# Pyrrole and N-Methylpyrrole as Models for Solvent Polarity and Solute-to-Solvent Hydrogen-Bonding Effects on Nitrogen NMR Shielding

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Nitrogen NMR shieldings of pyrrole-type nitrogen atoms are shown to be quite sensitive to solvent effects and seem to provide a means of insight into solvent-induced electron charge redistribution in five-membered heteroaromatic systems. Significant deshielding effects on the nitrogen nucleus are observed upon the formation of NH-to-solvent hydrogen bonds and, independently, upon the increasing solvent polarity, and this behavior is reproduced by quantum-mechanical calculations. A clear distinction is found between pyrrole-type and pyridine-type nitrogens from the point of view of the directions of solvent effects on the respective nitrogen shieldings. N-Methylpyrrole nitrogen shieldings in solutions are shown to provide a probe for an empirical scale of solvent polarity. © 1993 Academic Press, Inc.

## INTRODUCTION

Nitrogen atoms can be bound within aromatic heterocycles in essentially two modes, those we call pyridine- and pyrrole-type, respectively (Fig. 1); the former includes both six- and five-membered aromatic ring systems, while the latter is found only in five-membered ring moieties, save for some rare instances of junction sites in fused six-membered rings (1, 2). In conventional representations of the relevant bonding systems of nitrogen atoms, in the pyrrole type of bonding, the nitrogen atom supplies two electrons to the delocalized π-bond system of the aromatic ring involved and is linked by a planar system of three σ bonds to three neighboring atoms; in the pyridine type of bonding, the nitrogen atom supplies only one electron to the π-bond system and is linked directly by two σ bonds to two neighbors, and also bears lone-pair electrons which can be thought of as a part of the σ-bond system.

Nitrogen NMR shieldings (chemical shifts) have already been shown to provide a deep insight into molecular interactions that take place in solutions of aza-aromatic solutes (1–5), but the cases studied involved essentially pyridine-type nitrogen atoms which are hydrogen-bond acceptors (Fig. 1). The aim of the present study is to obtain some knowledge about how pyrrole-type nitrogen shieldings react to inter-

actions with solvent molecules, with particular attention to solute-to-solvent hydrogen-bonding effects when a pyrrole-type nitrogen is bonded directly to a hydrogen atom, and the latter can be involved in hydrogen bonds with solvent acceptor sites. This is exactly the opposite situation to that observed in the case of pyridine-type nitrogens, which are hydrogen-bond acceptors and interact with donor sites in protic solvents.

In the present work, we use, as before (1–6), the sign convention which attributes the plus sign to an increase in the magnetic shielding of a nucleus; this corresponds directly to the sign of values and changes in the magnetic screening (shielding) constant σ. We use therefore the term "nitrogen NMR shielding" rather than "nitrogen chemical shift," since the latter is usually associated with a reverse sign convention. Apart from the opposite signs, the two terms are equivalent.

## RESULTS AND DISCUSSION

The results of high-precision $^{14}$N NMR measurements of solvent-induced variations in the nitrogen shieldings of (I) and (II) (Fig. 2) are presented in Table 1. The data are corrected for bulk susceptibility effects, and their reported precision is such that the last digit is uncertain (see Experimental). The set of solvents employed represents a large variety of solvent properties from the point of view of polarity and hydrogen-bonding effects. The range of solvent effects on the nitrogen shielding of (I), about 8 ppm, is appreciably smaller than that observed for (II), about 15 ppm (Table 1), and the patterns of the effects are quite different for the two solutes. However, the highest shieldings in both cases are those for the relevant solutions in cyclohexane, and this leads to a preliminary conclusion that hydrogen-bonding and solvent polarity effects must deshield the nitrogen nuclei concerned. This is exactly opposite to the directions observed in the case of pyridine-like aromatic heterocycles (3, 5). In the $^{14}$N spectra of (II), for virtually all solutions examined, we observed the nitrogen resonance signal as a doublet which revealed a one-bond $^{14}$N–$^{1}$H spin–spin coupling of about 67 Hz. We did not pursue the problem of extracting precise values of the nitrogen–proton couplings, since $^{15}$N NMR is

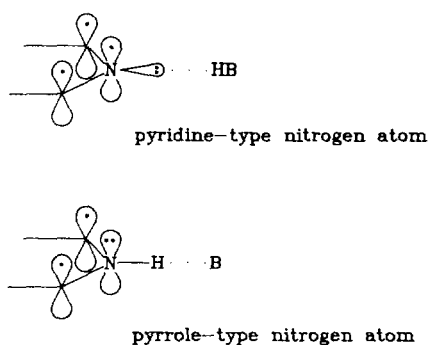‡ To whom correspondence should be addressed.

FIG. 1. A schematic representation of π- and σ-bond systems and hydrogen bonding for nitrogen atoms in aromatic heterocycles.



FIG. 2. Structures of the compounds studied.

more suitable for that purpose (*1, 2*): however, the appearance of nitrogen–proton couplings in the $^{14}N$ spectra of (II) in solutions has two important implications. First, it obviously means that the hydrogen atom of the NH moiety of (II) does not undergo intermolecular exchange at a rate which is set on the NMR time scale by the value of the coupling. The other inference is less obvious, and it is concerned with some general observations on $^{14}N$ quadrupole relaxation rates (*1, 2*); virtually all of the few known cases of the appearance of nitrogen–proton couplings in $^{14}N$ NMR spectra involve molecules and ions where the relevant nitrogen atoms bear significant and positive net charges. Thus, the $^{14}N$ spectra of the solutions of (II) seem to indicate that the lone-pair electrons of a pyrrole-type nitrogen atom are appreciably delocalized into the π-electron system of the aromatic ring.

Returning to the solvent-induced variations in the nitrogen NMR shieldings of (I) and (II), a question arises about a more detailed picture of the origin of such effects, and in order to unravel this we have employed the empirical scheme (*7-10*) of solvent and solute properties which can be expressed by the master equation

$$\sigma(i, j) = \sigma_0(i) + a(i)\alpha(j) + b(i)\beta(j)$$
$$+ s(i)[\pi^*(j) + d(i)\delta(j)], \quad [1]$$

where $i$ and $j$ stand for solute and solvent, respectively, $\sigma$ is the relevant nitrogen shielding, $\alpha$ represents hydrogen-bond donor strength of the solvent, $\beta$ represents its hydrogen-bond acceptor strength, $\pi^*$ is its polarity polarizability, and $\delta$ is a correction for polychlorinated solvents ($\delta = 0.5$) and aromatic solvents ($\delta = 1$). The solute terms, $a$, $b$, $s$, and $d$, represent the corresponding responses of the nitrogen shielding to a given property of the solvent employed, and $\sigma_0$ is the nitrogen shielding in the reference state which is approximated by a solution in cyclohexane. The solvent parameter set employed in the present work is given in Table 2, together with the least-squares-fitted estimates of the solute nitrogen shielding responses. Linear correlation coefficients
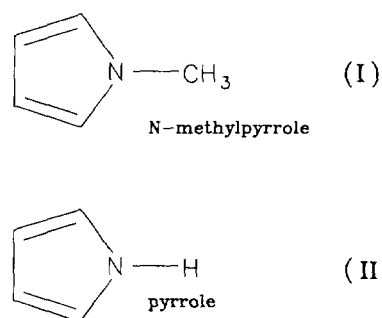
for the experimental values with respect to those retrieved by means of Eq. [1] are given in Table 1. Water as a solvent was excluded from the calculations for pyrrole, since the relevant parameter $\beta$ which characterizes the hydrogen-bonding properties of water as a bulk medium is too uncertain.

Terms $a$ (Table 2), which represent the responses of the nitrogen shieldings of (I) and (II) to solvent hydrogen-bonding donor strength, are hardly significant, and this shows

TABLE 1
Solvent Effects on Nitrogen NMR Shieldings
of Pyrrole and *N*-Methylpyrrole

| Solvent | Nitrogen NMR shielding (ppm) referred to neat nitromethane | | | |
| | *N*-Methylpyrrole | | Pyrrole[a] | |
| | Measured | Calculated | Measured | Calculated |
| --- | --- | --- | --- | --- |
| Cyclohexane | +235.19 | +235.07 | +238.77 | +238.30 |
| CCl₄ | +234.14 | +234.07 | +237.81 | +237.61 |
| Et₂O | +233.62[b] | +234.01 | +231.16[b] | +232.63 |
| Benzene | +232.88 | +233.17 | +235.87 | +236.04 |
| EtOH | +232.14 | +231.93 | +228.81 | +228.36 |
| Dioxane | +231.69 | +231.95 | +232.14 | +231.47 |
| MeOH | +231.37 | +231.17 | +229.85 | +229.14 |
| Acetone | +231.36 | +230.92 | +230.29 | +229.40 |
| CHCl₃ | +230.80 | +230.60 | +234.73 | +234.30 |
| CH₂Cl₂ | +230.74 | +230.43 | +234.34 | +234.01 |
| DMSO | +229.33 | +229.55 | +224.17 | +225.17 |
| CF₃CH₂OH | +228.54 | +228.82 | +232.28 | +233.18 |
| H₂O | +226.89 | +227.01 | +226.50 | —[c] |
| Correlation coefficient | 0.993 | | 0.981 | |

*Note.* All data are corrected for bulk susceptibility effects and relate to 0.2 *M* solutions at +35.0 ± 0.2°C.

[a] In almost all cases, the $^{14}N$ signal is a sharp doublet, spaced at about 67 Hz, as a result of one-bond $^{1}H$-$^{14}N$ spin–spin coupling.

[b] Measured at +30.0 ± 0.2°C.

[c] The parameterization of bulk hydrogen-bonding properties of water as a solvent is too uncertain, and we excluded this solvent from calculations for pyrrole.

### TABLE 2
Solvent Parameters Used and Least-Squares-Fitted Solute Parameters for a Set of Master Equations (*1*)

| Solvent | $\alpha$ | $\beta$ | $\pi^*$ | $\delta$ | Dielectric constant[a] |
|---|---|---|---|---|---|
| Cyclohexane | 0 | 0 | 0 | 0 | 1.87 |
| Et$_2$O | 0 | 0.47 | 0.27 | 0 | 3.89 |
| CCl$_4$ | 0 | 0 | 0.29 | 0.5 | 2.21 |
| Benzene | 0 | 0.10 | 0.59 | 1 | 2.25 |
| Dioxane | 0 | 0.37 | 0.55 | 0 | 2.19 |
| Acetone | 0.07 | 0.48 | 0.72 | 0 | 19.75 |
| DMSO | 0 | 0.76 | 1.00 | 0 | 45.80 |
| CH$_2$Cl$_2$ | 0.22 | 0 | 0.80 | 0.5 | 8.54 |
| CHCl$_3$ | 0.34 | 0 | 0.76 | 0.5 | 4.55 |
| EtOH | 0.86 | 0.77 | 0.54 | 0 | 24.20 |
| MeOH | 0.98 | 0.62 | 0.60 | 0 | 30.71 |
| H$_2$O | 1.13 | 0.18 | 1.09 | 0 | 76.70 |
| CF$_3$CH$_2$OH | 1.51 | 0 | 0.73[b] | 0 | |

| Solute | $a$ (ppm/unit scale) | $b$ (ppm/unit scale) | $s$ (ppm/unit scale) | $d$ (dimensionless) | $\sigma_0$ (ppm) |
|---|---|---|---|---|---|
| *N*-Me-pyrrole | −0.87 ±0.22 | −1.63 ±0.40 | −6.76 ±0.37 | −0.28 ±0.06 | +235.06 ±0.25 |
| Pyrrole | +0.02 ±0.66 | −8.00 ±1.26 | −7.06 ±1.25 | −0.38 ±0.17 | +238.30 ±0.71 |

[a] The constants were recalculated for a temperature of 35°C from the data available in Ref. (*13*).

[b] This value is based on our recent considerations concerning the $\pi^*$ scale of solvent polarity/polarizability [Ref. (*6*)].

that the pyrrole nitrogen lone-pair electrons are so involved in the delocalized $\pi$-electron system that they fail to accept any hydrogen bonds from protic solvents. This is in sharp contrast to the behavior of pyridine-type nitrogens (*3, 5*), where the lone-pair electrons act usually as strong acceptor centers for hydrogen bonding, with concomitant large upfield shifts of the nitrogen resonance signals (large and positive *a* terms).

The responses of the nitrogen shieldings of both (I) and (II) to solvent polarity effects are significant (the *s* terms of about −7 ppm per unit scale of $\pi^*$; Table 2) and similar to each other. Their signs indicate that the relevant nitrogen nuclei undergo a considerable deshielding with increasing polarity of the solvent employed. Effects in this direction are typically observed for nitrogen atoms whose bonding structures are conventionally described in terms of the $sp^2$ hybridization of the bonding orbitals and whose lone-pair electrons become significantly involved in a delocalized $\pi$-electron system (*1, 2*). Thus, analysis of the data for (I) and (II) suggests that the increasing polarity of the surrounding medium enhances the delocalization of the lone-pair electrons of a pyrrole-type nitrogen, leaving a partial positive charge on the latter. The direction of the response of pyrrole-type nitrogen shieldings to solvent polarity is thus just opposite to that observed for pyridine-type nitrogens (*3, 5*), where the nitrogen NMR data show that the solvent-induced polarization takes place in the direction of accumulating partial negative charges at the nitrogens involved. This seems

to be an important distinction in the nitrogen NMR characteristics of the two types of nitrogen atoms in aromatic rings.

In order to substantiate the foregoing arguments about the direction of electron charge shifting in pyrrole systems under the influence of solvent polarity, we carried out solvaton-type molecular orbital calculations of the nitrogen shielding variation, employing the INDO/S-SOS scheme described in Refs. (*11, 12*), which includes effects on the nitrogen shieldings of the dielectric constant of the medium; the values of the constants are given in Table 2, and the calculated results are reported in Table 3. They clearly show that the predicted changes in the nitrogen shielding of both

### TABLE 3
Solvaton Model Calculations for Medium Polarity Effects on Nitrogen NMR Shielding in *N*-Methylpyrrole and Pyrrole

| Dielectric constant $\epsilon$ | Calculated variation in the shielding (ppm) | |
|---|---|---|
| | *N*-Me-pyrrole | Pyrrole |
| 2.0 | 0 | 0 (arbitrary) |
| 4.0 | −1.13 | −1.43 |
| 10.0 | −1.70 | −2.27 |
| 20.0 | −1.97 | −2.63 |
| 40.0 | −2.08 | −2.68 |

(I) and (II) are in the deshielding direction with increasing dielectric constant, and that the magnitude of the effect should be similar for the two solutes. This is in perfect agreement with our experimental findings described above. Moreover, the same solvaton model MO calculations, when applied to pyridine-type nitrogen shieldings, predict an opposite direction of the changes induced (3, 5), and this is also in accord with the experimental data as well as with the reasoning on solvent-induced electron charge redistributions which has been given in the present section.

Thus far, we have considered some aspects of solvent-induced nitrogen NMR shielding variations which show similarities for (I) and (II); now we turn to some essential differences. An inspection of the data in Table 1 indicates that the range of solvent effects on the nitrogen shielding for pyrrole (II), from about +239 ppm in cyclohexane as a solvent to about +224 ppm in DMSO, is nearly twice that observed for its N-methyl derivative (I), from about +235 ppm in cyclohexane to about +227 ppm in water, and that the patterns of the changes are different. Since solvent polarity effects are nearly the same for the two solutes and solvent-to-solute hydrogen bonding effects are negligible, as was shown in the foregoing discussion, the only reason for the differences seems to lie in the hydrogen-bonding properties of the NH moiety of (II) with respect to solvent acceptor sites; needless to say, the N-methyl moiety of (I) should be devoid of such properties, save for some possible weak interactions of the methyl hydrogens with the solvent. This difference is revealed clearly by the application of Eq. [1] (Table 2) to the experimental data; the relevant term $b$ is rather nonsignificant for (I), but it attains quite an appreciable value of $-8$ ppm, per unit scale of $\beta$, in the case of (II). Thus, solute-to-solvent hydrogen bonding via the NH moiety of pyrrole results in a significant deshielding of the nitrogen nucleus concerned. The sign of the effect can be explained in terms of electron charge redistribution, using arguments which are similar to those invoked in the consideration of solvent polarity effects on the nitrogen NMR shieldings in pyrrole systems. If a negatively charged moiety, that in a solvent molecule, approaches the NH hydrogen of pyrrole and becomes involved in a hydrogen bond, the electron charge at the nitrogen atom should experience repulsion forces, and this should lead to an increased delocalization of the lone-pair electrons, from the nitrogen atom into the $\pi$-electron system of the aromatic ring. Thus, the nitrogen nucleus should experience a magnetic deshielding, as in the case of solvent polarity effects. This is again in sharp contrast with the effects of solvent-to-solute hydrogen-bonding effects for pyridine-type nitrogen atoms (3, 5), where the lone-pair electrons are directly involved in the hydrogen bonds, with a remarkable increase in the nitrogen NMR shielding which seems to correlate with the hydrogen-bond strength.

In order to corroborate the foregoing arguments about the effects on the pyrrole nitrogen shielding of NH-to-solute hydrogen bonding, we carried out ab initio GIAO-4-31G mo-

lecular orbital calculations for an isolated molecule of pyrrole which is approached by a water molecule with a subsequent formation of the NH $\cdots$ OH$_2$ hydrogen bond. The calculations predicted a deshielding effect, by about 30 ppm, on the nitrogen nucleus upon the formation of the hydrogen bond. The magnitude of the calculated effect seems to be exaggerated, in conflict with the analysis of the experimental data, but its sign is correct. Actually, the latter is important, since the difference in magnitudes is likely to come from the fact that the calculations employed a grossly simplified model where an isolated molecule of (II) is approached by a single molecule of water, while in solution the latter should certainly be involved in strong interactions with other molecules of water. Therefore, both theory and experiment show that appreciable deshielding effects are characteristic of the nitrogen resonance of pyrrole-type NH moieties under conditions where the hydrogen atom becomes involved in a hydrogen bond to an acceptor site in a solvent molecule. The latter effect operates in the same direction as those due to solvent polarity, and this explains the substantial difference between (I) and (II) as far as the relevant ranges of solvent effects on the nitrogen NMR shielding are concerned.

Since the effects of solvents on the nitrogen shielding of (I) are governed essentially by solvent polarity, the solute can potentially be employed as a probe for the latter, on the empirical scale $\pi^*$. We have already demonstrated (4) that the nitrogen NMR shielding of tert-butyl isocyanide can be used for this purpose, but there is certainly an advantage in having additional molecular probes which allow one to perform cross-checking of the results obtained. The nitrogen shieldings of (I) in a variety of solvents show a good linear correlation with those of tert-butyl isocyanide (Fig. 3) in the same set of solvents; thus, the two solutes are likely to provide a more reliable method, that based on nitrogen NMR, for determining relative polarities of solvents in terms of the $\pi^*$ scale.

Pyrrole-type nitrogen atoms can also be found in indolizine systems (Fig. 4), and solvent-induced effects on their nitrogen shieldings have already been considered in detail (6). They originate mostly from solvent polarity variations, and their signs are in accord with those found in the present work for (I) and (II); however, their magnitudes are much smaller than those for pyrrole systems. This seems to be intuitively correct, since the electron charge distribution in (III), where the nitrogen atom is bound directly to three "$sp^2$-hybridized" carbons, should be more symmetrical than those in (I) and (II).

## EXPERIMENTAL

Pure samples of the compounds studied were prepared from commercially available pyrrole, and from its N-methyl derivative, which was obtained according to a published procedure (15). Special attention was paid to the use of very pure and dry solvents as reported previously (4). All solutions

were prepared and handled under dry argon atmosphere in glove bags.

The nitrogen shieldings of 0.2 $M$ pyrrole and $N$-methyl-pyrrole in a large variety of solvents were measured by $^{14}$N NMR at 36.14 MHz (Bruker AM-500 spectrometer) and 35 ± 0.2°C; the temperature was maintained by a VT unit. Special precautions were taken to reduce the possible random and systematical errors to below 0.1 ppm upon comparing the nitrogen shieldings of the solute in different solvents. The shieldings were referenced externally to neat liquid nitromethane, using 10 mm/4 mm o.d. coaxial tubes. The inner tube contained 0.3 $M$ nitromethane in acetone-$d_6$, whose nitrogen shielding is +0.77 ppm from that of neat liquid nitromethane (1-3), under conditions where bulk susceptibility difference effects vanish (in concentric spherical sample/reference containers); the latter value was employed as a conversion constant. Thus, the content of the inner tube served as a precise reference to the neat nitromethane standard and also provided a source of deuterium lock for the system. The exact resonance frequency of the $^{14}$N signal of neat nitromethane was 36.141524 MHz, and recalculations which were carried out by methods outlined in Ref. (1) yielded a value of 36.136826 MHz for a bare nitrogen nucleus. The latter value was used in conjunction with the relevant resonance frequency differences in order to calculate the nitrogen NMR shieldings relative to that of the primary standard, neat nitromethane. The resonance frequencies of
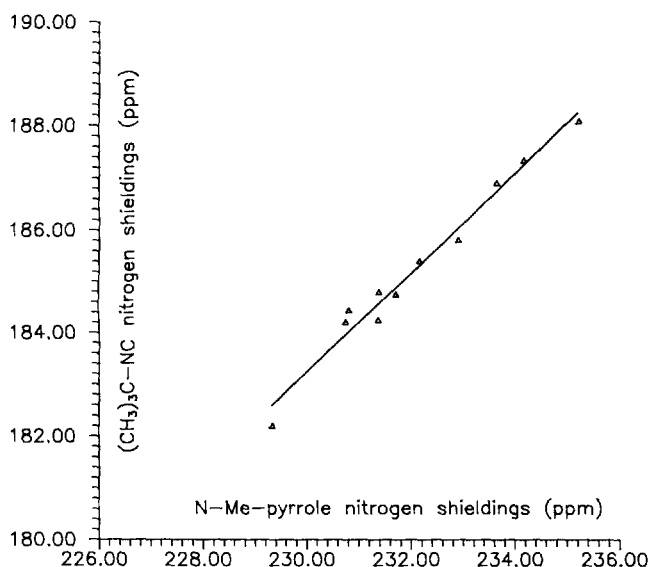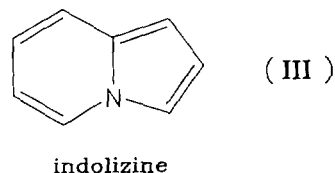


(III)

indolizine

FIG. 4. An example of a pyrrole-type nitrogen atom at a junction of aromatic rings. In this case, the only significant effect of solvents on the nitrogen shielding is represented (6) by $s = -1.78$ ppm according to Eq. [1].

the samples and the external standard were found by Lorentzian lineshape fitting of the relevant $^{14}$N NMR signals. The nitrogen shieldings obtained were then corrected for bulk susceptibility effects, according to procedures described in Refs. (1, 3); since dilute solutions were employed, their susceptibilities were assumed to be equal to those of the respective solvents at 35°C.

The INDO/S SOS calculations within the solvaton model framework (11, 12) as well as the GIAO-4-31G calculations were carried out on the University of Surrey Primenet System using standard geometries (14).

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FIG. 3. A plot of nitrogen NMR shieldings of (I) with respect to those of tert-butyl isocyanide in the same set of solvents. The data for the isocyanide are taken from Ref. (4), where the relevant solvent-induced variations in the nitrogen shielding were shown to be a measure of relative solvent polarities, those expressed on the scale concerned with Eq. [1].