Regiospecific Substituent Effects in 6-Substituted Purines As Measured by Proton Magnetic Resonance[1]

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The ^1H NMR spectra showed the H-2 signal at lower field than that of H-8 for purines **1–13**, but a crossover of the two proton peaks was observed for the 6-phenoxypurines **14–16**. Correlations of δ(H-2) and δ(H-8) with substituent constants σ_m, σ_p, σ_p^+ (calcd), F, and R were determined for **1–14**, and with Brown's σ_p^+ and Taft's σ_R^0 and σ_I for fewer compounds. For correlation with both δ(H-2) and δ(H-8), the σ_p set is the best, yielding correlation coefficients of 0.931 and 0.933, respectively. These δ(H)–σ correlations are impractical for predicting proton chemical shifts of 6-substituted purines. However, they are useful in sorting out the regiospecific effects and proportions of the field and resonance components of the 6-substituent, i.e., 65% resonance and 35% field for H-2, 44% resonance and 56% field for H-8, as derived from the polynomial equations 2 and 3, respectively. These observations are rationalized by considering contributions of the mesomeric structures a–e. Furthermore, because of the uniquely large resonance and field effects of the phenoxy group, the apparent crossover of H-2 and H-8 in **14–16** can be accounted for in the same manner using structures f and g.

Coburn et al.[2] reported the first linear correlation of the chemical shifts of the 8- and 2-hydrogen of eight 6-substituted purines plus purine itself with Brown's σ_p^+ and Taft's σ_R substituent constant, respectively. They also reported[3] similar relations for the ^{13}C chemical shifts of carbons 8 and 5 but not for the carbons at other positions for a variety of 6- and 2,6-substituted purines. In the course of our studies[4] of the electronic aspects and reactivities of purines and pyrimidines, we have examined the relationship between the proton chemical shifts (δ(H)) of 16 6-substituted purines and various sets of substituent constants (σ). We have found: (1) the δ(H)–σ correlations are impractical for predicting proton chemical shifts of 6-substituted purines; (2) the correlation coefficients (r) obtained are useful in sorting out the regiospecific effects and proportions of the field and resonance components of the 6-substituent; and (3) these effects are consistent with certain mesomeric contributions to the purine structure.

Results and Discussion

The chemical shifts of H-2 and H-8 of 16 purine compounds at 0.1–0.2 M in dimethyl sulfoxide are shown in Table I. The ^1H NMR peak assignments were made by virtue of partially 8-deuterated samples. The 6-phenoxypurines **14, 15,** and **16,** and trimethylpurin-6-yl ammonium chloride **13** were prepared by nucleophilic substitution of 50% 8-deuterated 6-chloropurine (**8**), whereas other 6-substituted purines were partially deuterated selectively at the 8-position upon heating in D_2O.[5] The relative order of H-8 at high field and H-2 at low field was obtained for purines **1–13,** but a crossover of the two proton peaks was shown by the phenoxypurines **14–16.**

Correlation of the proton chemical shifts with the substituent constants was accomplished by means of the regression equation

$$\delta(H) = a + b\sigma \quad (1)$$

The ^1H NMR chemical shift δ(H) reflects the electron density at that proton, whereas the substituent constant measures the ability of the 6-substituent to attract or repel electrons by virtue of its resonance and field effect. Since H-2 is meta to the 6-substituent and H-8 occupies the para-equivalent site, the five σ sets which are particularly meaningful in this correlation study are σ_m, σ_p, σ_p^+, F, and R. The σ_m and σ_p are the most venerable of the substituent constants and experimentally the two most complete and accurate sets of data available. The σ_p^+ values for all the substituents in this study are taken from the calculated σ_p^+ set derived by Swain and Lupton[6] based on 23 experimental data values. The first three σ sets have been analyzed by Swain et al.[6a] to contain % resonance of 22 ± 0%, 53 ± 0%, and 70 ± 0%, respectively. The F and R field and resonance constants proposed by the same group to gauge only the individual effects have 0 ± 0% and 100 ± 0% resonance. The δ(H-2) and δ(H-8) data of compounds **1–14** were fit into the above equation using a standard linear least-square routine with σ values of the five sets obtained from the Swain paper.[6] The corresponding σ constants for the p-methoxyphenoxy substituent in **15** and the p-nitrophenoxy in **16** are unknown; hence they are not included in the correlation. In addition, correlations for a smaller set of compounds were obtained with other popular substituent constants, e.g., the experimental σ_p^+ of Brown[7] (which lacks isopropoxy, methylsulfinyl, and methylsulfonyl), and Taft's[8] σ_R^0 and σ_I (both of which lack isopropoxy and trimethylammonium). The values for the parameters a and b for the five sets on a 14 compound base as well as those of the three smaller sets are given in Table II. Also shown are the correlation coefficients r for each of the constants. An r value close to unity implies that a high degree of correlation exists and that the proportions of field and resonance effects which constituted the given σ set are properly weighted. For correlation with both δ(H-2) and δ(H-8), the σ_p set is the best giving r values of 0.931 and 0.933, respectively. These parameters predict δ(H-2) 8.35 (obsd 8.20) and δ(H-8) 8.26 (obsd 8.17) for adenine, indicating the correct relative field position of H-2 and H-8, but do not predict the crossover in 6-phenoxypurine: δ(H-2) 8.56 (obsd 8.60) and δ(H-8) 8.34 (obsd 8.66). The calculated σ_p^+ correlates equally well with δ(H-2) but not with δ(H-8). Although Coburn et al.[2] obtained excellent correlation with r = 0.991 for δ(H-8) vs. σ_p^+, their study was done on nine purines (**1, 2, 3, 5, 6, 7, 8, 9, 11**), and the H-2, H-8 assignments were reversed for adenine (**2**) and 6-iodopurine (**5**).[9] After correcting for the latter, we have found that r is reduced slightly to 0.986 (or 0.984 with σ_p^+ calcd). However, inclusion of the trimethyl N^+ cation and the phenoxy group has led to r = 0.951 for the 11 purines, which further deteriorates to 0.897 for the entire 14 compound correlation. Thus, our present observation of r = 0.950 for σ_R^0 vs. δ(H-2) on the basis of 12 compounds should not be generalized in the absence of the isopropoxy and trimethylammonium derivatives.

From the five complete sets of correlation in Table II, it is apparent that the H-2 data correlate better than the H-8 data at >53% resonance and the reverse is true for <53% resonance. These trends are supported by the change in chemical shifts of the series of compounds in Table I relative to purine ($\Delta\delta$ = $\delta(H_{6\text{-substituted}}) - \delta(H_{purine})$). Thus, in **1** where the dimethylamino group has a large resonance effect (R = −0.848) but a

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Table I. ^{1}H NMR Chemical Shifts of 6-Substituted Purines in Dimethyl Sulfoxide

Registry no.	Compd	6-Substituent	H-2	H-8
938-55-6	1	$-N(CH_3)_2$	8.19	8.07
73-24-5	2	$-NH_2$	8.20	8.17
1074-89-1	3	$-OCH_3$	8.57	8.40
66085-16-3	4	$-OCH(CH_3)_2$	8.62	8.49
2545-26-8	5	-I	8.63	8.60
50-66-8	6	$-SCH_3$	8.75	8.47
2004-03-7	7	$-CH_3$	8.80	8.55
87-42-3	8	-Cl	8.80	8.73
120-73-0	9	-H	9.00	8.67
19769-31-4	10	$-SOCH_3$	9.05	8.75
2036-13-7	11	-CN	9.12	8.93
19769-32-5	12	$-SO_2CH_3$	9.19	8.95
13020-83-2	13	$-^+N(CH_3)_3Cl^-$	9.28	9.03
66085-17-4	14	$-O-C_6H_5$	8.60	8.66
5546-38-8	15	$-O-C_6H_4-p-OCH_3$	8.56	8.61
66085-18-5	16	$-O-C_6H_4-p-NO_2$	8.67	8.71

negligible field effect ($F = 0.031$), the $\Delta\delta$(H-2) of −0.81 ppm is greater than the $\Delta\delta$(H-8) of −0.60 ppm. For the ammonium salt **13** where the substituent has a large field effect only ($R = 0, F = 1.46$), the $\Delta\delta$'s are +0.28 ppm for H-2 and +0.36 ppm for H-8. In order to estimate the maximum correlation of δ(H) with the most optimum weighting of the resonance and field effects of the 6-substituent, the r values (y) vs. % resonance contribution (x) to the five σ sets were examined in terms of $y = f(x)$. The equations for H-2 and H-8 are best defined by the polynomials derived from a computer least-square routine as shown in eq 2 and 3, and they are plotted in Figure 1.

$$\text{H-2: } y = 0.163x^3 - 0.841x^2 + 0.914x + 0.654 \quad (2)$$

$$y_{max} = 0.938 \text{ at } x = 65\%$$

$$\text{H-8: } y = 0.315x^3 - 1.020x^2 + 0.720x + 0.787 \quad (3)$$

$$y_{max} = 0.934 \text{ at } x = 44\%$$

The $y_{max} < 1$ at any x value suggests that the δ(H) vs. σ should not be expected to be completely linear. The σ constants provide a good account of the 6-substituent effect on the excess charge densities at H-2 and H-8 which constitute major contribution to chemical shift values. However, they do not assess the perturbation of the ring current and magnetic anisotropy in the 6-substituted compounds which also affect chemical shifts. To test this, 6-hydroxypurine (hypoxanthine, δ(H-2) 8.03, δ(H-8) 8.17) and 6-mercaptopurine (δ(H-2) 8.23, δ(H-8) 8.42) which exist in the 6-keto form were used to replace 6-methoxy- and 6-methylthiopurine in the σ_p correlation. The r value for δ(H-2) drops from 0.931 to 0.815 and that for δ(H-8) from 0.933 to 0.900, showing the sensitivity of the correlation coefficients to the 6-keto nonbenzenoid structure. Another uncertainty is the solvent effects on the intermolecular interactions of the purine compounds, e.g., base stacking and hydrogen bonding. The purine chemical shifts were determined in dimethyl sulfoxide for solubility reason but the σ constants are based in aqueous media. Within such limitation, eq 2 indicates that δ(H-2) correlates best with 65% resonance and 35% field contribution of the 6-substituent, whereas eq 3 suggests that δ(H-8) fits best with 44% resonance and 56% field. Thus, the conclusion arrived at earlier by Coburn et al.[2] that "the mechanism of transmission of substituent effects is purely resonance from the 6- to the 2-position in the pyrimidine ring and a combination of induction and enhanced resonance from the 6- to the 8-position, across both rings" is now modified.

These regiospecific substituent effects can be rationalized by mesomeric contributions as shown in Scheme I.

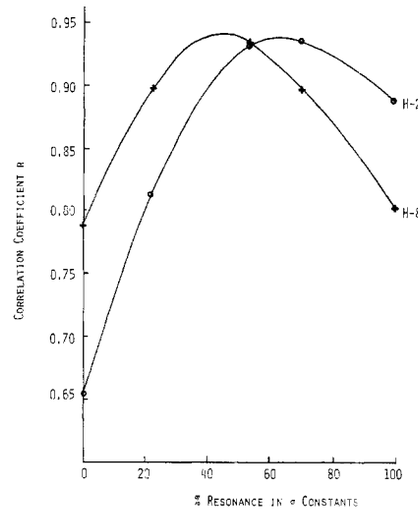


Figure 1. A plot of correlation coefficient r obtained from δ(H)–σ correlations vs. % resonance in σ constants for H-2 (○) and H-8 (+). The solid lines are generated from eq 2 and 3.

Although the 2-position, unlike the 8-position, is not in direct resonance with the 6-substituent, the larger resonance effect at the 2- than that at the 8-position implies that structures a and b contribute to the resonance hybrid to a greater extent than does c. This is reasonable since the negative charge is on nitrogen instead of carbon and since less charge separation is required in a and b vs. c. On the other hand, greater field effect is experienced at the more distant 8-position than at the closer 2-position by virtue of structure e. It has been found by Grant et al.[10] that this quinone type structure is the major contributing form to the resonance hybrid of 1-methylpurine and N-1 protonated purine. Its contribution places a positive charge on the imidazole ring and a negative charge on the pyrimidine ring, hence the increase in electron withdrawal from 8 relative to 2. The bond dipole effect as depicted in structure d accentuates electron withdrawal more at 2 than

Scheme I. Regiospecific 6-Substituent Effects

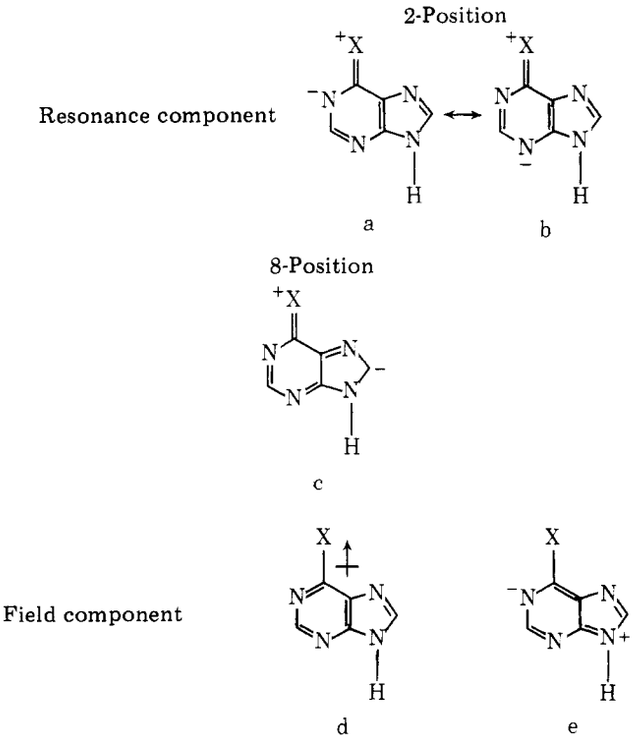
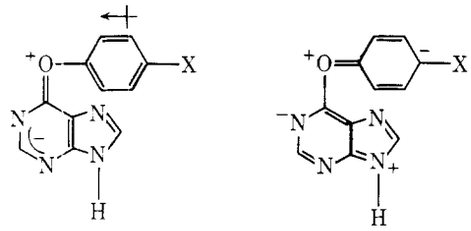


Table II. Linear Least-Square Parameters for Proton Chemical Shifts vs. Substituent Constants for 6-Substituted Purines 1–14

Compd	σ substituent constant	% resonance for σ	2-Hydrogen a	2-Hydrogen b	2-Hydrogen Correlation coefficient r	8-Hydrogen a	8-Hydrogen b	8-Hydrogen Correlation coefficient r
14 (1–14)	σ_m	22 ± 0	8.55	0.860	0.814	8.41	0.785	0.898
14 (1–14)	σ_p	53 ± 0	8.75	0.605	0.931	8.59	0.501	0.933
14 (1–14)	σ_p^+ (calcd)	70 ± 0	8.87	0.448	0.934	8.68	0.356	0.897
14 (1–14)	R	100 ± 0	8.99	0.829	0.890	8.77	0.618	0.803
14 (1–14)	F	0 ± 0	8.50	0.504	0.655	8.34	0.502	0.788
11 (except **4, 10, 12**)	σ_p^+ (exptl)	66 ± 5	8.87	0.427	0.901	8.71	0.383	0.951
12 (except **4, 13**)	σ_R^0	84 ± 10	9.00	1.371	0.950	8.78	1.051	0.882
12 (except **4, 13**)	σ_I	0 ± 5	8.51	0.779	0.525	8.33	0.858	0.700

at 8 due to proximity, but its effect is not expected to be the dominant one compared to the charge effects of structure e.

Of the 6-substituted purines shown in Table I, only in the case of 6-phenoxypurines does H-2 resonate at higher field strength than H-8. Indeed, the phenoxy group is unique in having the largest resonance constant ($R = -0.740$) among the 42 substituents whose resonance effects are calculated by Swain et al.[6] It also has a very large field effect ($F = 0.747$), thus giving it the largest combination σ values ($F + R = 1.487$) of the 6-substituent groups in compounds **1–14.** These large resonance and field constants of the phenoxy substituent can be manifested on the basis of structures f and g. Thus, the



f g

electron-donating resonance effect as well as the electron-withdrawing field effect of the phenoxy oxygen are both facilitated by the phenyl ring acting as an electron donor and electron sink, respectively. The regiospecificity of these two component effects follows the same trend as above. The resonance effect, felt more strongly at H-2, tends to shift the H-2 peak to higher field relative to purine. The resonance effect felt at H-8 is weaker, hence a lesser displacement of H-8 to higher field. At the same time the large electron-withdrawing field effect, felt more strongly at the 8-position, shifts the H-8 peak to lower field. The smaller field effect at the 2-position shifts H-2 to lower field but to a lesser extent than H-8. The final result is a crossover of H-2 and H-8.

In the case of the para-substituted 6-phenoxypurines **15** and **16,** the H-2 peak also appears at higher field than that of H-8. These data are compatible with structures f and g. The *p*-methoxy group in **15** will increase the contribution of **f** at the expense of g. This will increase the electron donating resonance effect of the phenoxy group by stabilizing the oxygen cation in f. The increased resonance effect will be felt more strongly at H-2 than at H-8. This will, therefore, cause a greater upfield shift for H-2 than H-8. The electron withdrawing field effect is diminished relative to 6-phenoxypurine since g contributes to a lesser extent. Nevertheless, the diminished field effect will be felt at H-8 to a greater extent than H-2 and will cause a greater downfield shift of H-8. Again, H-8 occurs at lower field. With the *p*-nitro group present in **16,** the above argument, although reversed, leads to the same conclusion. A greater contribution of structure g relative to f is expected for **16** relative to 6-phenoxypurine (**14**). This will lower the electron donating resonance effect more at H-2 but raise the electron-withdrawing field effect more at H-8. The net effect is that H-2 is moved upfield to a lesser extent than that of **14,** while H-8 is moved downfield to a greater extent, thereby maintaining the original crossover in 6-phenoxypurine.

Experimental Section

The ^1H NMR spectra were obtained using a Varian A-60A spectrometer or a Perkin-Elmer R-12 spectrometer. NMR samples were prepared at 0.1–0.2 M solutions in dimethyl sulfoxide containing 1% sodium 2,2-dimethyl-2-silapentane-5-sulfonate. Ultraviolet spectra were obtained with a Cary 14 spectrophotometer. The 6-substituted purines **1–13** as well as hypoxanthine and 6-mercaptopurine are known compounds, and most are available from Cyclo, Aldrich, and Sigma Chemical Co. The partially 8-deuterated samples of the above were prepared according to published procedures.[5] The preparations of the three 6-phenoxypurines **14, 15,** and **16** are shown below. Melting points are uncorrected. Combustion analyses were performed by M-H-W Laboratories, Garden City, Mich.

6-Phenoxypurine (14), 6-*p*-Methoxyphenoxypurine (15), and 6-*p*-Nitrophenoxypurine (16). A phenol melt containing 200 mg of 6-chloropurine (**8**) (or 50% 8-deuterated) was stirred at 110 °C for 3.5 h. To the cooled mixture was added 25 mL of ether and 5 mL of water, and the pH of the aqueous layer was adjusted to 5. The resulting suspension was cooled, filtered, and the residue recrystallized from 2-propanol to yield 192 mg (70%) of 6-phenoxypurine (**14**): mp 217–218 °C; λ_{max} (EtOH) 254 nm (ε 17 000).

Anal. Calcd for $C_{11}H_8N_4O$: C, 62.26; H, 3.80; N, 26.40. Found: C, 62.50; H, 3.98; N, 26.56.

By using *p*-methoxyphenol in the above procedure, 6-*p*-methoxyphenoxypurine (**15**) was obtained: mp 201–202 °C, λ_{max} (EtOH) 257 nm (ε 11 300).

Anal. Calcd for $C_{12}H_{10}N_4O_2$: C, 59.42; H, 4.16; N, 23.21. Found: C, 59.22; H, 4.10; N, 23.13.

By using *p*-nitrophenol in the above procedure, 6-*p*-nitrophenoxypurine (**16**) was obtained: mp 206–207 °C dec; λ_{max} (EtOH) 271 nm (ε 15 000).

Anal. Calcd for $C_{11}H_7N_5O_3$: C, 51.36; H, 2.74; N, 27.23. Found: C, 51.09; H, 2.54; N, 27.48.

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Registry No.—Phenol, 108-95-2; *p*-methoxyphenol, 150-76-5; *p*-nitrophenol, 100-02-7.

References and Notes

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Substituent and Medium Effects on Nitrogen-15 Shieldings of Compounds with >C=N Bonds (Imines, Oximes, and Phenylhydrazones)[1a]

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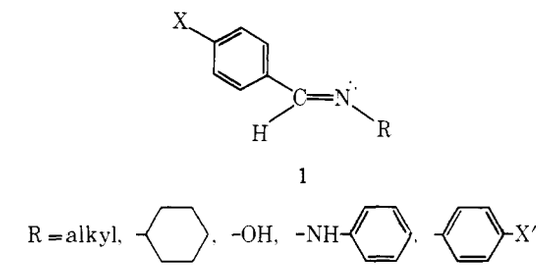
The ^{15}N chemical shifts of 13 *N*-(arylmethylidene)alkanamines, seven *N*-(arylmethylidene)azanols, five 1-(arylmethylidene)-2-phenyldiazanes, and 11 *N*-(arylmethylidene)arenamines have been determined at the natural-abundance level of ^{15}N in several solvents. The shifts of several of the *N*-(phenylmethylidene)alkanamines with different alkane groups have been analyzed in terms of α-, β-, and γ-methyl substituent effects. For those *N*-(arylmethylidene)azanes substituted at the para position, linear correlations with Hammett σ parameters having negative slopes are found for the ^{15}N chemical shifts. However, the ^{15}N shifts of *N*-(phenylmethylidene)arenamines (substituted at the para position of the arenamine moiety) are essentially insensitive to the nature of the substituent. The slopes of the Hammett correlations become more negative with increasing proton-donating power of the solvent for most series of compounds studied. In general, the ^{15}N shifts were found to be 5–12 ppm toward higher fields in methanol compared to chloroform, and except for the alkylidenazanols (oximes), about the same in dimethyl sulfoxide as in chloroform. In contrast, the alkylidenazanol resonances move 13–16 ppm downfield for the change from chloroform to dimethyl sulfoxide.

Systematic nitrogen nuclear magnetic resonance (NMR) studies, which were previously limited by inaccuracies of the ^{14}N NMR data and the expense and difficulties of using ^{15}N-enriched materials,[2] can now be carried out easily with ^{15}N isotope at the natural-abundance level and are expected to lead to a more complete understanding of the factors which contribute to the shieldings of nitrogen nuclei.

Previous studies of structural effects on ^{15}N shifts largely have been confined to systems containing sp^3-hybridized nitrogen atoms.[3–6] Both saturated systems in which inductive and steric effects should dominate and unsaturated systems containing aromatic groups capable of conjugative interaction have been investigated. Thus, the ^{15}N shifts in alkanamines have been found to change with alkyl substituents in much the same manner as ^{13}C shifts in structurally related compounds.[3] Such correlations further substantiate the belief that substituent-induced shielding changes result from external perturbations which are common to several nuclei.[7–9] Investigations of ^{15}N shifts of the amine nitrogens of substituted benzenamines[4–6] have revealed the importance of the inductive and resonance effects of the individual substituents. The basic assumption in all of these correlations is that substituents may be expected to alter the electron density at the nitrogen atom and the C–N bond order, thus causing changes in the paramagnetic part of the Ramsey shift equations.

We report here further evaluation of steric, electronic, and medium effects on ^{15}N chemical shifts for the specific case of imino nitrogens. The bonding in these types of nitrogen can be usefully regarded as involving a C–N σ and a C–N π bond with a lone electron pair on nitrogen which, to the first approximation, is not considered to be involved with the π-bonding orbitals.

In this work, we have chosen to study a number of arylmethylidenamines, azanols, and diazanes with the general structure **1**. These substances, in principle, will allow for conjugation of the unsaturated nitrogen with the *C*-aryl group



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through the C=N π bond and/or of the unshared pair on nitrogen with an *N*-aryl group. The importance of such conjugation was expected to be revealed by the variation of the nitrogen shieldings with the nature of the substituent group (X or X′) on the aryl groups from *p*-N(CH$_3$)$_2$ to *p*-NO$_2$.

Experimental Section

The natural-abundance ^{15}N spectra were recorded on a Bruker WH-180 spectrometer operating at 18.25 MHz in the Fourier-transform mode employing quadrature detection and complete noise–proton decoupling. Samples were run as 20 or 36 mol % solutions in chloroform, dimethyl sulfoxide, or methanol contained in 25-mm o.d. precision-ground sample tubes, with 17–22-mL sample volumes. Chemical shifts are reported in parts per million (ppm) upfield with respect to 1.0 M ^{15}N-enriched nitric acid in deuterium oxide contained in a 5-mm o.d. NMR tube. The deuterium oxide was used to produce the field lock signal. The optimum conditions for observation of the imino nitrogen signals of the compounds studied here were found to have a pulse width of 55 μs (70° pulse angle), a repetition rate of 30 s, and gated proton decoupling for which the decoupler was on only during acquisition of data (no NOE). Under these conditions, the sample remained at ambient probe temperature (25 °C), and typical spectra required 200 accumulations to provide an adequate signal-to-noise ratio. Gated proton decoupling during acquisition is preferable to no decoupling to ensure removal of any nitrogen–proton couplings which might broaden the signal and thus reduce the signal-to-noise ratio. For measurement of the shifts of the amino nitrogen signals in the phenyldiazanes, continuous proton decoupling was

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