H$) was determined by plotting the data for equation (ii).

The relative rate constant (k_X/k_H), normalised to the rate constant for (**1**), was calculated from the concentrations of X-(**1**) and (**1**) determined by h.p.l.c. [JASCO TWINCLE instrument attached to a UVIDEC-100-III UV detector; detection wavelength was 240 or 245 nm; eluant was n-hexane–chloroform (1:1 to 4:1 v/v); flow rate 1.0—3.0 ml min^{-1}].

Molecular Orbital Calculations.—UHF MNDO Calculations (MOPAC) were carried out for X-(**1**) and NO with HITAC M-680H computers at the Computer Centre of the University of Tokyo and Institute for Molecular Science. Only the torsion angle between the two rings, the length of the bond connecting the two rings, and the bond angle [N(imidazoline)–C(imidazoline)–C(benzene)] were optimised. The electron densities on the nitroxyl function and the frontier orbital energies were calculated with the optimised geometries.

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References

1 E. F. Ullman, J. H. Osiecki, D. G. B. Boocock, and R. Darcy, *J. Am. Chem. Soc.*, 1972, **94**, 7049.
2 J. S. Nadeau and D. G. B. Boocock, *Anal. Chem.*, 1977, **49**, 1672.
3 J. S. Nadeau, M. E. Treen, and D. G. B. Boocock, *Anal. Chem.*, 1978, **50**, 1871.
4 (*a*) J. H. Osiecki and E. F. Ullman, *J. Am. Chem. Soc.*, 1968, **90**, 1078; (*b*) D. G. B. Boocock, R. Darcy, and E. F. Ullman, *ibid.*, p. 5945; (*c*) D. G. B. Boocock and E. F. Ullman, *ibid.*, p. 6873; (*d*) E. F. Ullman, L. Call, and J. H. Osiecki, *J. Org. Chem.*, 1970, **35**, 3623; (*e*) E. F. Ullman, L. Call, and S. S. Tseng, *J. Am. Chem. Soc.*, 1973, **95**, 1677; (*f*) J. N. Herbert, P. W. Kopf, E. H. Poindexter, and B. E. Wagner, *J. Chem. Soc., Dalton Trans.*, 1975, 998; (*g*) L. S. Kaminsky and M. Lamchen, *J. Chem. Soc. C*, 1966, 2295; (*h*) L. Call and E. F. Ullman, *Tetrahedron Lett.*, 1973, 961.
5 M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, 1977, **99**, 4899.
6 P. I. Abell, *Trans. Faraday Soc.*, 1964, **60**, 2214.
7 M. M. Martin and G. J. Gleicher, *J. Am. Chem. Soc.*, 1964, **86**, 242.
8 M. M. Martin and G. J. Gleicher, *J. Am. Chem. Soc.*, 1964, **86**, 233.
9 R. W. Henderson and R. D. Ward, Jr., *J. Am. Chem. Soc.*, 1974, **96**, 7556.
10 W. A. Pryor and W. H. Davis, Jr., *J. Am. Chem. Soc.*, 1974, **96**, 7557.
11 A. Zavitsas and J. A. Pinto, *J. Am. Chem. Soc.*, 1972, **94**, 7390.
12 R. W. Henderson, *J. Am. Chem. Soc.*, 1975, **97**, 213.
13 P. Schmidt and K. U. Ingold, *J. Am. Chem. Soc.*, 1978, **100**, 2493.
14 K. Murofushi, K. Abe, and M. Hirota, *J. Chem. Soc., Perkin Trans. 2*, 1987, 1829.
15 Values taken from H. H. Jaffé, *Chem. Rev.*, 1953, **53**, 191.
16 J. J. P. Stewart, 'A General Molecular Orbital Package (MOPAC), Quantum Chemistry Program Exchange No. 464.
17 S. Limatibul and J. W. Watson, *J. Org. Chem.*, 1972, **37**, 4491.
18 M. Lamchen and T. W. Mittag, *J. Chem. Soc. C*, 1966, 2300.

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