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NITROGEN NMR SHIELDINGS OF SOME NITRO DERIVATIVES OF 2-AMINO-4-METHYLPYRIDINE SYSTEMS

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High precision ^{14}N NMR shieldings (chemical shifts), bulk susceptibility corrected, are reported for dilute solutions in pure, dry acetone for a group of nitro derivatives of (N-substituted) 2-amino-4-methylpyridines, with nitro substituents in either positions 5 or 3 or both, where at least some of these should reveal serious steric hindrance between the substituents involved. The nitrogen shieldings as well as the corresponding PM3 optimized geometries show quite clearly that the 5-nitro derivatives are planar or nearly planar, without any significant hindrance to the π-conjugation throughout the molecular system concerned, while the 3-nitro derivatives experience deviations from coplanarity of the pyridine ring and the nitro and amino substituents, with concomitant impairment of π-conjugation between these moieties. The nitrogen shieldings of the pyridine nitrogen atoms in N-nitramino-2-alkyl-4-methyl 3 (or 5)-nitropyridines indicate that the N-nitramino group acts as a modest donor of π-electrons, much weaker with respect to the donor strength of amino, alkylamino, or phenylamino substituents.

Keywords: aminonitromethylpyridines, nitramines, nitrogen chemical shifts, nitrogen shieldings, ^{14}N NMR, PM3 calculations, substituent effects, steric effects.

In recent years attention has been attracted by N-substituted derivatives of 2-amino-5-nitropyridine, owing to their promising nonlinear optical properties in the crystalline state [1-3]. These molecules possess high molecular hyperpolarizability and a highly delocalized π-electron system bearing an electron donor, the amino group, as well as an electron acceptor, the nitro group. Substituents in such positions provide a pathway to intramolecular charge transfer. The molecules studied in the present work, derivatives of 2-amino-4-methyl-3-nitropyridine and 2-amino-4-methyl-5-nitropyridine, are interesting from the point of view of new substitution at the amino moiety, where the substituents include alkyl and aryl groups as well as the N-nitro group. Although 2-amino-substituted 3- and 5-nitropyridines have already been investigated by means of UV, IR, ^1H NMR, and interaction dipole moments [4-10], there are only fragmentary data in the literature about the nitrogen NMR of alkylamino- and alkylnitraminonitropyridines [11, 12]. Additionally, compounds of this type have been employed as new nucleophilic substitution or transacylation catalysts [13-16]; as intermediate compounds for herbicides [17, 18], insecticides [19] and antibacterials [20]. Elucidation of the structural and electronic properties of the compounds studied is an important step toward understanding the mechanism of their biological activity. For this purpose, ^{14}N NMR shieldings have been measured here for a set of compounds

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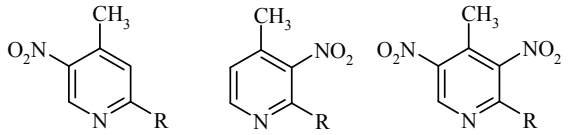


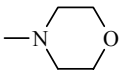
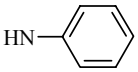
R	Cpd.	Cpd.	Cpd.
NH_2	**1**	**8**	
$NHCH_3$	**2**	**9**	**14**
$NHCH_2CH_3$	**3**		**15**
	**4**	**10**	
	**5**	**11**	
$N(CH_3)NO_2$	**6**	**12**	
$N(CH_2CH_3)NO_2$	**7**	**13**	

Fig. 1.

which included N-substituted derivatives of 2-amino-4-methylpyridine with nitro substituents at positions 3 or 5, or both. The aim of this study was to employ ^{14}N NMR shieldings as a probe for electronic interactions between the substituents and the aromatic ring with due attention paid to steric effects. Steric crowding can disturb the coplanarity of the nitro group or the amino substituent with the aromatic ring (especially in 2-amino-3-nitro- and 2-amino-4-methyl-3,5-dinitropyridines), thus rendering the π-electron conjugation less effective.

RESULTS AND DISCUSSION

The structures of compounds **1**-**15** are presented in Fig. 1, and their ^{14}N NMR spectral data are collected in Table 1. The ^{14}N NMR of the compounds studied will be discussed with a view to probing the ground state electronic distribution in these molecular frameworks. Inspecting the ^{14}N NMR shielding ranges (Table 1) shows specific regions for each type of nitrogen in these molecules: aromatic C-nitro groups, from +4 to +12 ppm, nitramino N-nitro groups, from +29 to +34 ppm, pyridine nitrogen atoms, from +76 to +122 ppm, amino groups, from + 271 to +307 ppm, and nitramine amino moieties, from +178 to +199 ppm. Attention is drawn to the sign convention employed in the present work, as was done before [11, 21]; a plus sign corresponds to an increase in nuclear magnetic shielding. Thus we use the term nitrogen shielding rather than chemical shift. The two terms are equivalent in magnitude but are of opposite sign.

The pyridine ring nitrogen NMR shielding reflects the nature of the substituents involved. In 2-amino-substituted derivatives **1**-**5**, **8**-**11**, and **14**, **15** the shielding of the aromatic nitrogen is within +114 to +122 ppm, but when the substituent is changed to an alkyl-N-nitramino group (compounds **6**, **7**, **12**, and **13**), the aromatic ring nitrogen shieldings decrease to about +75 through +86 ppm. This large change, by about 35 ppm, is accompanied by changes in the nitrogen shielding of the 2-amino and the nitro groups. Upon passing from alkylamino to alkylnitramino-substituted pyridines, the shielding of the amino group decreases by about 110 ppm, but the shielding of the 3- and 5-nitro groups increases, on the average, by 3 ppm. For nitrobenzene in acetone, the NO_2 shielding amounts to +9.23 ppm (bulk susceptibility corrected) [22], but in the compounds studied the shielding of the nitro group varies from +3.93 to +11.98 ppm, and depends on the substituents involved.

TABLE 1. Nitrogen NMR Shielding of the Compounds Studied, Referenced to Neat Liquid Nitromethane, Bulk Susceptibility Corrected, 32°C

Compound (0.1 M solution in acetone)	Nitrogen NMR shielding (ppm)		
	Pyridine nitrogen	Nitro nitrogen	Amino substituent nitrogen (s)
1	+117.49	+8.60	+298.57
2	+122.22	+8.39	+299.62
3	+121.83	+8.51	+282.28
4	+117.38	+9.02	+288.28
5	+116.05	+9.26	+270.65
6	+86.37	+11.34	+190.61 (amino) +32.60 (N-nitro)
7	+85.97	+11.18	+177.93 (amino) +34.04 (N-nitro)
8	+106.16	+6.79	+304.16
9	+117.76	+7.22	+306.49
10	+97.37	+3.93	+306.72
11	+108.85	+8.06	+280.72
12	+76.27	+11.98	+199.29 (amino) +29.26 (N-nitro)
13	+75.91	+12.05	+188.09 (amino) +30.64 (N-nitro)
14	+114.16	+10.12 (3-NO_2) +11.59 (5-NO_2)	+298.03
15	+115.68	+10.13 (3-NO_2) +11.65 (5-NO_2)	+281.61

For a given substituent in position 2, there is a striking difference in the nitrogen shieldings between the corresponding 5-nitro and 3-nitro derivatives of N-substituted 2-amino-4-methylpyridines, and this concerns all of the nitrogen atoms. This is clearly seen for the atoms involving the following pairs of compounds: **1→8**, **2→9**, and **5→11**. In these sequences, the pyridine nitrogen nucleus invariably experiences a deshielding effect of about -8 ppm, that of the nitro groups becomes slightly deshielded by about -1.5 ppm, while the amino nitrogen shielding is significantly augmented, by about +8 ppm (Table 2). Analogous, albeit much stronger, effects are observed for the pair **4→10**, where the bulky N-morpholino substituent is likely to force the 3-nitro group of **10** out of the plane of the pyridine ring. The fact that in the foregoing pairs of derivatives of pyridine the nitrogen shielding of the 5-nitro group is higher that of the 3-nitro group enables one to assign the more shielded nitro nitrogen nucleus to the 5-nitro group in the corresponding 3,5-dinitro derivatives **14** and **15** (Table 1).

These effects show clearly that the steric interactions in the 3-nitro isomers are responsible for the systematic changes in the nitrogen NMR shieldings upon passing from a given 5-nitro isomer to the corresponding 3-nitro derivative. In order to verify this we carried out semiempirical geometry optimizations using the PM3 method which is likely to provide geometries similar to those obtained by low-level *ab initio* methods. In all of the cases considered (see footnotes to Table 2), 3-nitro isomers show medium to high distortions from coplanarity of the ring system and the substitutuents involved, by about 10° (compounds **8**, **9**, **11**) to 80° (compound **10**), and this concerns the 3-nitro groups as well as the amino substituents. The largest distortion predicted by the calculations for compound **10** is in a perfect agreement with the largest perturbations of the nitrogen shieldings observed. The largest distortion, about 80°, is predicted by the calculations for the N-morpholino substituent and the 3-nitro group in **10**. On the other hand, in analogous computations, the 5-nitro isomers reveal planar or nearly planar geometries.

TABLE 2. Differences in Nitrogen NMR Shieldings Between 3-Nitro and 5-Nitro derivatives of 2-Amino-4-methylpyridines

Pairs of isomers concerned	Nitrogen NMR shielding increment (ppm)		
	Pyridine nitrogen	Nitro nitrogen	Amino nitrogen
1→8	-11.3	-1.8*	+5.6
2→9	-4.5	-1.2*	+6.9
5→11	-7.2	-1.2*	+10.8
4→10	-20.0	-5.1*[2]	+19.4

* In these cases the PM3 optimized geometries show twisting of the 3-NO_2 plane, by about 10°, with respect to the pyridine ring, while the corresponding 5-NO_2 group is coplanar with the latter. The same applies to the 2-amino moieties involved.

*[2] The twist angle amounts to about 80° for the 3-NO_2 group and the amino moiety of the N-morpholyl substituent.

The directions of changes induced in the nitrogen shieldings upon passing from the 5-nitro to the 3-nitro isomers (Table 2) suggest, as can be inferred from some general rules that govern nitrogen shielding [21], that the π-electron conjugation between the pyridine ring and the substituents involved is significantly impaired, particularly in compound **10**, and all of this is in accord with the foregoing computations.

The computations for the 3-nitro isomers **8**, **9**, and **11**, where the 2-amino-substituents contain NH moieties, show that the distance between the hydrogen atom and the nearest oxygen atom of the 3-nitro group, in spite of the non-planar structure, amounts to about 1.8 Å, which is still within the range of weak hydrogen bonds. The existence of such intramolecular hydrogen bonding has already been suggested for some of the present compounds as well as for some analogous derivatives of pyridine, on the basis of various spectroscopic results and dipole moment measurements [4-10].

As far as the nitrogen shieldings of the nitro groups are concerned, especially interesting is that of compound **10**, where the nitro group is flanked by a methyl group and a bulky substituent, the N-morpholyl moiety. This arrangement of substituents should force the NO_2 group out of the plane of the pyridine ring. Actually, the NO_2 nitrogen shielding is much weaker (about +4 ppm) in comparison with those of the NO_2 groups in other compounds (about +7 to +12 ppm). The direction of the shift indicates that the conjugation is impaired between the π-electron systems of the pyridine ring and the NO_2 group in **10**, in accord with the foregoing.

If we compare the nitrogen shielding of pyridine in acetone, +62.5 ppm [11], with those obtained in the present work as well as those reported in the literature on 2-aminopyridines [21], it is obvious that the 2-amino substituent significantly enhances the pyridine nitrogen shielding, by roughly +50 ppm. The amino substituent at this position acts as a strong donor of π-electrons to the delocalized π-electron system concerned, provided that the amino substituent is coplanar or nearly coplanar with the aromatic ring system. On the other hand the amino nitrogen shielding decreases with increasing conjugation of its lone pair electrons with the π-electrons of the ring [21]. This is exactly what we observe here when steric effects force the amino lone pair into a position where the conjugation is less effective (Table 2).

Now we turn to the role of N-nitramino substituents at position 2, those in compounds **6**, **7**, **12**, and **13**. Generally, the pertinent nitrogen shieldings of the pyridine nitrogen are higher than that of unsubstituted pyridine but much lower than those of 2-amino-substituted derivatives. This suggests that the nitramino substituent acts as a donor of π-electrons, but its donor strength is much lower than those of amino substituents.

For the 2-nitramino derivatives, there is also a striking difference between the shieldings of the pyridine nitrogen if we compare the corresponding 5-nitro and 3-nitro isomers. The latter show pyridine nitrogen shielding of about +75 ppm, while those of about +85 ppm are observed for the former. Evidently, steric effects induce severe distortions from coplanarity in the case of the 3-nitro-substituted isomers, in accord with the foregoing observations and computations relating to the 2-amino derivatives. The properties of the 2-nitramino substituent as a modest donor of π-electrons have already been observed in the nitrogen shieldings of 6-methyl-2-nitramino-5-nitropyridines [11]. We also performed PM3 optimizations of the geometries of the nitramino derivatives **6**, **7**, **12**, and **13**. The results were similar to those for the 2-amino derivatives as far as coplanarity distortions were concerned.

The nitramino moiety as such is generally planar, particularly in polar solvents and when its π-electron system is conjugated with some other π-electrons. However, it can also attain a slightly pyramidal arrangement of the bonds of the nitrogen atom [23]. The PM3 computations in the present work revealed slightly pyramidal nitramino moieties in cases of serious steric hindrance (compounds **12** and **13**) and twisting of the whole of the moiety, by about 80°, from the optimal arrangement for π-electron conjugation.

A word of comment is necessary here about some significant differences in the amino nitrogen shieldings upon passing from an $N(R)CH_3$ moiety to the corresponding $N(R)CH_2CH_3$, i. e., in the following pairs of compounds: **2→3**, **6→7**, **12→13,** and **14→15**. The result is invariably a deshielding effect on the amino nitrogen, by about -15 ppm. This is a manifestation of the so-called β-effects of alkyl groups. It has already been demonstrated [21] that nitrogen magnetic shielding decreases significantly in the following sequence of alkyl substitution at a nitrogen atom for a given X residue:

$$CH_3N(X)\rightarrow RCH_2N(X)\rightarrow R_2CHN(X)\rightarrow R_3CN(X),$$

where R is an alkyl group and X represents any atom or group of atoms. The name of the effects comes from the fact that in each of the foregoing steps a saturated carbon atom is introduced to the β-position with respect to the nitrogen atom involved. Each step results in a deshielding effect on the nitrogen, and the nature of this seems to stem from the increasing migration of the electron charge, in the direction of the nitrogen atom, across the C–N single bond [24]. In the present case, the differences between the methyl and ethyl derivatives represent a single β-effect, that involving the $CH_3N(X)\rightarrow RCH_2N(X)$ step.

Nitrogen NMR shieldings (chemical shifts) seem to provide an effective probe for monitoring electron redistribution within heavily substituted pyridine systems, with due attention paid to steric hindrance induced obstructions to coplanarity and the concomitant impairment of π-electron delocalization troughout such molecular systems. The shieldings of the pyridine nitrogen atoms provide a measure of π-electron donor strength of substituents, indicating that N-nitramino groups act as weak donors while amino groups are strong donors of π-electrons.

EXPERIMENTAL

Compounds **1**-**15** were prepared according to published procedures [25, 26]. The nitrogen magnetic shieldings (chemical shifts) of the systems studied were measured using high-precision ^{14}N NMR spectra; these were taken on a Bruker Avance DRX-500 spectrometer (11.7 T) at 35.0±0.2°C, as maintained by a VT unit, at a frequency of 36.14 MHz (90° pulse, 40 μs; acquisition 0.111 s; 4.521 Hz/pt). Efforts were made in order to reduce random and systematic errors in the shieldings to below 0.1 ppm. External liquid nitromethane was employed as reference by means of 10 mm/4mm o.d. coaxial tubes, where the inner tube contained 0.3M nitromethane in acetone-d_6 as a direct reference and a source of deuterium lock; the nitrogen shielding of this solution is +0.77 ppm from that of neat liquid nitromethane [21]. This value is obtained from measurements using concentric spherical sample/reference containers in order to eliminate magnetic bulk susceptibility effects.

The value of +0.77 ppm is used as a conversion constant, and since the measurements were taken for dilute solutions in pure acetone, the values of the shieldings thus obtained, with respect to that in neat liguid nitromethane, are bulk-susceptibility corrected. The exact resonance frequency of the ^{14}N signal of neat nitromethane was 36.141524 MHz, from which a value of 36.136826 MHz was obtained for the bare nitrogen nucleus [21]. The latter value was used in conjunction with the relevant resonance frequency differences to calculate the nitrogen shieldings relative to that of neat nitromethane. Lorentzian lineshape fitting of the ^{14}N resonance signals was employed to produce values for the precise resonance frequencies of both the samples and reference used. A very pure and dry acetone solvent was used as reported previously [22], and the solutions were prepared and handled under a dry argon atmosphere. The semiempirical quantum-mechanical optimizations were carried out using the PM3 method implemented in the ^{TM}HyperChem-5 software package (Hypercube, Inc).

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