A Theoretical Study of the Charge Distribution of Aminopyridines, Aminopyrimidines, and Some Diazine *N*-Oxides

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We have carried out STO-3G minimal basis set *ab initio* calculations to determine the charge distribution, using the YSP population analysis, of mono- and di-substituted aminopyridines, mono-, di-, and tri-substituted aminopyrimidines, and some mono- and bi-cyclic diazines and their corresponding mono-*N*-oxides. Our results indicate that the nitrogen charge densities do reflect the trend in the corresponding ^{15}N chemical shifts, provided the nitrogen atoms have similar hybridization and substitution patterns. The amino-substituent effects are fully discussed. We have also shown that there exists a linear correlation between the ring nitrogen charge density of heteroaromatic derivatives and that of the homologous carbon atoms of the corresponding benzene derivatives. We have also studied, using the correlation between 1*s* orbital energies and gas-phase proton affinities, the intrinsic basicity of amino-pyridines and pyrimidines. Our results indicate that the ring nitrogens are the most basic sites in both families of compounds. In the particular case of aminopyrimidines the intrinsic basicities of both ring nitrogens are practically identical. These results are always in fairly good agreement with the ^{15}N n.m.r. spectra of these molecules in acidic media. The charge distribution of the mono-*N*-oxide derivatives of diazine confirm the correlation between charge densities and chemical shifts. Their ^{15}N n.m.r. spectra can be explained in terms of the contribution of mesomeric forms, which accumulate electronic charge at *ortho*- and *para*-positions, relative to the oxidized nitrogen atom.

Aminopyrimidines are the basic structural units of natural products of biological interest (nucleosides, nucleotides, purines, *etc.*) [1] and some of them exhibit a noticeable pharmacological activity. Trimethoprim[2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine], for instance, is an effective antibacterial agent; [2] methotrexate (which is an aminopteridine derivative) is useful in the treatment of a common form of childhood leukemia; [3] other aminopyrimidine derivatives (acarnidines) are novel antiviral and antimicrobial agents.[4] This explains the large amount of research carried out on aminopyridine and aminopyrimidine derivatives.

From ^{13}C n.m.r., visible, and u.v. spectroscopic studies [1,3] the pharmacological activity is thought to be closely related to the ring-nitrogen atom of the pyrimidine system, through the formation of a complex between the pyrimidine derivative and some kind of bacterial enzyme.[2] This conclusion has resulted in considerable number of ^{15}N n.m.r. studies on these (pyridines, aminopyridines, pyrimidines, and aminopyrimidines) [4-8] and related (purines, pteridines, *etc.*) [9-12] compounds.

Previous investigations on substituted pyridines and pyrimidines using the ^{14}N n.m.r. technique are almost classical,[13-17] but, as is well known, while ^{15}N resonance lines are usually very sharp, the line-broadening, due to quadrupole-induced relaxation, present in ^{14}N n.m.r. does not permit individual nitrogen resonances to be well resolved, and uncertainties in the line positions are frequent.

Nevertheless, an unambiguous assignment of the resonance lines is not always possible, even when using ^{15}N n.m.r. techniques. The molecules in this paper (aminopyrimidines) clearly illustrate this problem. The nitrogen atoms of the amino-groups present their resonance lines in a region quite separate from that typical of the ring nitrogen atoms and no assignment problem arises; but it is quite difficult to assign the resonance lines which correspond to each ring nitrogen, and in most cases, if this assignment is not arbitrary, it is made using some empirical rule, such as the correlation between the ^{15}N chemical shifts of aminopyridines (and aminopyrimidines) and the ^{13}C chemical shifts of the corresponding amino-substituted benzenes.[8] Correlations between ^{14}N chemical shifts of diazines and their mono-*N*-oxides have also been used for assignment purposes.[8,18]

Witanowski *et al.*[19] have indicated that there exists a linear relationship between the ^{15}N chemical shifts of azine and azole nitrogens and the calculated electron densities. A similar conclusion was reached by Hensen and Messer [20] in the study of halogenopyridines. DiGioia *et al.*[7] considered these (apparent) correlations to be fortuitous, since no correlation could be established between ^{15}N chemical shifts of methyl-substituted pyridines and semi-empirically calculated charge densities. However, the substituent effects of alkyl groups are so small that the observed differences in the ^{15}N chemical shifts in methylpyridines are only a few p.p.m. In consequence, any secondary effect can easily change the trend expected from the charge distribution and therefore the absence of correlation, in this particular case, may not be conclusive. On the other hand, it is a well established fact, both from the experimental [21,22] and the theoretical [23,24] point of view, that ^{13}C chemical shifts do reflect the trend of the charge densities on carbon atoms of similar hybridization and substitution.

One of the aims of this paper is to investigate whether similar behaviour, subject to the same restrictions, can be established for ^{15}N chemical shifts. For this purpose we have chosen amino-substituted pyridines and pyrimidines because (a) their biological activity makes them very interesting, (b) they constitute a large set of compounds in which the ring nitrogens fulfil the conditions of similar hybridization and substitution, and (c) the amino-group substituent effects are large enough to guarantee that any possible relationship between ^{15}N chemical shifts and charge densities would not be substantially affected by other effects.

We also include a discussion of the effect of nitrogen oxidation on the charge distribution of mono- and bi-cyclic diazines. These *N*-oxides present an interesting structural problem, the relative importance of the mesomeric forms, in which the N–O bond behaves either as an electron donor or acceptor. The ^{15}N n.m.r. spectra of these compounds might be explained in terms of the relative contribution of these mesomeric forms, which would also provide useful inform-

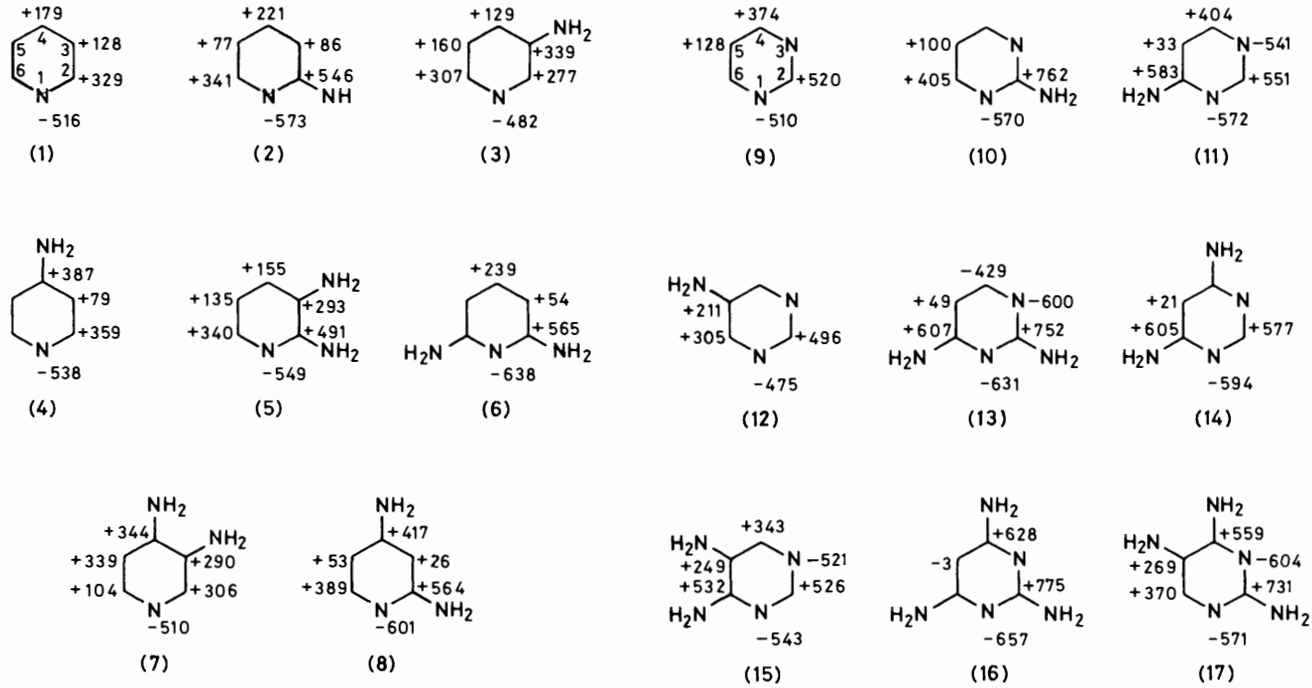

Figure 1. YSP charge distribution (10^{-3} electron) of aminopyridine derivatives

Figure 2. YSP charge distribution (10^{-3} electron) of aminopyrimidine derivatives

ation on their activity as drug metabolites and potent mutagenic agents.[25,26]

Calculations

We have carried out *ab initio* calculations, using a STO-3G minimal basis set, on (a) all mono- and di-substituted aminopyridines, (b) all mono-, di-, and tri-substituted aminopyrimidines, and (c) the following diazines: pyrimidine, pyrazine, pyridazine, phthalazine, cinnoline, quinazoline, and quinoxaline and their corresponding mono-*N*-oxides.

In order to avoid prohibitive geometry optimizations we have used the experimental structure [27] for pyridine, all monoaminopyridines, and monocyclic diazines. As no experimental geometries are available for the remaining molecules included in this study, we have adopted the following geometrical model: the aromatic ring was kept identical to that of the corresponding parent compound (pyridine or pyrimidine) and for the amino-group the experimental structure of this group in the 4-aminopyridine was adopted. In the particular case of the mono-*N*-oxides, and taking into consideration that nitrogen oxidation introduces noticeable distortions to the aromatic rings, we have used in our *ab initio* calculations the corresponding INDO fully optimized geometries, since it has been pointed out [28] that this method yields reliable geometries for this kind of compound. The same criterion was adopted for the non-oxidized bicyclic diazines.

The corresponding charge distributions were obtained using the YSP population analysis,[29,30] which has been proved [23,24] to be a reliable partition technique in this kind of charge distribution calculation. In all cases we have employed the standard density basis defined in ref. 29 and an average scaling factor of 1.5 for hydrogen atoms in the NH_2 groups and of 1.3 for hydrogens bonded to carbon atoms.[29]

Results and Discussion

Charge Densities and ^{15}N *Chemical Shifts.*—We present, in Figures 1 and 2, the charge distributions corresponding to amino-substituted pyridines and pyrimidines, respectively. Systematically, amino-substitution in the 2-position relative to a ring nitrogen atom causes the greatest negative change in the charge density on that nitrogen atom, whilst 4-substitution causes a smaller negative change and 3-substitution a positive one. Besides, in agreement with the trend observed in the ^{15}N chemical shifts, these substituent effects are almost additive. In fact, there is reasonably good agreement between the calculated nitrogen charge densities and the charge densities predicted by assuming constant increments of -57, $+34$, and -22 me$^-$ (calculated for the monoaminopyridines) for 2-, 3-, and 4-aminosubstitution, respectively (see Table 1).

It is also clear, from Table 1, that, within each family of compounds, the nitrogen net charge variation parallels that of the corresponding ^{15}N chemical shifts. The pyridine nitrogen charge density undergoes, upon 3-substitution, as indicated above, a change of $\Delta q = +34$ me$^-$, while the ^{15}N chemical shift varies only by $\Delta\delta = -0.9$ p.p.m. However, if one assumes that there exists a linear correlation between Δq and $\Delta\delta$ for the monosubstituted aminopyridines, one finds that a variation of -0.9 p.p.m. in the chemical shift should correspond to a change of $+38$ me$^-$ in the charge density. This also indicates that the small value of $\Delta\delta$ observed in this compound cannot be taken as evidence that the aromatic system remains practically unperturbed upon γ-substitution.[8]

Assuming this qualitative parallelism between Δq and $\Delta\delta$ (which, in the case of pyrimidines, holds for both ring nitro-

Table 1. Variation of the nitrogen charge density (Δq) and the ^{15}N chemical shift ($\Delta\delta$) of aminopyridines and aminopyrimidines, relative to the parent compounds

	$10^3\Delta q/e^-$				$\Delta\delta$ (p.p.m.) [a]	
	N-1		N-3		N-1	N-3
Compound	Calc.[e]	Pred.[f]	Calc.[e]	Pred.[f]		
Monoaminopyridine						
(2)	−57				−50.8	
(3)	+34				−0.9	
(4)	−22				−40.7	
Diaminopyridine						
(5)	−33	−23			−51.5	
(6)	−122	−114			−86.0	
(7)	+6	+12			−36.3	
(8)	−85	−79			−74.0 [b]	
Monoaminopyrimidine						
(10)	−60	−57	−60	−57	−45.1	−45.1
(11)	−62	−57	−31	−22	−47.9	−36.1
(12)	+35	+34	+35	+34	−12.0	−12.0 [b]
Diaminopyrimidine						
(13)	−121	−114	−90	−79	−79.7	−88.6
(14)	−84	−79	−84	−79	−64.6	−64.6
(15)	−33	−23	−11	+12	−47.8	−48.7
Triaminopyrimidine						
(16)	−147	−136	−147	−136	−104.7 −176.7 [d]	−104.7 −176.7 [d]
(17)	−61	−45	−94	−80	−134.0 [c]	−134.0 [c]
(18)	−60	−45	−60	−45	−67.9 −96.9 [c]	−67.9 −96.9 [c]

[a] All values taken from ref. 8 (solvent DMSO, unless otherwise noted). [b] Values predicted assuming a linear correlation between Δq and $\Delta\delta$. [c] Solvent: DMSO–0.2 equiv. HCl. [d] Solvent: trifluoroacetic acid. [e] Charge densities calculated using YSP population analysis. [f] Charge densities predicted assuming constant increments of −57, +34, and −22 me^- for 2-, 3-, and 4-substitution, respectively.

gens) we can estimate for 2,4-diaminopyridine (8) a $\Delta\delta_N$ value (not measured at present) of −74 p.p.m. Analogous prediction can be made for 5-aminopyrimidine (12), which should exhibit the smallest deviation, relative to pyrimidine (9), of all monosubstituted amino-derivatives.

For triaminopyrimidines our results predict the greatest increment in the ring nitrogen charge to occur in 2,4,6-triaminopyrimidine (16), followed by (17) and (18), respectively, while the greatest variation on the ^{15}N chemical shifts [8] is observed in (17). However, in order to increase the solubility of this compound in dimethyl sulphoxide (DMSO) it is necessary to decrease the pH of the solvent,[8] and under these experimental conditions both ring nitrogens would be protonated and, in consequence, the corresponding nitrogen resonance line is considerably shifted to lower fields.[7,13,31] In fact, if one considers the variations in the chemical shifts with the three compounds in an acidic medium (and therefore diprotonated) the trend observed parallels, once more, that of the charge densities. On the other hand, our results indicate that the ring nitrogen atoms in 2,4,5-triaminopyrimidine (17) have different net charges, while the observed chemical shifts (in DMSO + 0.2 equiv. HCl) are identical; this can be taken as further evidence that the molecule is diprotonated under such experimental conditions.

From the results presented here we can conclude that the calculated charge densities cannot be directly equated with but *do reflect* the trend of the ^{15}N chemical shifts and, in consequence, they can be used for assignment purposes, at least in those compounds where the substituent effects are of some importance.

As we have indicated before, it has been shown [21–24] that ^{13}C chemical shifts reflect the trend of charge densities for carbon atoms of similar hybridization and substitution and, according to our previous discussion, similar behaviour can be expected for ^{15}N chemical shifts. On the other hand, it has been established [8] that there exists a linear relationship between the amino-substituent effects on ^{15}N shifts of aminopyridines (and aminopyrimidines) and the corresponding amino-substituent effects on the ^{13}C shifts of amino-substituted benzenes. Therefore, it is reasonable to expect a similar correlation between the charge densities of corresponding pairs of compounds.

In order to study this possible relationship, we have calculated the YSP charge distributions of aniline, 1,2-diamino-, and 1,3-diamino-benzene. The geometry used for the first compound was the experimental one [32] and for the diamino-benzene derivatives we have kept the same ring structure of aniline and identical conformation for the two amino-groups.

We present in Figure 3 the charge density (relative to the parent compound) of the ring nitrogen atom of amino-substituted pyridines *versus* the charge density (relative to benzene) of the corresponding carbon atom in the related aminobenzene derivative. It is evident that there exists a linear correlation similar to that found [8] between ^{15}N and ^{13}C chemical shifts. This confirms that ^{15}N chemical shifts do

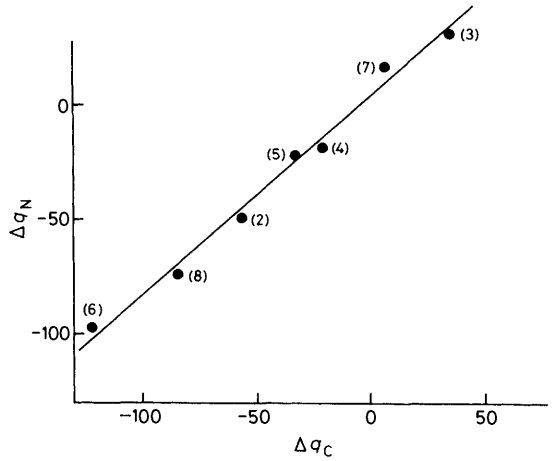

Figure 3. Nitrogen charge density (relative to pyridine) in aminopyridine derivatives *versus* the corresponding carbon charge density (relative to benzene) in amino-substituted benzenes

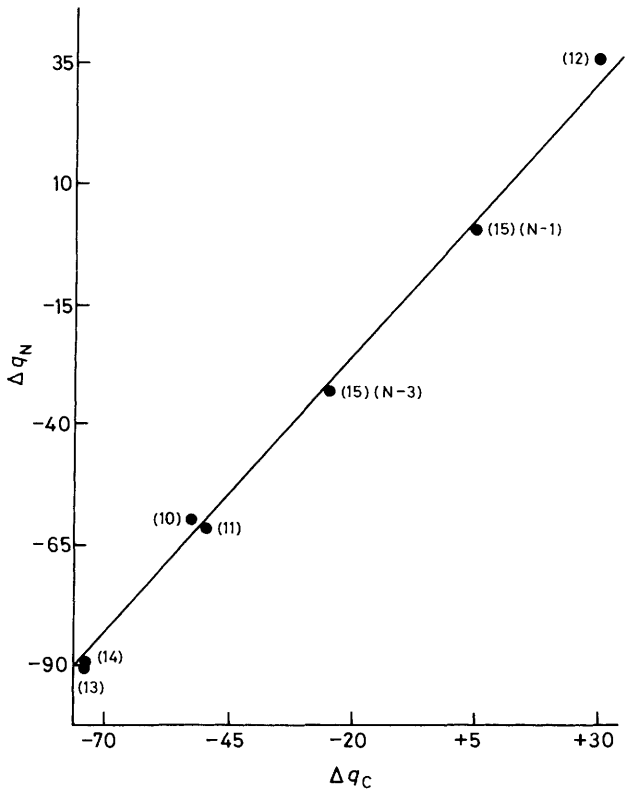

Figure 4. Nitrogen charge density (relative to pyrimidine) in aminopyrimidine derivatives *versus* the corresponding carbon charge density (relative to pyridine) in aminopyridine derivatives

reflect the trend in the charge densities of nitrogen atoms of similar hybridization and substitution.

In Figure 4 we have plotted the ring nitrogen charge density (relative to pyrimidine) of amino-substituted pyrimidines *versus* the charge density (relative to pyridine) of the corresponding carbon atom in the related aminopyridine derivative. The linear correlation that exists between both sets of charge densities indicates, once more, that the ring nitrogen charge density in heteroaromatic systems is influenced by the same factors that affect the carbon charge density in benzene derivatives, and is again similar to the one between the corresponding chemical shifts.[8]

Table 2. Predicted gas-phase proton affinities (kcal mol^{-1}) for aminopyridine derivatives

	Basic centre		
Compound	N-1	NH_2 [a]	NH_2 [a]
(1)	218.5		
(2)	229.8	206.3	
(3)	218.7	203.7	
(4)	226.8	202.5	
(5)	227.7	206.3 (3)	209.9 (2)
(6)	236.7	209.3 (2)	209.3 (6)
(7)	227.1	205.0 (4)	205.9 (3)
(8)	235.8	204.6 (4)	209.4 (2)

[a] Numbers in parentheses indicate the carbon atom to which the amino-group is attached.

Table 3. Predicted gas-phase proton affinities (kcal mol^{-1}) for aminopyrimidine derivatives

	Basic centre				
Compd.	N-1	N-3	NH_2 [a]	NH_2 [a]	NH_2 [a]
(9)	210.2				
(10)	220.2		205.5		
(11)	220.5	219.9	201.8		
(13)	229.8	229.9	203.4 (6)	206.9 (2)	
(14)	229.0	229.0	203.5 (4)	203.5 (6)	
(15)	220.8	220.4	203.7 (4)	202.7 (5)	
(16)	238.3	238.3	205.2 (4,6)	208.3 (2)	
(17)	230.0	229.2	210.5 (2)	204.7 (4)—207.3 (5)	
(18)	228.7	228.7	205.1 (4,6)	205.4 (5)	

[a] Numbers in parentheses indicate the carbon atom to which the amino-group is attached.

Proton Affinities.—We present in this section a study of the intrinsic proton affinity (PA) of the most basic sites (ring nitrogens and amino-groups) of amino-substituted pyridines and pyrimidines, since there is some evidence [1,3] that the biological activity of these kinds of compounds is related to the protonation of the ring nitrogens. The intrinsic proton affinities (see Tables 2 and 3) were calculated using the linear correlation obtained between 1*s* orbital energies and gas-phase PAs.[33,34] This correlation, as has been discussed elsewhere,[34] is different for ring nitrogen atoms and amino-groups, since different relaxation energies are involved in the 'core' ionization process in both cases. Therefore, the intrinsic PAs of amino-groups were calculated using equation (4) of ref. 33, while those of the ring nitrogens were obtained using equation (1) of ref. 34. Use of the latter implies that the linear correlation between N_{1s} orbital energies and gas-phase PAs which holds for pyridines is also valid for pyrimidines.

In aminopyridines (see Table 2) the most basic site of the molecule is always the ring nitrogen atom. This result agrees with the experimental observation [8] that, even in a quite acidic medium (FSO_3H), monoaminopyridines present ^{15}N resonance lines which correspond to a mixture of a mono- and a di-cation. Only in the case of 2-aminopyridine (2), which according to our results has the most basic amino-group of the three monosubstituted derivatives, the diprotonation seems to be [8] more complete. Moreover, in a similar trend to that observed in the charge densities and chemical shifts, double β-substitution (6) causes a noticeable increase in the basicity of the ring nitrogen. The same effect, albeit smaller, takes place for β,δ substitution (8), while the introduction of

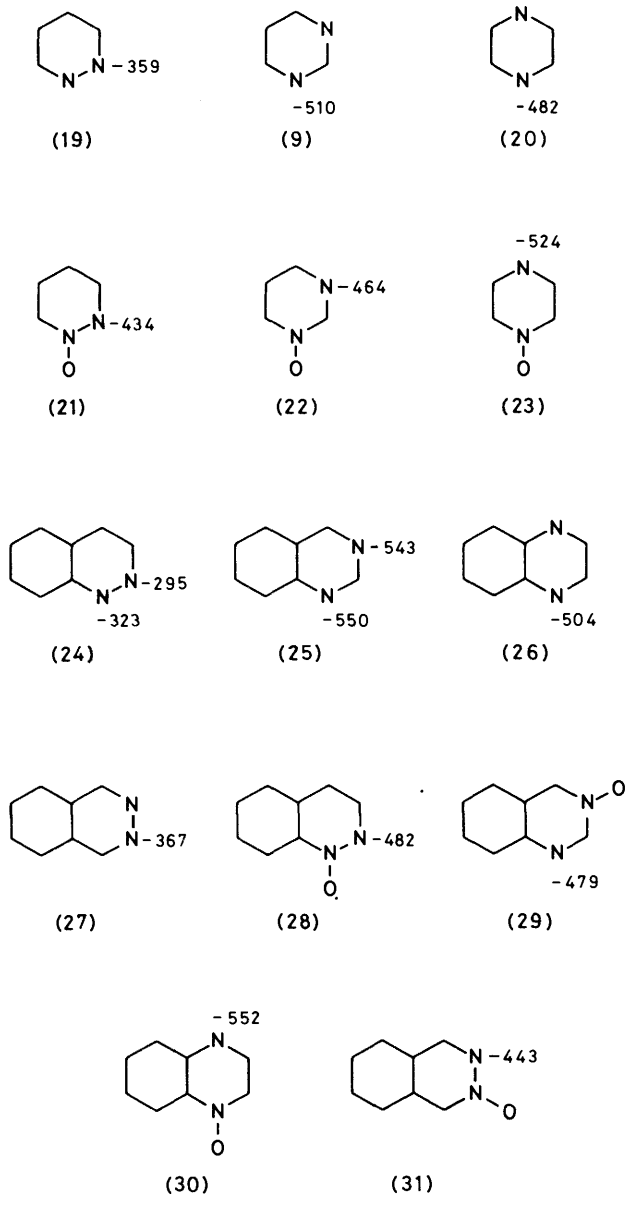

Figure 5. Nitrogen charge densities of mono- and bi-cyclic diazines and their corresponding mono-*N*-oxides

a second amino-group in the γ-position (5) only changes the ring nitrogen PA slightly.

It should be emphasized that, within the aminopyrimidine series, even in those cases where the two nitrogen atoms are not equivalent by symmetry, their intrinsic PAs are practically identical (see Table 3). This result is again in good agreement with the finding of Stadeli *et al.*[8] that ^{15}N n.m.r. spectra of these compounds, in acidic media, indicate that they undergo complete diprotonation. As in the case of aminopyridines, the basicity of the amino-groups is considerably low compared to that of the ring nitrogens, in agreement with the experimental evidence that no protonation of the NH_2 groups takes place, even in strongly acidic media.

The basicity of 2,4,6-triaminopyrimidines (16) is very high, explaining the fact that this compound is already diprotonated in moderately (trifluoroacetic acid) acidic media. It must be noticed, however, that the basicity of the other two triamino-derivatives (17) and (18) is quite low and comparable with that of the diamino-substituted pyrimidines. This means that the introduction of a third amino-group at position 5, which has a small effect on the charge density of the ring nitrogens, has also little influence on their basicity.

From the previous discussion, we can conclude that the basicity and the nitrogen charge density of these compounds are effected in the same way by the substituent. It must be taken into account, however, that this conclusion is only valid when dealing with the same kind of substituent and cannot be extrapolated to different substituents, since, as has been shown,[34] no correlation can be established, in general, between PAs and charge densities.

Table 4. Variation, upon oxidation, of the charge density (Δq) and ^{15}N chemical shift ($\Delta\delta$) of the non-oxidized nitrogen atom of monocyclic and bicyclic diazines

Compounds	$10^3\Delta q/e^-$	$\Delta\delta$ (p.p.m.) [a]
Monocyclic diazines		
(21) – (19)	−75	−53.9
(22) – (9)	+46	+4.5
(23) – (20)	−42	−24.1
Bicyclic diazines		
(28) – (24)	−187	−76.0 [b]
(29) – (25)	+71	+7.4
(30) – (26)	−48	−27.0
(31) – (27)	−76	−42.9

[a] Values taken from ref. 8 (solvent DMSO). [b] Value predicted assuming a linear correlation between Δq and $\Delta\delta$.

Nitrogen Oxidation Effects.—We aim to show the influence of nitrogen oxidation of mono- and bi-cyclic diazines on their charge distribution (to explain the origin of the shifts observed in the ^{15}N n.m.r. spectra) as well as on their geometrical conformation, by means of an analysis of the contribution of different mesomeric forms.

We present in Figure 5 the nitrogen charge densities of the parent compounds pyridazine (19), pyrimidine (9), pyrazine (20), cinnoline (24), quinazoline (25), quinoxaline (26), and phthalazine (27) and their corresponding mono-*N*-oxides (21)—(23) and (28)—(31), respectively. We have restricted our discussion to the nitrogen atoms since, as we have indicated above, any possible correlation between charge densities and ^{15}N chemical shifts can only be expected when similar hybridization and substitution of the nitrogen atom under consideration are guaranteed. These conditions are only fulfilled by the non-oxidized nitrogen atoms; on the other hand, as the effects of oxidation on charge density give enough information for our purposes we can restrict our discussion to those nitrogen atoms.

The calculated nitrogen charge densities are in good agreement with the observed behaviour of the corresponding ^{15}N shifts. In both mono- and bi-cyclic diazines, the non-oxidized nitrogen atom increases its charge density upon nitrogen oxidation, and the corresponding ^{15}N n.m.r. resonance signal is shifted to lower frequencies, with only two exceptions, pyrimidine (9) and quinazoline (25) (see Table 4). In these two cases, the non-oxidized nitrogen atom becomes less electronegatively charged than in the parent compound and the ^{15}N n.m.r. resonance line is shifted in both molecules to higher frequencies. Therefore, the experimental shifts, upon oxidation, of the non-oxidized nitrogen signals of diazines can be explained if one assumes that these shifts reflect the charge densities of the nitrogen atom, which does not undergo a drastic change either on hybridization or substitution. Using

the same assumption, we can predict that the resonance line of the non-oxidized nitrogen of cinnoline *N*-oxide must undergo the greatest displacement, to low frequencies, of all bicyclic diazines (see Table 4).

It is also clear that nitrogen oxidation of diazines systematically accumulates electronic charge at *ortho*- [compare the charge densities of (19) and (21), (24) and (28), or (27) and (31)] and *para*-positions [compare the charge distribution of (20) and (23) or that of (26) and (30)]; a concomitant decrease of the oxidized nitrogen charge density and that of the *meta*-position [compare charge densities of (9) and (22) or (25) and (29)] takes place, in agreement with the observed high-frequency shift undergone by the signal of the non-oxidized nitrogen atom of pyrimidine and quinazoline and the low-frequency shift observed in the remaining diazine *N*-oxides.

Conclusions.—From our results we can conclude that the observed ^{15}N chemical shifts do reflect the trend in the nitrogen charge densities, provided the nitrogen atoms have similar hybridization and substitution and the substituent effects are strong enough not to be substantially altered by secondary effects. This relationship is similar to the one found, on both experimental and theoretical grounds, between ^{13}C chemical shifts and charge densities for carbon atoms which fulfil the same conditions.

We have also shown that there exists a linear correlation between the ring nitrogen charge density of heteroaromatic derivatives and that of the corresponding carbon atom of the related benzene derivative. This finding seems to confirm our previous conclusions, since it has been shown that a similar correlation between the corresponding ^{15}N and ^{13}C shifts can be established.

Our calculated PAs indicate that, at least in the gas-phase, the ring nitrogens are the most basic sites of amino-substituted pyridines and pyrimidines. For the latter the intrinsic basicities of both ring nitrogens are practically identical in all cases. These results are always in a fairly good agreement with the observed ^{15}N shifts of these compounds in acidic media.

The charge distribution of the mono-*N*-oxides derivatives of mono- and bi-cyclic diazines confirm the existence of a correlation between the nitrogen charge density and the ^{15}N shift. The low-frequency shift, upon oxidation, of the non-oxidized nitrogen atom of diazines can be explained in terms of a considerable contribution of mesomeric forms which accumulate electronic charge at *ortho*- and *para*-positions relative to the oxidized nitrogen atom. A simultaneous decrease of the charge density at the *meta*-position explains the high-frequency shift observed in the particular cases of pyrimidine and quinazoline.

Acknowledgements

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