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# *Ab Initio* Calculations on Large Molecules Using Molecular Fragments. Nitroxide Spin Label Characterizations[1]

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**Abstract:** An *ab initio* procedure, designed for investigation of large molecules and based upon studies of molecular fragments, is used to characterize various nitroxide spin labels. Several structural parameters are examined through calculations on nitroxide, methyl nitroxide, and dimethyl nitroxide. The calculated values of $R_{NO}$ agree well with values determined experimentally in larger nitroxides. Also, the potential associated with out-of-plane motion is shown to be extremely shallow. Finally, the staggered conformations around the CN bonds are calculated to be preferred in both methyl nitroxide and dimethyl nitroxide. Spin densities and isotropic hyperfine coupling constants are evaluated for the above molecules and several other molecules, *i.e.*, di-*tert*-butyl nitroxide, 2,2,5,5-tetramethylpyrrolidin-1-oxyl, and 2,2,6,6-tetramethylpiperidin-1-oxyl, that are useful as spin labels in biological systems. As expected, the results indicate that essentially all the $\pi$-electron spin density is localized in the nitroxide group. However, the calculated spin density distribution between N and O shows a marked basis set dependence, with very small basis sets giving reasonable estimates of trends, but unreliable estimates of absolute magnitudes of spin densities. The effect of an external applied electric field on the spin density and $^{14}N$ isotropic hyperfine coupling constants is also assessed, in order to simulate the environment found in excitable membranes. The results indicate that rather large fields (>500,000 V/cm) are required to produce measurable changes in the $^{14}N$ isotropic hyperfine coupling constants. Finally, MO ordering of $H_2NO$ is examined and compared to other available data.

## I. Introduction

An *ab initio* procedure (the molecular fragment procedure), designed for the investigation of large molecular systems and based upon studies of molecular fragments, has been developed over the past several years and has been used to investigate problems involving various types of closed-shell molecular systems.[2a] The utility and applicablility of the molecular fragment procedure for closed-shell systems have been analyzed recently,[2b] and its extension to open-shell systems has been described. Specifically, investigations have been carried out on several hydrocarbons,[3] and on a number of excited states of formaldehyde and its radical ions.[4] This paper continues the characterization of the molecular fragment procedure in open-shell systems, reporting the results of a study of nitroxide free radicals.

The first stable nitroxide was reported in 1959,[5] although their existence was postulated earlier in 1956 by Rogers, Johnson, and Trappe.[6,7] Since that time, these molecules have developed as important probes in both biological[8] and excited state studies.[9] Despite their great utility as probes and spin labels, the literature on the basic properties of the nitroxides is still quite sparse and contains much conflicting information, especially concerning the geometry of the nitroxides and the localization or lack thereof of the unpaired electron.

This study examines several important nitroxides in order to characterize the electronic and geometric features of these molecules and to assess their effect upon properties such as the spin density distribution. In addition, an estimate of the effect on the spin density and associated properties produced by electric fields of the order found in excitable membranes is obtained using a finite-field procedure. The results are discussed in terms of the effect of such "membrane generated" electric fields on the spin density distribution in various nitroxide spin labels.

## II. Theoretical Techniques

The basis set consists of normalized, nonorthogonal, floating spherical Gaussian orbitals (FSGO) defined as follows

$$G_i^{\sigma}(\mathbf{r}) = (2/\pi\rho_i^2)\exp\{-(\mathbf{r} - \mathbf{R}_i)^2/\rho_i^2\} \tag{1}$$

where $\rho_i$ is the orbital radius, and $\mathbf{R}_i$ is the location of the FSGO relative to some arbitrary origin. $\pi$-type orbitals are represented by a fixed linear combination of two FSGO's placed symmetrically on a line passing through the given atom and perpendicular to the $\pi$ plane, *i.e.*

$$G_i^{\pi}(\mathbf{r}) = [2(1 - \Delta_{\mathrm{ud}})]^{-1/2}(G_{\mathrm{u}}^{\sigma} - G_{\mathrm{d}}^{\sigma}) \tag{2}$$

where $G_{\mathrm{u}}^{\sigma}$ and $G_{\mathrm{d}}^{\sigma}$ are FSGO's placed above and below the atom, respectively. $\Delta_{\mathrm{ud}}$ is the overlap integral between $G_{\mathrm{u}}^{\sigma}$ and $G_{\mathrm{d}}^{\sigma}$.

The position and size of each FSGO is determined *via* energy minimization calculations on molecular fragments chosen to mimic various anticipated bonding environments.[10,11] The orbitals so obtained are then used as basis functions for an unrestricted Hartree-Fock self-consistent field molecular orbital[12] (UHF-SCF-MO) calculation on a particular large molecule of interest.

The first-order density matrices for $\alpha$- and $\beta$-spin electrons,[13] $\mathbf{P}^{\alpha}$ and $\mathbf{P}^{\beta}$, that result from the SCF calculations[12,14,15] are defined as

$$P_{rs}^{\eta} = \sum_{i}^{p \text{ or } q} C_{ri}^{\eta} C_{si}^{\eta}, \quad \eta = \alpha \text{ or } \beta \tag{3}$$

where $C_{ri}^{\eta}$ is the MO coefficient corresponding to the $r$th FSGO in the $i$th MO. The charge and bond order matrix is given by

$$\mathbf{P} = \mathbf{P}^{\alpha} + \mathbf{P}^{\beta} \tag{4}$$

while the corresponding spin density matrix is given by

$$\mathbf{P}^{\mathrm{SD}} = \mathbf{P}^{\alpha} - \mathbf{P}^{\beta} \tag{5}$$

The effect of an electric field on the spin density has been investigated using a finite field procedure.[16-18] The procedure is based on the direct inclusion of electric field terms in the molecular Hamiltonian, *i.e.*

$$\mathcal{H} = \sum_{\mu} h_{\mu}(\mathbf{f}) + \sum_{\mu>\nu}(1/r_{\mu\nu}) \tag{6}$$

where

$$h_{\mu}(\mathbf{f}) = -\frac{1}{2}\nabla_{\mu}^2 - \sum_{\alpha}\frac{Z_{\alpha}}{r_{\alpha\mu}} - \mathbf{f}\cdot\mathbf{r}_{\mu} \tag{7}$$

and $\mathbf{f}$ is the electric field strength. Minimization of the total energy with respect to the linear variation coefficients, $C_{ri}^{\eta}$, leads to a set of coupled UHF equations which differ from the usual set[3,4] in that they implicitly contain the electric field dependence

$$\mathbf{F}^{\eta}(\mathbf{f})\mathbf{C}_i^{\eta}(\mathbf{f}) = \Delta\mathbf{C}_i^{\eta}(\mathbf{f})\epsilon_i(\mathbf{f}) \tag{8}$$

These equations are then solved in a self-consistent field manner for various values of the electric field. Equation 9 shows the explicit electric field dependence of the Fock matrix elements

$$F_{rs}^{\eta}(\mathbf{f}) = H_{rs} - \mathbf{f}\cdot(\mathbf{m})_{rs} + J_{rs} - K_{rs}^{\eta} \tag{9}$$

where

$$(\mathbf{m})_{rs} = \langle\chi_r|\mathbf{r}|\chi_s\rangle \tag{10}$$

Table I. Molecular Fragment Data

| Fragment | Orbital radius ($\rho$) | Distance from the heavy atom |
|---|---|---|
| $CH_4$ | $\rho_{CH} = 1.67251562$ | 1.23379402 |
| | $\rho_{C} = 0.32784375$ | 0.0 |
| $:NH_3$ | $\rho_{NH} = 1.47683593$ | 0.94031372 |
| (planer, "sp$^2$") | $\rho_{N} = 0.27814453$ | 0.0 |
| | $\rho_{\pi} = 1.51198608$ | ±0.1 |
| OH | $\rho_{OH} = 1.23671871$ | 0.74647773 |
| ("sp") | $\rho_{O} = 0.24028227$ | 0.00057129[a] |
| | $\rho_{LP\text{-}\sigma} = 1.28753780$ | 0.21614258 |
| | $\rho_{LP\text{-}\pi} = 1.19741696$ | ±0.1 |
| | $\rho_{\pi} = 1.12242182$ | ±0.1 |

[a] This position is along the OH bond, displaced in the direction of the H nucleus.

and $H_{rs}$, $J_{rs}$, and $K_{rs}^{\eta}$ take on their usual meanings.[3,4] The basis orbitals, $\chi_r$ and $\chi_s$, are either $\sigma$- or $\pi$-type FSGO's as given by eq 1 and 2. The charge and bond order and spin density matrices, $\mathbf{P(f)}$ and $\mathbf{P}^{\mathrm{SD}}\mathbf{(f)}$, are still formed in the same manner, although they implicitly contain the electric field dependence. Thus, the change in spin densities due to the presence of an electric field can be determined in a straightforward manner.

## III. Structural Studies

**1. The Fragment Parameters.** As mentioned above, the position and size of each FSGO is determined *via* energy minimization calculations on molecular fragments, chosen to mimic various anticipated bonding environments.[10,11] The current fragments[2b] were developed over a period of time and represent the results of considerable testing and examination of prototype closed-shell molecules. While it is entirely possible that a modified or new set of fragments may be desirable to describe excited and open-shell systems adequately, it seems both expedient and desirable first to test the capabilities of existing fragments, which were developed for closed-shell systems, to help establish whether there is a need for additional fragments.

Only three fragments are necessary to describe all of the nitroxide free radicals which are examined in this study. The optimized FSGO parameters for these fragments are reproduced in Table I. The proper method of combining these fragments to form a large molecule has been explained in detail in earlier closed-shell papers.[2b]

In each of the studies to follow, the effect of spin contamination[19-21] has been ignored and has been assumed to be negligible. This assumption is based on initial studies of $\langle S^2\rangle$ in nitroxide and methyl nitroxide. For example, the calculated values of $\langle S^2\rangle$ for $H_2NO$ ranged only from 0.750 to 0.755 in the four different basis sets examined. This indicates that spin contamination is not likely to cause difficulties, regardless of the basis set employed.

**2. Nitroxide.** The simplest member of the nitroxide free radical class of molecules is $H_2NO$. It was first prepared in 1965,[22,23] but the geometry of this radical still has not been determined experimentally, due to its short lifetime. However, in 1970 Salotto and Burnelle[24] reported the results of a UHF study on the geometry of $H_2NO$. They concluded that $H_2NO$ is nonplanar, with an out-of-plane angle ($\theta$) of 26° and an HNH angle of 116°. However, the nonplanar structure was reported to be only 1.19 kcal/mol more stable than the planar structure. They also determined the bond lengths of NO and NH to be 2.53 and 1.87 $a_0$, respectively.

The planar geometry was used as the starting point in the current study. The total energy at various NO bond lengths is presented in Table II. A three-point parabolic fit of the data gives an optimum NO bond length of 2.38 $a_0$, with a corresponding energy of $-110.795130$ $E_a$. Fixing the NO

Table II. Total Energy of $H_2NO$ for Various Values of $R_{NO}$ and the Out-of-Plane Angle ($\theta$)[a]

| $R_{NO}$ | Total energy, $E_a$ |
|---|---|
| A. NO Bond Length[b] | |
| 2.30 | −110.789232 |
| 2.38 | −110.795129 |
| 2.45 | −110.790400 |
| 2.53 | −110.776117 |
| B. Out-of-Plane Angle[c] | |
| $\theta$, deg | |
| 0 | −110.795129 |
| 10 | −110.795587 |
| 18 | −110.796395 |
| 20 | −110.796603 |
| 30 | −110.797157 |
| 40 | −110.795682 |
| 50 | −110.790215 |

[a] The NH bond length is 1.87 $a_0$. [b] For these variations, the HNH angle was fixed at 116°, and the molecule was assumed to be planar. [c] For these variations, the NO bond length was fixed at 2.38 $a_0$.

Table III. Total Energy of Methyl Nitroxide for Various Values of the Angle-of-Rotation ($\phi$) and Out-of-Plane Angle ($\theta$)

| $\phi$, deg | Total energy, $E_a$ |
|---|---|
| A. Rotational Variation at $\theta = 0°$ | |
| 0 | −144.049149 |
| 15 | −144.049404 |
| 30 | −144.050023 |
| 45 | −144.050643 |
| 60 | −144.050900 |
| B. Rotational Variation at $\theta = 18°$ | |
| 0 | −144.048300 |
| 15 | −144.048341 |
| 30 | −144.049029 |
| 45 | −144.049963 |
| 60 | −144.050591 |
| 75 | −144.050547 |
| 90 | −144.049858 |
| 105 | −144.048928 |
| C. Out-of-Plane Variation at $\phi = 60°$ | |
| $\theta$, deg | |
| 0 | −144.050900 |
| 10 | −144.050855 |
| 18 | −144.050591 |
| 30 | −144.048930 |

bond length at 2.38 $a_0$ and the NH bond length at 1.87 $a_0$, the total energy of $H_2NO$ was then examined as a function of the out-of-plane angle. These results are also presented in Table II and Figure 1. A three-point parabolic fit of the data gives an optimum angle of 27.7° and the corresponding energy is −110.797209 $E_a$. Thus, the nonplanar structure is calculated to be 1.30 kcal/mol more stable than the planar structure.

It is seen that both the calculated out-of-plane angle and depth of the potential well are in excellent agreement with the values reported by Salotto and Burnelle. Furthermore, the NO bond length calculated in the current study agrees within approximately 1.2% of the values determined experimentally for larger stable nitroxides (2.41[25] and 2.40[26] $a_0$). However, the NO bond length of 2.53 $a_0$ reported by Salotto and Burnelle for $H_2NO$ is significantly larger than found in the current study. Since the basis sets used by Salotto and Burnelle were substantially larger than those used in this study, it was of interest to explore the source of this discrepancy in greater detail.

In an earlier study on HNO using similar basis sets, Salotto and Burnelle[27] reported an NO bond length of 2.50 $a_0$. For that case, the bond length is known experimentally[28] to be 2.29 $a_0$. Hence, since the Salotto and Burnelle basis sets are seen to overestimate the NO bond length when compared to experimental data on HNO, it appears likely that a similar effect may have occurred in the case of $H_2NO$.

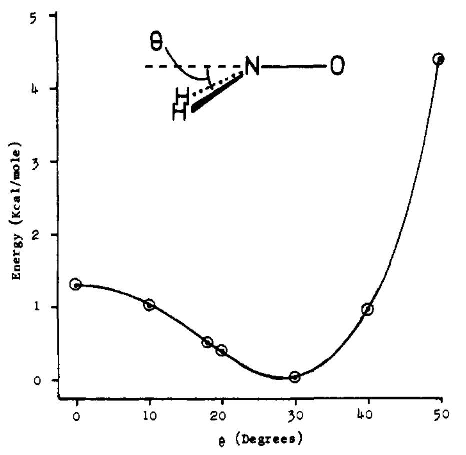


Figure 1. Total energy of $H_2NO$ as a function of the out-of-plane angle.

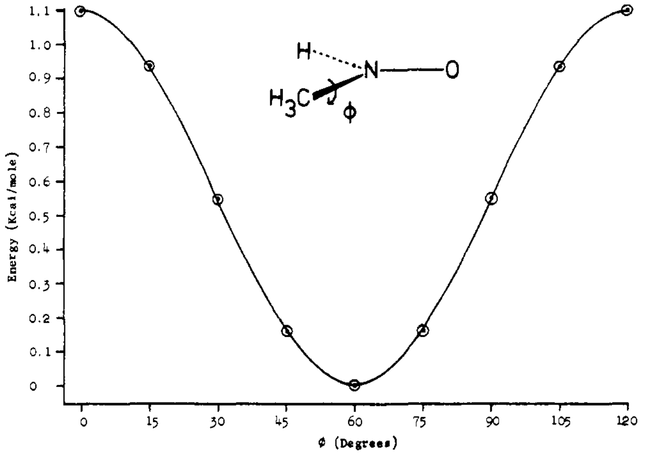


Figure 2. Total energy of methyl nitroxide as a function of rotation about the CN bond.

**3. Methyl Nitroxide.** This simple alkyl derivative of nitroxide is also shortlived and, consequently, very little is known experimentally about its structure. However, Chapelet-Letourneux, *et al.*,[29] argue from esr spectra and analogies to acetaldehyde that the most stable structure is probably one in which a CH bond is eclipsed with the NO bond.

To examine this question, the NO, CN, CH, and NH bond lengths were fixed at 2.38, 2.85, 2.06, and 1.95 $a_0$, respectively. These values are representative of those found in larger nitroxides.[25,26,30] The bond angles formed at the carbon atom were taken to be tetrahedral, and the CNH angle was fixed at 130°, a value approximating those frequently found in larger nitroxides.[25,26,30] The clockwise angle of rotation ($\phi$) was incremented in steps of 15° for both the planar ($\theta = 0°$) and nonplanar ($\theta = 18°$) structures. An out-of-plane angle of 18° was chosen since it is also an approximate average value found for many larger stable nitroxides.[31] Planarity for the larger nitroxides refers to the planarity of the Y(X)N—O moiety.

Total energy, at the various angles of rotation for the "planar" structure, is presented in Table III and Figure 2. The corresponding energies for the nonplanar structure are also presented in Table III. The results of both rotations are quite similar, and the staggered conformation ($\phi = 60°$) is

Table IV. The $\pi$ Charge and Bond Order Matrix Elements[a] for "Planar" Methyl Nitroxide as a Function of the Angle of Rotation ($\phi$)

| $\phi$, deg | $p_N$ | $p_O$ | $p_{NO}$ |
|---|---|---|---|
| 0 | 1.839 | 1.165 | 0.367 |
| 15 | 1.839 | 1.165 | 0.367 |
| 30 | 1.839 | 1.164 | 0.367 |
| 45 | 1.840 | 1.163 | 0.366 |
| 60 | 1.840 | 1.163 | 0.366 |

[a] These and all other charge and bond order matrix elements are given over a symmetrically orthonormalized basis. See ref 33.

Table V. Total Energy of Dimethyl Nitroxide for Various Values of the Angles-of-Rotation ($\phi$, $\phi'$) and Out-of-Plane Angle ($\theta$)

| $\phi$, deg | $\phi'$, deg | Total energy, $E_a$ |
|---|---|---|
| A. Rotational Variation at $\theta = 0°$ | | |
| 60 | 60 | −177.286052 |
| 60 | 30 | −177.285420 |
| 60 | 0 | −177.284773 |
| 0 | 0 | −177.282998 |
| B. Out-of-Plane Variation at $\phi = \phi' = 60°$ | | |
| $\theta$,deg | | |
| 0 | | −177.286052 |
| 10 | | −177.286197 |
| 18 | | −177.286313 |
| 30 | | −177.285396 |

observed to be more stable than the eclipsed conformation, in contrast to the prediction of Chapelet-Letourneux, *et al.*[29] However, the energy difference between the eclipsed and staggered conformations is seen to be quite small, *i.e.*, 1.10 kcal/mol for the planar structure.

To examine this conformational question in greater detail, it is of interest to consider acetaldehyde, which is the analogous aldehyde. In that case, the eclipsed conformation is found experimentally[32] to be more stable by 1.16 kcal/mol, and 1.5 kcal/mol more stable in molecular fragment studies.[33] However, the CCH angle is 117.5°, while the corresponding CNH angle in methyl nitroxide has been taken to be 130°. Hence, the repulsive interaction between the NH hydrogen and the $CH_3$ hydrogens will be reduced, thus reducing the typical barrier to rotation about the CN bond.

Also, hydrogen bonding, if it were present, would be expected to stabilize the eclipsed conformer. During the course of a study on amides,[2a] it was observed that hydrogen bonding could be detected from an examination of the changes which occur in the $\pi$ charge and bond order matrix elements. The $\pi$ charge and bond order matrix elements for methyl nitroxide as a function of the rotational angle are presented in Table IV. As is seen from the table, the charge and bond order elements are virtually unaffected by changes in the rotational angle. Thus it appears that there is no evidence to support the formation of an intramolecular hydrogen bond in methyl nitroxide.

Although the conformational results of the current study are rationalized above, care must be taken to point out possible effects which have not yet been taken into account. There is a certain amount of basis set inflexibility in the $\pi$ system (consisting of only two $p_\pi$ orbitals) which is doubly occupied by the $\alpha$-spin electrons. Also, configuration interaction effects are only partially accounted for in UHF calculations,[4] and hence cannot be ruled out when such small energy differences are involved. Finally, the choice of other geometric parameters by analogy to larger nitroxides, *e.g.*, the CNH angle, may affect such small energetic differences.

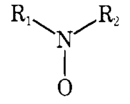
It is also found that the planar staggered structure is more stable than the nonplanar structure, as shown in Table III. It must be stressed, however, that the total energy increases very slowly with increasing out-of-plane angle, perhaps making the question of linearity or lack thereof one more of semantics than of substance.

**4. Dimethyl Nitroxide.** Using arguments similar to those used for methyl nitroxide, Chapelet-Letourneux, *et al.*,[29] proposed that the most stable conformation of this dialkyl derivative of nitroxide has two CH bonds eclipsed with the NO bond. In the current studies, the geometry chosen was the same as that of methyl nitroxide, with the NH hydrogen replaced by $CH_3$. The total energy was examined at several values of $\phi$ for the two methyl groups. The results presented in Table V show that the staggered–staggered ($\phi = \phi' = 60°$) conformation is calculated to be the most stable, with the energy difference between the staggered–staggered and eclipsed–eclipsed conformations being 1.92 kcal/mol. This is seen to be approximately twice the barrier found in methyl nitroxide, and indicates the consistency of the calculations. Furthermore, it indicates that the discussion given above concerning the differences between the current results and those predicted by Chapelet-Letourneux, *et al.*,[29] may also be appropriate here.

Although Table V shows the nonplanar staggered–staggered conformation to be the most stable, the differences in total energy may be too small to be useful or reliable as quantitative estimates. However, for all three nitroxides studied above, it can be concluded that the potential curves as a function of the out-of-plane angle are extremely shallow.

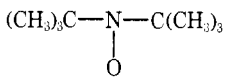
## IV. Spin Densities

The general structure (I) of stable nitroxide free radicals which have been found useful as spin labels is as follows:



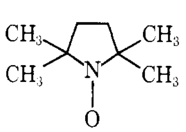
I

It is known that the basic esr spectrum is unaffected by the nature of the R groups.[34] Three specific molecules were selected for inclusion in the current study as representatives of this class, *i.e.*, di-*tert*-butyl nitroxide (II), 2,2,5,5-tetramethylpyrrolidine-1-oxyl (III), and 2,2,6,6-tetramethylpiperidin-1-oxyl (IV). These systems contain 81, 79, and 87 electrons, respectively.

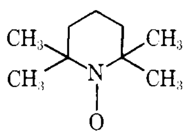


$(CH_3)_3C{-}\underset{\displaystyle O}{\underset{|}{N}}{-}C(CH_3)_3$

II



III



IV

The nuclear geometry of (II) ($C_8H_{18}NO$) was taken essentially from the electron diffraction study of Andersen and Andersen.[30] However, the NO, CC, and CH bond lengths were fixed at 2.38, 2.91, and 2.06 $a_0$, respectively.[35] The CNC angle was fixed at 130°, and these molecules were each constrained to a planar configuration. This is not totally unjustified in view of the lack of other definitive data, and the shallowness of the calculated potential curves as shown in the previous section. The nuclear geometry of (III) ($C_8H_{16}NO$) was taken from the crystal structure of a derivative compound determined by Boeyens and Kruger.[26] The nuclear geometry of (IV) ($C_9H_{18}NO$) was taken from the crystal structure of a derivative compound determined by Bordeaux and Lajzerowicz.[25] However, in both cases, the NO bond length was fixed at 2.38 $a_0$.[35]

It is generally agreed in experimental studies[36] that the

Table VI. Approximate Values of the Spin Density on the Nitrogen Atom of Simple Nitroxides

| Molecules or class of molecules | Approximate value of $P_N^{SD}$ [a] | Ref |
|---|---|---|
| 2,2,6,6-Tetramethyl-4-piperdon-1-oxyl | 0.5 | 36 |
| Simple nitroxides | 0.9 | 34 |
| Dimethyl nitroxides | 0.23 | 37 |
| Nitroxide | 0.5 | 38 |
| Simple nitroxides | 0.6 | 39 |
| Nitroxide, dimethyl nitroxide | ≤0.35 | 40 |

[a] See ref 41.

Table VII. Spin Density Distribution for Several Nitroxide Free Radicals at Various Values of the Out-of-Plane Angle ($\theta$)

| Molecule | $\theta$, deg | $P_N^{SD}$ [a] | $P_O^{SD}$ [a] | $P_N^{SD} + P_O^{SD}$ |
|---|---|---|---|---|
| $H_2NO$ | 0 | 0.158 | 0.842 | 1.000 |
| | 18 | 0.152 | 0.846 | 0.998 |
| | 30 | 0.143 | 0.853 | 0.996 |
| $CH_3HNO$ | 0 | 0.160 | 0.837 | 0.997 |
| | 18 | 0.154 | 0.840 | 0.994 |
| $(CH_3)_2NO$ | 0 | 0.164 | 0.831 | 0.995 |
| | 18 | 0.155 | 0.835 | 0.990 |
| II | 0 | 0.158 | 0.823 | 0.981 |
| III | 0 | 0.156 | 0.823 | 0.979 |
| IV | 0 | 0.160 | 0.821 | 0.981 |

[a] See ref 41.

unpaired spin density, $P_X^{SD}$ (X = N, O), is almost entirely localized in the $\pi$ orbitals of the nitrogen and oxygen atoms. However, there is practically no agreement concerning the distribution of the spin density between the nitrogen and oxygen atoms, as indicated in Table VI, where the reported nitrogen spin density, $P_N^{SD}$, ranges from 0.23[37] to 0.9[34] in previous studies.[34,36-40]

The spin densities calculated in the current study are presented in Table VII. In comparison to Table VI, it is seen that the current values of $P_N^{SD}$ are smaller than previously reported experimental values. Table VII also indicates that the unpaired spin is almost entirely located on the NO group, with approximately 1% or less delocalization occurring when rings are formed. The effects of basis set choice on these results are discussed below. The data also show that the spin density on the nitrogen atom is relatively insensitive to a change in the out-of-plane angle.[41] Therefore, the following studies will deal primarily with the planar conformations.

## V. Effects of an Applied Electric Field

**1. Spin Densities.** In this study the electric field[42] was chosen to lie along the NO bond axis (the origin was chosen at the oxygen atom, and the negative $x$ axis points toward the nitrogen atom) in the negative direction. Such a field tends to move the electrons toward the more electronegative oxygen atom, and would maximize the effect on the nitrogen and oxygen $\pi$-spin densities. At low electric field strengths such as might be present in biological membranes, *i.e.*, $f_x \sim 10^{-5}$–$10^{-4}$ $E_a/ea_0$ ($5 \times 10^4$–$5 \times 10^5$ V/cm), almost no change in calculated spin density was found. In fact, electric fields on the order of $10^{-3}$ $E_a/ea_0$ are required to produce significant changes in spin density. The results of several such calculations carried out on nitroxide radicals are summarized in Table VIII and compared to available data.[22,23,43-45] Of particular interest is relative independence of the spin density change with respect to the radical studied. Also, an examination of $P_O^{SD}$ in the presence of a field showed that $P_N^{SD}(\mathbf{f}) + P_O^{SD}(\mathbf{f}) \simeq 1$, as was observed in the field free case (see Table VII).

**2. $^{14}$N Isotropic Hyperfine Coupling Constants.** It is also of interest to relate the change in spin density at the nitrogen atom due to the presence of an electric field to the change in the nitroxide $^{14}$N isotropic hyperfine coupling constant, $a_N$. The Karplus–Fraenkel[46] relation has been used successfully to determine isotropic hyperfine coupling constants, for planar $\pi$-electron radicals, and the lack of spin delocalization from the nitroxide group suggests that it may also be useful in the current study. This relation for the nitroxide $^{14}$N splitting constants (in gauss) is given by[47]

$$a_N = Q_N P_N^{SD} + Q_O P_O^{SD} \tag{11}$$

where $Q_N = 24.2$ and $Q_O = 3.6$ G respectively.

From the previous discussion (see also Tables VII and VIII), it is justified to assume that

$$P_N^{SD} + P_O^{SD} \cong 1.0 \tag{12}$$

both in the presence and absence of an electric field. Equation 11 can then be rewritten as

$$a_N = (Q_N - Q_O)P_N^{SD} + Q_O \tag{13}$$

and

$$a_N' = (Q_N - Q_O)P_N^{SD\prime} + Q_O \tag{14}$$

where the primes indicate the presence of an electric field, and it is assumed that the Karplus–Fraenkel relationship, eq 11, holds in the presence of an external electric field. Thus, the change in the isotropic hyperfine coupling constant is given by

$$\Delta a_N = a_N' - a_N \tag{15}$$

$$= (Q_N - Q_O)(P_N^{SD\prime} - P_N^{SD}) \tag{16}$$

$$= (Q_N - Q_O)\Delta P_N^{SD} \tag{17}$$

or

$$\Delta a_N = 20.6\Delta P_N^{SD} \tag{18}$$

Using eq 18, the values of $\Delta a_N$ for the various nitroxide free radicals at $f_x = -1.0 \times 10^{-2}$ $E_a/ea_0$ have been calculated and listed in Table VIII. From that table it is clear that $\Delta a_N$ is effectively constant for all nitroxides investigated.

Table VIII. Effect of an External Electric Field on Spin Density[a]

| | | $f_x = 0.0$ [c] | | $f_x = -0.001$ [c] | | | $f_x = -0.01$ [c] | | |
|---|---|---|---|---|---|---|---|---|---|
| Molecule[b] | Exptl $a_N$ [c] | $P_N^{SD}$ | $a_N$ [i,j] | $P_N^{SD}$ | $\Delta P_N^{SD}$ | $\Delta a_N$ [c] | $P_N^{SD}$ | $\Delta P_N^{SD}$ | $\Delta a_N$ [c] |
| $H_2NO$ | 11.9[d] | 0.158 | 6.85 | 0.160 | 0.002 | 0.023 | 0.172 | 0.014 | 0.29 |
| $CH_3HNO$ | 13.8[e] | 0.160 | 6.90 | | | | 0.174 | 0.014 | 0.29 |
| $(CH_3)_2NO$ | 15.2[f] | 0.164 | 6.98 | | | | 0.177 | 0.013 | 0.27 |
| II | 15.1[g] | 0.158 | 6.85 | | | | 0.172 | 0.014 | 0.29 |
| III | 15.3[h] | 0.156 | 6.81 | | | | 0.170 | 0.014 | 0.29 |
| IV | 16.3[i] | 0.160 | 6.90 | | | | 0.174 | 0.014 | 0.29 |

[a] The relationship $P_N^{SD}(\mathrm{f}) + P_0^{SD}(\mathrm{f}) \cong 1.0$ still holds in the presence of an applied electric field. [b] The structures of II, III, and IV are given in the text. [c] Electric field strengths ($f_x$) in $E_a/ea_0$, and isotropic hyperfine coupling constants ($a_N$) in G. [d] See ref 22. [e] See ref 22 and 23. [f] See ref 22. [g] See ref 43. [h] See ref 44. [i] See ref 45. [j] Calculated using eq 11 and 12.

Table IX. Comparison of Molecular Orbital Energies for Planar $H_2NO$

| MO symmetry | Salotto and Burnelle[a] | Molecular fragment approach[b] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Basis set A | | Basis set B | | Basis set C | | Basis set D | |
| | $\alpha$ | $\alpha$ | $\beta$ | $\alpha$ | $\beta$ | $\alpha$ | $\beta$ | $\alpha$ | $\beta$ |
| $2b_1$ ($\pi$*) | −0.4151 | −0.0554 | 0.5723 | −0.1512 | 0.3215 | −0.2145 | 0.2140 | −0.2396 | 0.1090 |
| $2b_2$ (n) | −0.4983 | −0.1406 | −0.1018 | −0.1863 | −0.1584 | −0.2712 | −0.2512 | −0.2908 | −0.2661 |
| $5a_1$ | −0.6579 | −0.3924 | −0.2536 ($1b_1$) | −0.4291 | −0.3017 ($1b_1$) | −0.5438 ($1b_1$) | −0.4025 ($1b_1$) | −0.5438 ($1b_1$) | −0.3978 ($1b_1$) |
| $1b_1$ ($\pi$) | −0.6817 | −0.4120 | −0.3481 ($5a_1$) | −0.4518 | −0.3963 ($5a_1$) | −0.5523 ($5a_1$) | −0.5218 ($5a_1$) | −0.5521 ($5a_1$) | −0.5270 ($5a_1$) |
| $1b_2$ | −0.7425 | −0.5578 | −0.5502 | −0.6046 | −0.5925 | −0.6793 | −0.6666 | −0.6798 | −0.6691 |
| $4a_1$ | −1.0933 | −0.9698 | −0.9044 | −1.0432 | −0.9822 | −1.0893 | −1.0282 | −1.1149 | −1.0560 |
| $3a_1$ | −1.4715 | −1.3821 | −1.3127 | −1.3989 | −1.3492 | −1.5258 | −1.4841 | −1.5103 | −1.4625 |
| $2a_1$ | | −12.9920 | −12.9911 | −13.1097 | −13.1079 | −13.2758 | −13.2721 | −13.3034 | −13.3003 |
| $1a_1$ | | −17.0669 | −17.0571 | −17.1639 | −17.1588 | −17.3926 | −17.3884 | −17.3916 | −17.3861 |
| $P_N^{SD}$[c] | | 0.158 | | 0.341 | | 0.483 | | 0.422 | |
| $a_N$[d] | | 6.82 | | 10.63 | | 13.55 | | 12.29 | |

[a] See ref 24. [b] The basis sets are explained in the text. [c] $P_N^{SD} = \Sigma_t^{\pi} P_{tt}^{SD}$, where $t$ is summed over all $\pi$ orbitals. [d] Calculated using eq 11 and 12. Values in gauss. Experimentally observed: 11.9 G.[22]

Thus, when an electric field of approximately $-1.0 \times 10^{-2}$ $E_a/ea_0$ is applied, one obtains an easily observable effect on the isotropic hyperfine coupling constant of the nitrogen atom. On the other hand, if $f_x = -1.0 \times 10^{-3}$ $E_a/ea_0$, the calculated change in $a_N$ is only 0.023, which would be on the borderline of detectability (±0.02 G).[39] Therefore, electric strengths on the order of those found in excitable membranes (~$10^{-5}$–$10^{-4}$ $E_a/ea_0$) are not expected to produce observable changes in $a_N$. This conclusion agrees with that of Griffith, *et al.*,[39] based on estimates obtained using Hückel MO theory.

## VI. MO Structure

Many examples in closed-shell systems have shown that valence MO ordering obtained by the molecular fragment procedure is identical in almost all cases to that obtained using more extended basis sets. Unfortunately, such comparisons on open-shell systems are more difficult to carry out, due to the lack of suitable extended basis set UHF calculations. However, Salotto and Burnelle[24] have examined the MO structure of $H_2NO$ using an extended basis set. Their results give the following electron configuration of planar nitroxide: $(1a_1)^2(2a_1)^2(3a_1)^2(4a_1)^2(1b_2)^2(1b_1(\pi))^2(5a_1)^2(2b_2(n))^2(2b_1(\pi^*))^1$. In the current studies, the ordering of the $\alpha$ MO's is the same as that reported by Salotto and Burnelle. However, the current results for $\alpha$ and $\beta$ MO's are not identical with each other, and for the $\beta$ MO's, the $1b_1$ and $5a_1$ molecular orbitals are interchanged. These orbital energies are tabulated in Table IX (basis set A).

As Salotto and Burnelle's[24] calculations were carried out at a larger NO internuclear distance (2.52 $a_0$ *vs.* 2.38 $a_0$), the MO ordering obtained in the present calculations at 2.53 $a_0$ was also examined to ascertain whether the NO bond distance would produce any changes. No changes were observed, *i.e.*, MO ordering was invariant at an NO bond distance of 2.53 $a_0$.

For molecules with closed-shell ground states, a linear relationship has been established between the orbital energies of valence orbitals calculated by the molecular fragment procedure and those calculated using more extensive basis sets.[2b] As a first test of fragment suitability, it is obviously of interest to see if a similar relationship exists for open-shell states. The form of the relationship is

$$\epsilon_i^{\text{ref}} = a\epsilon_i^{\text{MF}} + b \qquad (19)$$

where the $\epsilon_i^{\text{MF}}$ are valence molecular orbital energies obtained using the molecular fragment procedure, and the $\epsilon_i^{\text{ref}}$ are similar quantities taken from more extensive basis set calculations. A least-squares fit of the data for $\alpha$ MO's reported by Salotto and Burnelle yields the following parameters: $a = 0.7811$ and $b = -0.3580$ (see Table X). These values are in the same range as those found in closed-shell studies.[26] This indicates that, as in the closed-shell studies, the open-shell molecular fragment procedure also gives larger spacings than those obtained in more extensive basis set studies, and will result typically in calculated vertical ionization potentials being uniformly too small.

## VII. Basis Set Improvements

**Initial Studies on Nitroxide.** From the previous discussion, it is clear that, while the minimum FSGO basis (basis set A, see Tables I and IX) provides a reasonable description of geometric and MO structure, it may be deficient with respect to the calculation of spin densities. As pointed out earlier, the spin densities calculated in the current study are seen to be outside the range of those previously reported (see Table VI), in contrast to more recent studies which indicate that the spin densities on the nitrogen and oxygen

Table X. Approximate Linear Relationship[a] between MO's of Molecular Fragment and More Extensive Basis Sets[b]

| Basis set | $a$ | $b$ | $S^c$ | $\rho^d$ |
|---|---|---|---|---|
| A | 0.7811 | −0.3580 | 0.0330 | 0.9967 |
| B | 0.7997 | −0.3070 | 0.0422 | 0.9945 |
| C | 0.7886 | −0.2449 | 0.0290 | 0.9974 |
| D | 0.8028 | −0.2288 | 0.0306 | 0.9971 |

[a] The coefficients "$a$" and "$b$" in this table are those of eq 19 in the text. [b] The large-basis set calculations used for this comparison are in ref 24. [c] $S$ is the root-mean-square deviation from the least-squares line. For details, see ref 2b. [d] $\rho$ is the correlation coefficient. For details, see ref 2b.

atoms are nearly equal.[3] Two of the most likely reasons that might lead to this result are: (1) the lack of diffuse $\pi$-type basis functions on both the nitrogen and oxygen atoms, which may be necessary components of the $\pi^*$ orbital; and (2) the inflexibility of the $\pi$ and $\pi^*$ orbitals when only two basis functions are available to describe the $\pi$ bonding portion of the system. It is obvious that these two considerations are inseparable. These problems were first noticed in the study of formaldehyde,[4] and a more complete discussion is presented there.

In order to investigate the effect of basis set improvement, several preliminary studies have been carried out, and are summarized in Table IX. It should be emphasized, however, that these results indicate only the kinds of improvements which can be obtained, and are not necessarily final recommendations.

Basis set A (ten orbitals) is the original molecular fragment basis set (Table I) which has been used in all of the calculations discussed above. Basis set B (12 functions) adds two $p_\pi$ orbitals to basis set A, one on nitrogen and one on oxygen. The orbital radius is 2.5, and the FSGO's are located ±0.2 $a_0$ above and below the atoms.[48] These are added to increase the flexibility of the $\pi$ system and to provide more diffuse basis functions which may be necessary to obtain an adequate description of the $\pi^*$ orbital. Basis set C (16 orbitals) adds two more p orbitals and two s orbitals to basis set B. The two additional p orbitals are used to complete the 2p subshell on nitrogen, and the parameters are the same as those listed in Table I. The s orbitals are centered on the hydrogen atoms with an orbital radius of 1.4, and they serve to increase the flexibility of the basis description in the CH bonding region. Basis set D (19 orbitals) adds three more p orbitals to basis set C. Two of the functions are $p_\pi$ orbitals, one on nitrogen and one on oxygen. The orbital radius is 5.0, and the FSGO's are located ±0.15 $a_0$ above and below the atoms. The last p orbital is placed on the oxygen atom along the NO axis. The parameters are the same as those listed in Table I.

As is seen in Table IX, the $1b_1$ and the $5a_1$ MO's are still interchanged for the $\beta$ MO's using basis set B, and they are interchanged for both the $\alpha$ and $\beta$ MO's using basis sets C and D. These new data have again been fit to that of Salotto and Burnelle.[24] The resulting parameters for eq 19 are shown in Table X. From these data, it is concluded that the slope remains approximately constant, and the first-order effect of increasing the size of the basis set is simply to lower all the valence orbital energies uniformly. These observations provide further evidence that small basis sets may be devised that are *just* as useful as large basis sets for examining properties that depend on the relative spacing of the orbital energies.

A study of the effect of these different basis sets on the spin density distribution of $H_2NO$ in the planar conformation was also conducted. The geometry used here was that of Salotto and Burnelle.[24] The calculated spin density on the nitrogen atom as indicated in Table IX is 0.158, 0.341, 0.483, and 0.422 for basis sets A through D, respectively. These results indicate an obvious basis set dependence, and that care must be exercised when predicting magnitudes of spin densities using small basis sets. It is of interest to note that the values found using basis sets C and D are both in excellent agreement with the work of Hayat and Silver,[36] and the calculated hyperfine splitting constant for basis set D is in good agreement with the measured value.

Using basis set C, which was the simpler basis set that gave good agreement with the spin densities reported by Hayat and Silver,[36] the change in $P_N^{SD}$ due to the presence of an electric field is calculated to be 0.0038 and 0.0396 at $f_x = -1.0 \times 10^{-3}$ and $f_x = -1.0 \times 10^{-2}$ $E_a/ea_0$, respectively. The corresponding changes in $a_N$ are calculated by eq 18 to be 0.08 and 0.82 G, only three to four times larger than indicated with basis set A, even though the value of the spin density itself has changed enormously. This indicates that, although perhaps not appropriate for predictions of absolute magnitudes of spin densities, small basis sets may be used effectively to examine *changes* in $a_N$. In any case, the trend still indicates that fields in the range of $10^{-5}$ to $10^{-4}$ $E_a/ea_0$ will not have an observable effect on the $^{14}N$ isotropic coupling constants. Since the isotropic part represents primarily the "contact" interaction at the nucleus itself, it is not necessarily surprising that rather large electric fields are required to produce a measurable effect on $a_N$, as the electrons close to nuclei are tightly bound.

It should also be pointed out that, due to the difference in the nature of the interaction, no definitive conclusions can be drawn from the current study concerning the magnitude of the effect of an applied electric field on the *anisotropic* hyperfine coupling constants, which is also of great interest in the study of membrane dynamics. The anisotropic part of the hyperfine coupling operator represents an electron dipole-nuclear dipole interaction, and thus will be influenced more by the more easily polarized electrons further removed from the nucleus. Further studies to quantify the magnitude of this effect are contemplated.

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$$\rho^{SD} = \sum_{r,s} P_{rs}^{SD} \chi_r \chi_s$$

but rather represents a type of "spin occupation number." Other contributions, arising from off-diagonal $\mathbf{P}^{SO}$ elements which are affected by planarity or lack thereof, are hence not included in the Mulliken-type analysis utilized here.
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# A General Definition of Ring Puckering Coordinates

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**Abstract:** A unique mean plane is defined for a general monocyclic puckered ring. The geometry of the puckering relative to this plane is described by amplitude and phase coordinates which are generalizations of those introduced for cyclopentane by Kilpatrick, Pitzer, and Spitzer. Unlike earlier treatments based on torsion angles, no mathematical approximations are involved. A short treatment of the four-, five-, and six-membered ring demonstrates the usefulness of this concept. Finally, an example is given of the analysis of crystallographic structural data in terms of these coordinates.

Although the nonplanar character of closed rings in many cyclic compounds has been widely recognized for many years, there remain some difficulties in its quantitative specification. An important first step was taken by Kilpatrick, Pitzer, and Spitzer in their 1947 discussion of the molecular structure of cyclopentane.[1] Starting with the normal modes of out-of-plane motions of a planar regular pentagon,[2] they pointed out that displacement of the $j$th carbon atom perpendicular to the plane could be written

$$z_j = (2/5)^{1/2} q \cos\,(2\psi + 4\pi(j - 1)/5) \qquad (1)$$

where $q$ is a puckering amplitude and $\psi$ is a phase angle describing various kinds of puckering. By considering changes in an empirical potential energy for displacements perpendicular to the original planar form, they gave reasons to believe that the lowest energy was obtained for a nonzero value of $q$ (finite puckering) but that this minimum was largely independent of $\psi$. Motion involving a change in $\psi$ at constant $q$ was described as pseudorotation. Subsequent refinement of this work has involved models in which constraints to require constant bond lengths are imposed[3,4] and extensions to larger rings[5-7] and some heterocyclic systems are considered.[8]

Although the correctness of the model of Kilpatrick, *et al.*,[1] and the utility of the $(q, \psi)$ coordinate system is generally accepted, application to a general five-membered ring with unequal bond lengths and angles is not straightforward. Given the Cartesian coordinates for the five atoms (as from a crystal structure), determination of puckering displacements $z_j$ requires specification of the plane $z = 0$. A least-squares choice (minimization of $\Sigma z_j^2$) is one possibility, but the five displacements relative to this plane cannot generally be expressed in terms of two parameters $q$ and $\psi$ according to eq 1.

An attempt to define a generalized set of puckering coordinates which avoids these difficulties was made by Geise, Altona, Romers, and Sundaralingam.[9-11] Their quantitative description of puckering in five-membered rings involves the five torsion angles $\theta_j$ rather than displacements perpendicular to some plane. These torsion angles are directly derivable from the atomic coordinates and are all zero in the planar form. They proposed a relationship of the form[11]

$$\theta_j = \theta_m \cos\,(P + 4\pi(j - 1)/5) \qquad (2)$$

for these torsion angles where again $\theta_m$ is an amplitude and $P$ is a phase angle. Given values for the five $\theta_j$, the phase $P$ is obtained from