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Ten-π-Electron Nitrogen Heterocyclic Compounds. VIII. Semi-empirical Calculations of Chemical-Shifts of Ring-protons and of Methyl-protons.

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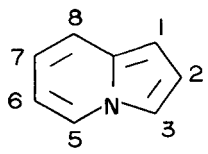
The chemical-shifts of the ring protons and of the methyl protons of some unsubstituted and some methylpolyazanidenes have been calculated by a semi-empirical method utilizing charge-densities obtained from HMO calculations. The success of this method lies in the choice of the reference compound, pyrrocoline.

The factors which contribute to the shielding of aromatic protons have been the subject of numerous papers (1-6). It is now well established that the shielding of a proton arises from two types of induced magnetic fields. The larger of the two types is associated with the induced circulations of pairs of electrons of the C-H bond. Pople (1) classifies this shielding as "local diamagnetic shielding". This shielding is sensitive to the presence of nearby electric poles and dipoles (2) and also depends upon the effective electronegativity of the atom to which the proton is bonded. The shielding of protons also involves, in most cases, a contribution due to the anisotropy of induced circulations of electrons about neighboring nuclei. Hall, Hardisson and Jackman (2) have discussed the various effects that variations of structure in aromatic systems have upon these two shielding contributions. While semi-quantitative evaluation of the effects of the ring current and changes in the π-electron charge densities upon the shielding values of aromatic protons is possible, the effects of the hybridization of the carbon atom bearing the proton under study and the diamagnetic anisotropy of the σ-framework (expected to be of a low order of magnitude) cannot as yet be evaluated with any quantitative certainty. The summation of the inductive and direct field effects of heteroatoms can be obtained from suitable reference compounds. The effects of unequal charge distributions can be calculated by the semi-empirical equation (5): $\sigma_i = 12.5 \times 10^{-6} \sum_r (1-q_r) R_{ir}^{-2} \cos\phi_{ir} - 17.0 \times 10^{-6} (\sum_r (1-q_r) R_{ir}^{-2})^2$ where R_{ir} is the distance between the ith proton and the rth atom of the ring, ϕ_{ir} is the angle which the line R_{ir} makes with the C-H bond axis, q_r is the π-electron density on atom r. This equation was recently used by Schweizer (5) and by Jackman (6), and is based upon the work of Schaefer and Schneider (4) and Musher (7). Since the calculation of charge densities by the simple HMO methods is a fairly straight-forward procedure, it would be of considerable utility, if one could calculate the chemical shifts of the protons in related heteroaromatic systems without having to take recourse to the more sophisticated SCFMO calculations. If the geometries of the systems under discussion are essentially the same, it becomes feasible to exclude the ring-current effects in the calculations, since they will be essentially the same for all of the compounds under investigation. Thus, if one chooses one particular ring-system as a reference, one can estimate the effect of the excess charge densities upon the shielding values of the ring protons by means of simple HMO calculations. The difference between the observed and calculated chemical shift positions will then reflect the contribution to the chemical shifts due to the ring-current anisotropy, the effects of the hybridization of the carbon atom bearing the proton under study and the diamagnetic anisotropy of the σ-framework, as well as the error introduced by the use of the HMO method and the discrepancies due to the crudeness of the model in general. We do anticipate, however, that these discrepancies will be of the same order of magnitude for related systems and will be cancelled by this treatment. Our recent interest in polyazaindenes prompted us to investigate this semi-empirical approach for these types of compounds. The most reasonable reference compound to be used for such a comparison is certainly pyrrocoline (I).* Table



I records the charge-field effect contribution, as calculated from the HMO method for each of the protons in pyrrocoline, and the experimentally ob-

*The ideal reference compound would, of course, be the indenyl carbanion, which is however not suitable because of the presence of the excess unit charge. The numbering system used for the compounds discussed in this paper, and in earlier papers of this series, is employed in order to facilitate the discussion of the results.

TABLE I

Calculation of Chemical Shifts and D Parameters for Pyrrocoline

	Position						
	1	2	3	5	6	7	8
charge densities, $-q_i$	1.180	1.079	1.155	0.980	1.032	1.014	1.007
the effect of $-q_i$	1.94	1.61	1.93	0.97	0.93	0.80	0.80
ring current contribution	-2.30	-2.02	-2.30	-2.38	-2.04	-2.04	-2.38
τ calculated*	3.92	3.87	3.91	2.87	3.17	3.04	2.70
τ observed	3.72	3.36	2.86	2.24	3.69	3.50	2.75
D	-2.50	-2.53	-3.35	-3.01	-1.52	-1.58	-2.33

*calculated relative to τ (benzene) at 2.73, assuming the ring current contribution in benzene is -1.55 ppm.

TABLE II

Calculation of Chemical Shifts for Various Polyazaindenes

	Position:					
Imidazo[1,2-a]pyridine	2	3	5	6	7	8
charge densities, $-q_i$	1.036	1.112	0.947	1.022	0.976	1.017
the effect of $-q_i$	1.57	1.82	0.68	0.70	0.39	0.71
D*	-2.53	-3.35	-3.01	-1.52	-1.58	-2.33
τ calculated	3.32	2.75	1.95	3.46	3.09	2.66
τ observed	2.52	2.52	1.91	3.35	2.97	2.49
$\Delta\tau$(observed-calculated)	-0.80	-0.23	-0.04	-0.11	-0.12	-0.17

*See Table I and text

	Position:				
Imidazo[1,2-a]pyrimidine	2	3	5	6	7
charge densities, $-q_i$	1.032	1.102	0.854	1.019	0.866
the effect of $-q_i$	1.46	1.81	-0.12	0.51	-0.34
D*	-2.53	-3.35	-3.01	-1.52	-1.58
τ calculated	3.21	2.74	1.15	3.27	2.36
τ observed	2.33	2.42	1.31	3.16	1.46
$\Delta\tau$(observed-calculated)	-0.88	-0.32	+0.16	-0.11	-0.90

	Position:						
Imidazo[1,5-a]pyridine	1	2	3	5	6	7	8
charge densities, $-q_i$	1.125	--	1.048	0.976	1.020	1.004	0.999
the effect of $-q_i$	1.81	--	1.62	0.93	0.79	0.63	0.72
D*	-2.50	--	-3.35	-3.01	-1.52	-1.58	-2.33
τ calculated	3.59	--	2.55	2.20	3.55	3.33	2.67
τ observed	2.73	--	2.03	2.12	3.59	3.42	2.66
$\Delta\tau$(observed-calculated)	-0.86	--	-0.52	-0.08	+0.04	+0.09	-0.01

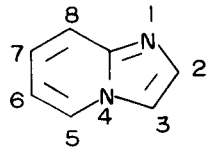
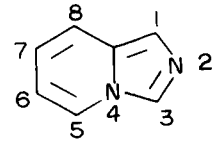
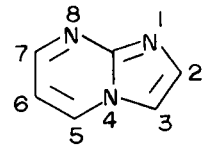
TABLE III

Calculation of D_{methyl} Parameters for Various Methylpyrrocolines

	Position of Substitution of Methyl Groups					
	1	2	3	5	6	7
charge density ($-q_i$)	1.069	0.978	1.020	0.871	0.920	0.918
the effect of $-q_i$	+0.19	-0.06	+0.055	-0.36	-0.22	-0.23
τ (observed)	7.60	7.60	7.73	7.81	7.88	7.83
D_{methyl} (τ observed - the effect of $-q_i$)	7.41	7.66	7.68	8.17	8.10	8.06

TABLE IV

Calculation of Chemical-Shifts of Methyl Protons

Compound	Position of CH_3-	D_{methyl} (a)	$-q_i$ (b)	the effect of -q:	τ (calculated)	τ (observed)
	2	7.66	0.938	-0.17	7.49	7.60
	3	7.68	1.010	+0.03	7.71	7.73
	5	8.17	0.840	-0.45	7.72	7.77
	6	8.10	0.932	-0.19	7.91	8.02
	7	8.06	0.875	-0.35	7.71	7.80
	5 (c)	8.17	0.835	-0.46	7.71	7.68
	7 (c)	8.06	0.870	-0.36	7.70	7.78
	1	7.41	1.010	+0.03	7.44	7.52
	3	7.68	0.923	-0.21	7.47	7.47
	5	8.17	0.864	-0.38	7.79	7.75
	3 (d)	7.68	0.923	-0.21	7.47	7.13
	5 (d)	8.17	0.863	-0.38	7.79	7.45
	7	8.06	0.766	-0.64	7.42	7.42
	5 (c)	8.17	0.750	-0.69	7.48	7.40
	7 (c)	8.06	0.767	-0.64	7.42	7.42

(a) See Table III and Text. (b) Charge density of C atom bearing the methyl group. (c) Refers to 5,7-dimethyl compound. (d) Refers to 3,5-dimethyl compound.

served chemical shifts of the corresponding protons. The difference between these two values is designated as D and represents the semi-empirical parameter to be employed in the calculations of the proton shielding values for the various polyazaindenes.

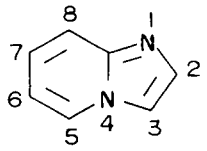
The ring-current contribution for each of the protons in pyrrocoline, as calculated by the dipole model of Pople is given in Table I.

It is of some interest to note that the agreement between the calculated and observed chemical shifts of the pyrrocoline protons is quite good, even though the calculations of the ring-current contribution are based upon the dipole model approach (8) and the charge densities were obtained by the HMO method. The larger discrepancies for the protons in the vicinity of the nitrogen atom are almost certainly due to the inductive and/or direct field effect of this heteroatom.

CALCULATIONS OF THE CHEMICAL SHIFTS OF VARIOUS POLYAZAINDENES:

Imidazo[1,2-a]pyridine (II).

We would anticipate that the replacement of C_1 of pyrrocoline (I) by a nitrogen atom should strongly affect the chemical-shift of the proton on C_2 due to the anisotropy contribution of this heteroatom. The



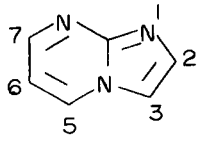
II

anisotropy contribution should diminish rapidly with the distance between the heteroatom and the proton in question, since it depends upon R^{-3} (where R is the distance between the two atoms being considered). The data presented in Table II are in substantial agreement with these expectations.

We find a satisfactory correlation between the calculated and predicted chemical-shifts for all of the protons in imidazo[1,2-a]pyridine with the exception of the proton on C_2 which resonates at a more deshielded position than that calculated in the absence of N_1. The discrepancy (-0.80 ppm) can be largely attributed to the anisotropy effect of N_1.

Imidazo[1,2-a]pyrimidine (III).

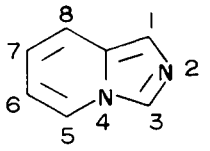
The replacement of C_8 and of C_1 of pyrrocoline by nitrogen atoms affords a system (imidazo[1,2-a]-pyrimidine) which is related to the imidazo[1,2-a]-pyridines insofar as the N_1 anisotropy is concerned. We would predict that the difference between the calculated and observed values of H_2 should be the same as that found for imidazo[1,2-a]pyridine. The anisotropy contribution of N_8 would present itself by a discrepancy between the calculated and observed chemical-shift of H_7. We do indeed find (Table II), that the difference between the calculated and observed chemical-shifts for H_2 and H_7 (-0.88 ppm and -0.90 ppm, respectively) are essentially the same.



III

Imidazo[1,5-a]pyridine (IV).

The N_2 anisotropy effect is expected to cause a difference in the calculated and observed chemical shifts of the protons on C_1 and on C_3. The variance for H_1 (0.86 ppm) is of the same order of magnitude as that observed for the protons on the carbon atom



IV

adjacent to the heteroatom in all of the previously described compounds. The N_2 anisotropy contribution to H_3 (-0.52 ppm) is less than the corresponding contribution to H_1.*

The magnitude of the anisotropy effect of a pyridine-type nitrogen atom was estimated by Nakagawa, *et al.* (9) to be about 0.8 ppm and by Tori (10) to be about 0.35 ppm. The former of these values is of the same order of magnitude as the same effect for the sp^2 nitrogen atoms in the five-membered rings of the systems discussed in this communication, and suggests that the value (0.25 ppm) derived by Makisumi, Watanaba and Tori (11) is somewhat low.

CHEMICAL SHIFTS OF THE METHYL PROTONS OF SOME METHYLPOLYAZAINDENES

The chemical-shifts of the protons of various methylpolyazaindenes can be calculated by the same semi-empirical approach as is used for the calculation of the chemical shifts of the ring protons.

By choosing the various methylpyrrocolines as reference compounds, it should be possible to predict the chemical-shifts of the methyl protons from changes in the charge-distribution alone.

We have calculated the charge densities of the carbon atoms bearing the methyl groups by employing the concept developed by Matsen (12) and

*It has been suggested (J. H. Reynolds, THE EFFECTS OF NITROGEN SUBSTITUTION ON AROMATICITY, Ph.D. Thesis, University of Washington, 1964) that there should be no difference between the *N*-anisotropy contribution (-0.6 ppm) to a proton on a carbon flanked by either one or two sp^2 nitrogen atoms.

Stevenson (13). These authors treat a methyl group as a "pseudo-heteroatom" which contributes a pair of electrons to the π-system. Thus, we are "extending" the π-system of the rings by the addition of the methyl group.

The charge-field effect equation relates the chemical-shifts to the resonance positions of the protons in benzene. Since we are utilizing the methylpyrrocolines as reference compounds, the difference between the observed chemical-shifts of the methyl protons and the charge-effect of the methylpyrrocolines would correspond to the summation of the effects of the ring-current *and* the "standard" reference, thus we can use this value (D_{methyl}) as the parameter to be employed for the calculation of the chemical-shifts of the methyl protons of the various polyazaindenes.

The agreement between the calculated and predicted resonance positions is quite good (Table IV). The only significant discrepancy is observed in 3,5-dimethylimidazo[1,5-a]pyridine. This is certainly not unexpected in view of the possible *peri* interaction between the two methyl groups.

It is also of some interest to mention that the presence of nitrogen atoms adjacent to the methyl group bearing carbon atom does not appear to significantly effect the chemical shifts of the methyl protons by its anisotropy effect. This might well be explained by considering that anisotropy effects fall off rapidly (R^{-3}) with the distance between the proton under study and the anisotropic center.

EXPERIMENTAL

Imidazo[1,5-a]pyridines.

These compounds were prepared by the method of J. D. Bower and G. R. Ramage (*J. Chem. Soc.*, 2834 (1955)). Two of these compounds have not previously been reported.

5-Methylimidazo[1,5-a]pyridine: pale yellow oil, b.p. 112-113/0.7 mm; B·CH_3I: m.p. 190°.

Anal. Calcd. for $C_9H_{11}N_2I$: C, 39.44; H, 4.04; N, 10.22. Found: C, 39.51; H, 4.13; N, 9.82.

3,5-Dimethylimidazo[1,5-a]pyridine: m.p. 62-63°; B·CH_3I: m.p. 218°.

Anal. Calcd. for $C_9H_{10}N_2$: C, 73.94; H, 6.84; N, 19.16. Found: C, 73.83; H, 6.84; N, 19.34.

Pyrrocolines.

These substances were prepared by the method of D. O. Holland and J. H. C. Nayler (*J. Chem. Soc.*, 1657 (1955)) by Mr. R. Brumbaugh of this department.

Calculations.

Charge-field effects.

The C-C distances were taken to be 1.40 Å. The C-H bond distances used were 1.08 Å. The charge-field effect on the methyl hydrogens was calculated by taking the distance from the ring carbon atom bearing the methyl group in question, to the H on this group. The value employed was 2.12 Å. Since the distances from the methyl group protons to carbon atoms other than the carbon bearing the methyl groups are significantly larger than in the ring-proton calculations, the charge-field effect contributions of these atoms were neglected.

Ring-Current Effects.

The 6-membered and 5-membered rings were assumed to be regular hexagons and pentagons, respectively. The sides were taken to be 1.40 Å each.

NMR Spectra.

The nmr data reported in Tables II, III and IV were obtained in our laboratories and are published in detail elsewhere (14-17). Some of these spectra have also been reported by Black and coworkers (18). Our spectra are in essential agreement with theirs, except for the τ_7 position in 1-azaindolizine and the τ_6 position of 2-azaindolizine which are reported in their Table 3 by 1 τ unit too high and 1 τ unit too low, respectively, and appear to be typographical errors. The nmr data of pyrrocoline used in this paper are those of Black and coworkers (18). The data of the methylpolyazaindenes refer to deuteriochloroform solutions (5-6%), all other data are for dilute carbon tetrachloride solutions.

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