Correlation of Ring Nitrogen Substituents with Carbon-13 Nuclear Magnetic Resonance Data in Azoloazines

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Carbon-13 nuclear magnetic resonance data have been acquired on 22 azoloazines. Chemical shifts have been correlated by a step-wise linear multiple regression with nitrogen substituents in both the 5- and 6-membered rings using pyrrolo[1,2-*a*]pyridine as the reference for chemical shift correlation. The data demonstrate that a highly correlated set of chemical shift parameters exist. Nitrogen substitution in the five-membered ring produces larger cross-ring effects than are oberved in the five-membered ring when substitution occurs in the six-membered ring. Within the six-membered ring a constant *para*- substituent parameter is noted. The *meta*- and *para*- parameters are more complex and fall into two groups for each parameter. Within the five-membered ring, a highly regular chemical shift pattern is observed which reflects an attenuated perturbation from nitrogen substitution in the six-membered ring.

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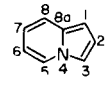
I. Introduction.

Indolizine and its aza analogs represent 10 π-electron systems, isoelectronic with the indenyl anion (see Table I). In general, these systems are regarded as heteroaromatic, mainly from proton nmr spectroscopy studies [1]. Initial studies on chemical reactivity also supports this view, although some recent investigations on particular azaindolizines revealed that their "aromatic stability" is not as high. Examples of ring opening, isomerization, borohydride reduction or epoxidation of double bonds and, recently, the 1,3-dipolar cycloaddition of diazoalkanes to the C(7)-C(8) double bond [2], based on knowledge collected from our previous ^{13}C nmr studies in this area [3,4], have been described and x-ray investigations on azolopyridazines show considerable bond delocalization [5]. Therefore, azaindolizines are better described as bicyclic systems consisting of a π-excessive and a π-deficient ring. This fits well with the observed chemical reactivity since, in general, electrophilic substitutions occur in the five-membered part and the nucleophilic substitutions in the six-membered ring of these bicyclic systems. Early studies [6-10] on benzimidazole, purine, quinoline, isoquinoline, and other related nitrogen heterocycles demonstrated the presence of cross-ring polarization effects before it was observed in indolizine and its aza analogs. Finally, it should be emphasized, that the number and positions of extra nitrogen atoms in indolizine greatly influence the reactivity.

Carbon-13 magnetic resonance studies have been used successfully in the azaindolizine series for investigating the aromatic properties of pyrrolo[1,2-*a*]pyridine and its 1-,2-,3- and 8-aza analogs [11]. Furthermore, carbon-13 nmr techniques have been used to study the site of proto-

Table 1

Systems



Compound Number	Extra nitrogen at position	Name	Prepared according to lit Ref
1	—	Pyrrolo[1,2-*a*]pyridine (Indolizine)	25
2	1	Imidazo[1,2-*a*]pyridine	26
3	2	Imidazo[1,5-*a*]pyridine	27
4	3	Pyrazolo[1,5-*a*]pyridine	28
5	1,2	1,2,4-Triazolo[4,3-*a*]pyridine	29
6	1,3	1,2,4-Triazolo[1,5-*a*]pyridine	14
7	1,5	Imidazo[1,2-*b*]pyridazine	30
8	1,7	Imidazo[1,2-*a*]pyrazine	31
9	1,8	Imidazo[1,2-*a*]pyrimidine	32
10	2,3	1,2,3-Triazolo[1,5-*a*]pyrmidine	41
11	1,2,3	Tetrazolo[1,5-*a*]pyridine	33
12	1,2,5	1,2,4-Triazolo[4,3-*b*]pyridazine	34
13	1,2,6	1,2,4-Triazolo[4,3-*c*]pyrimidine	35
14	1,2,7	1,2,4-Triazolo[4,3-*a*]pyrazine	31
15	1,2,8	1,2,4-Triazolo[4,3-*a*]pyrimidine	36
16	1,3,5	1,2,4-Triazolo[1,5-*b*]pyridazine	14
17	1,3,6	1,2,4-Triazolo[1,5-*c*]pyrimidine	19
18	1,3,7	1,2,4-Triazolo[1,5-*a*]pyrazine	14
19	1,3,8	1,2,4-Triazolo[1,5-*a*]pyrimidine	37
20	1,2,3,5	Tetrazolo[1,5-*b*]pyridazine	38
21	1,2,3,6	Tetrazolo[1,5-*c*]pyrimidine	39
22	1,2,3,8	Tetrazolo[1,5-*a*]pyrimidine	40

nation or quaternization of several azaindolizines and from the obtained data it could be concluded that the N-1 tautomer is the predominant species [3]. This technique has proven to be very useful for structural assignment of hydroxy-azaindolizines. The "hydroxy form" has been shown to be the predominant species in neutral solution and, from the chemical shift data, information regarding the conformation of some 8-hydroxy- and 8-methoxy analogs have been obtained [4].

Although proton magnetic resonance has been used frequently in connection with the structural assignments of azaindolizines, small differences in chemical shifts often do not allow unambiguous assignments. This is particularly the case in the fused *s*-triazoloazines. The synthesis may afford either the kinetically favoured systems of the type **5** and **12-15** (see Table 1) or the thermodynamically more stable isomers of the type **6** and **16-19** [12-14]. Differences in chemical shifts between H_3 and H_2 in these systems are usually very small, *i.e.*, on the order of about 0.5 ppm. Therefore, for the synthetic compounds of the above mentioned types and when considering the posibility of isomerization as well as eventual non-availability of an authentic specimen of the other possible isomer the structure assignments may not be straightforward. For example, reaction between some amino or diazoheterocycles and 1,3-dicarbonyl compounds with subsequent cyclization can yield two isomeric systems in addition to positional isomers [15-18]. That the rearrangement may occur under very mild reaction conditions could be shown in the case of attempted synthesis of *s*-triazolo[4,3-*c*]pyrimidine **13** when only the isomeric *s*-triazolo[1,5-*c*]pyrimidine **17** was isolated [19-20]. The above observations are of course valid also for more complex tricyclic or polycyclic systems as, for example, azolopyridopyrimidines [21-22]. There are several other examples where proton nmr evidence may not always be conclusive and carbon-13 magnetic resonance is to be expected to give better results. Among others, this technique could be useful to study (3 + 2) photocycloaddition to *s*-triazolopyridazines [23] or telesubstitution reactions [24].

In view of the above mentioned results it appears appropriate to report on the carbon-13 chemical shifts of various azaindolizines for purposes of identification. Moreover, a study of the effects of number and position of ring nitrogens to the carbon-13 chemical shifts is made.

II. Experimental Results.

A. Compound Preparation.

The investigated compounds were prepared according to literature as quoted in Table 1.

B. Spectroscopic Techniques.

All compounds, as designated in Table I, were dissolved in reagent grade DMSO or DMSO-d_6. Dioxane was added (approximately 5% volume/volume) as the internal standard. The ^{13}C spectra were recorded on a Varian XL-100-15 spectrometer. Peak assignments were made by a combination of single frequency decoupling for most of the protonated carbons based on known proton chemical shifts and by means of correlation diagrams for the quaternary carbons and those methine resonances that could not be clearly assigned be decoupling techniques. Large systematic shifts in the ^{13}C nmr data were often clearly definitive as described below. Proton spectra were obtained on a Varian EM-390 and Jeol JNM 60-HL instruments.

The carbon-13 chemical shifts of all compounds studied are given in Table II.

Table II

C-13 Chemical Shifts, $\delta 13_C$ (ppm) [a]

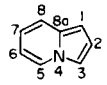
Compound No.	1	2	3	5	6	7	8	8a
1	99.44	114.07	113.01	125.61	110.44	117.16	119.56	133.35
2	—	133.2	112.9	126.5	111.7	124.1	116.9	145.0
3	120.0	—	129.1	123.8	112.8	119.8	118.5	130.8
4	97.4	132.5	—	129.6	112.7	124.2	118.9	140.6
5	—	—	136.5	125.1	113.5	128.0	115.0	148.6
6	—	153.8	—	129.1	114.2	130.1	116.2	150.0
7	—	133.5	116.7	—	143.8	117.3	125.5	138.4
8	—	135.0	114.5	120.7	128.7	—	142.9	140.2
9	—	135.1	112.7	136.0	109.4	150.9	—	148.9
10	126.7	—	—	126.3	116.5	126.5	118.8	134.4
11	—	—	—	126.5	117.4	133.2	115.3	148.2
12	—	—	139.0	—	146.6	121.2	124.6	143.3
13	—	—	141.0	141.8	—	136.4	110.7	148.2
14	—	—	137.1	118.1	129.2	—	143.5	144.4
15	—	—	135.7	133.9	109.9	155.4	—	152.8
16	—	152.5	—	—	144.6	123.0	125.9	144.1
17	—	155.6	—	142.3	—	144.4	111.7	151.1
18	—	154.5	—	122.7	131.7	—	142.9	145.6
19	—	155.8	—	137.3	110.9	155.5	—	154.7
20	—	—	—	—	148.4	125.9	125.6	143.2
21	—	—	—	140.4	—	146.0	110.0	149.0
22	—	—	—	135.1	113.4	158.9	—	154.4

[a] Relative to TMS: in DMSO, except for **1** (in deuteriochloroform).

III. Chemical Shift Correlation.

The chemical shifts for the twenty two compounds studied have been linearly correlated with the position of the nitrogen atoms by means of a standard step-wise multiple regression program. The linear regression parameters are given in Table III. The constant terms for C_2, C_3, C_5, C_6,

Table III



Linear Regression parameter of Azoloazines

	C_2	C_3	C_5	C_6	C_7	C_8	C_{8a}
F Ratio	859.0	1491.0	379.0	764.3	356.0	976.8	23.0
R	0.9997	0.9998	0.9978	0.9987	0.9974	0.9991	0.9620
Standard Error of Estimate	0.6	0.4	0.6	0.9	1.2	.55	2.3
Substituent Shift Parameters							
N_1	19.4 ± 0.8	0.3 ± 0.1	0.3 ± 0.4	1.1 ± 0.6	6.9 ± 0.9	−3.1 ± 0.4	13.1 ± 1.6
N_2		22.9 ± 0.3	−2.1 ± 0.3	2.3 ± 0.4	2.8 ± 0.6	−0.7 ± 0.3	−0.2 ± 1.1
N_3	19.9 ± 0.4		2.2 ± 0.3	2.7 ± 0.4	5.6 ± 0.6	−0.1 ± 0.3	3.5 ± 1.0
N_5	−0.5 ± 0.6	3.1 ± 0.4		31.7 ± 0.6	−6.8 ± 0.9	9.6 ± 0.4	−5.7 ± 1.6
N_6	2.1 ± 0.8	0.3 ± 0.5	13.5 ± 0.5		9.7 ± 1.1	−4.7 ± 0.5	0.3 ± 2.0
N_7	1.2 ± 0.6	1.1 ± 0.4	−6.4 ± 0.4	16.5 ± 0.7		27.1 ± 0.4	−4.0 ± 1.8
N_8	2.0 ± 0.6	−0.5 ± 0.4	9.0 ± 0.4	−3.3 ± 0.6	26.3 ± 0.9		4.7 ± 1.6
Constant	114.1	113.0	126.4	110.6	117.7	119.3	133.0

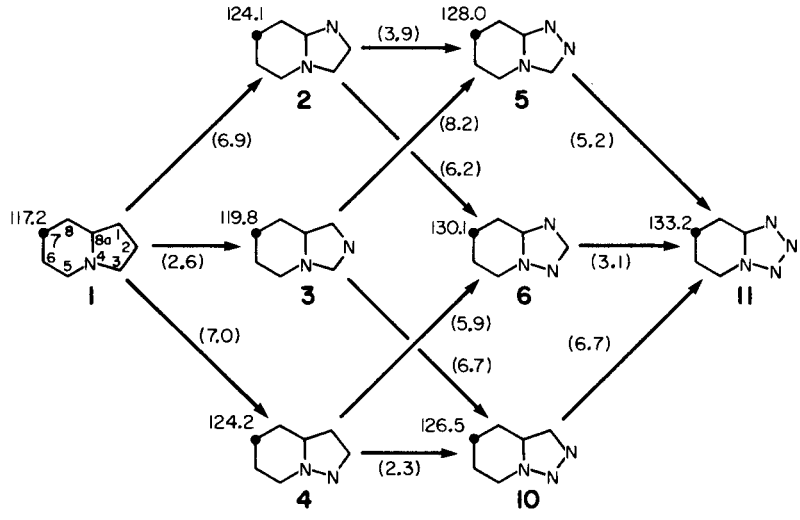


Figure 1. Example of use of the regression parameters in Table III to predict chemical shifts at position C-7. Numbers in parenthesis are the substituent effects between pairs. For the pair differing only in a N_1, the substituent value of 5.9, 6.7, 6.9, 8.2 were found (four arrows with positive slopes). Those differing only in a N_2 give 2.3, 2.6, 3.1, 3.9 (four horizontal connective arrows); and for N_3 the values are 5.2, 6.2, 6.7, and 7.0 (four arrows with negative slopes). These values indicate both the extent of similarity and the scatter in data used to obtain regressional parameters.

C_7, C_8 and C_{8a} are nearly identical to the individual chemical shift values for indolizine (see Table II) which was taken as the base ring system to which all other nitrogen analogs were compared. The F ratios and correlation coefficients are indicative of the highly correlated nature of the data with the largest error found at C_{8a}. Previous studies [6-10] have demonstrated that parameterization at bridgehead positions are less highly correlated than other ring carbons. This effect is apparently due to the complications associated with manifestation of electronic effects in both rings as sensed by the bridghead carbon.

The data correlations in Table III are linear in a step wise manner with each additional nitrogen that is added to the indolizine ring. The addition of a nitrogen to either the 5- or 6-membered ring (or both) produces relatively weak electronic perturbations and, thus, additivity effects are preserved.

An illustrative example of the use of the data in Table III will be useful in understanding the chemical shifts in the compounds studied. In Figure 1, we illustrate the use of the regression parameters in predicting the chemical shift of C-7 in compounds **1**, **2**, **3**, **4**, **5**, **6**, **10**, and **11**. The maximum error in the seven compounds (with **1** used as the basic ring system for comparison) is ±1.3 ppm. Similar comparisons can be made for any of the other carbons. In the stepwise regression analysis it is clear that the order in which *N*-substitution occurs in the 5-membered ring does not effect the shift at C-7. The minor discrepancies that are noted arise from the inherent error in the determination of the coefficient. From these data, it appears that C-7 is particularly sensitive to cross-ring substituent effects (6.9, 2.6, and 7.0 ppm, respectively for N_1, N_2, and N_3 substitution), more so than C-5, C-6, or C-8.

Substitution in the six-membered ring, as expected, produces much larger effects at the *ortho*-position of nitrogen substitution. These substitution effects are given in Table IV. The *ortho*-shift effects appear to fall into three general groups based on magnitued (26.3, 27.1, and 31.7; 9.7, 13.5, and 16.5, and 4.7 ppm at C-8a). Nitrogen substitution at C-6 produces the smaller *ortho*-substituent effects (9.7 and 13.5 ppm) than those at 5, 7, and 8 except for the anomalous value at C-8a.

The *meta*-substituent effects are of comparable value and are considerably smaller than the *ortho*-values and of opposite sign. There are only three values for the *para*-substituent effects and these are of positive sign. The *para*-effect at C-8a (0.3 ±2.0 ppm) appears to be anomalous although the two examples of meta-parameters at C-8a (−5.7 and −4.0 ppm) are not significantly different from the other *meta*-shift effects. The unusually low values of *ortho*- and *para*-effects at C-8a reflect the unusual electronic environment experience by C-8a as a bridgehead carbon which serves as the probe for cross-ring effects.

Table IV

	Position of Nitrogen	Position of Carbon	Substituent Effect
ortho			
	5	6	31.7 ± 0.6
	6	5	13.5 ± 0.5
	6	7	9.7 ± 1.1
	7	6	16.5 ± 0.7
	7	8	27.1 ± 0.4
	8	7	26.3 ± 0.9
	8	8a	4.7 ± 1.6
meta			
	5	7	−6.8 ± 0.9
	5	8a	−5.7 ± 1.6
	6	8	−4.7 ± 0.5
	7	5	−6.4 ± 0.4
	7	8a	−4.0 ± 1.8
	8	6	−3.3 ± 0.6
para			
	5	8	9.6 ± 0.4
	8	5	9.0 ± 0.4
	6	8a	0.3 ± 2.0

In the case of those compounds which have nitrogen substituents in the six-membered ring, the linear regression parameters tend to be less than those cross-ring effects produced in the six-membered ring by substitution in the five-membered ring. Three of the entries in Table V are essentially zero, within experimental error. Of the 15 regression parameters associated with shift changes in the six-membered ring produced by substitution in the five-membered ring, twelve are outside the range of experimental error.

Table V

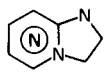
Effects of Nitrogen Substitution in the Six-Membered Ring on Carbon C-2 and C-3

Position of Nitrogen	C-2	C-3
5	−0.5 ± 0.6	3.1 ± 0.4
6	2.1 ± 0.8	0.3 ± 0.5
7	1.2 ± 0.6	1.1 ± 0.4
8	2.0 ± 0.6	−0.5 ± 0.4

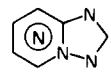
The preceeding discussion demonstrates that the chemical shifts at C-1, C-2, C-3, are dominated by the number and location of the nitrogen substituents in the five-membered ring and, for convenience, we can group the com-

pounds studied into four families as follows, where the position of the nitrogen in the six-membered ring is variable.

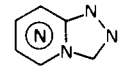
Scheme I



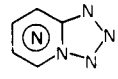
2, 7, 8, 9



6, 16, 17, 18, 19



5, 12, 13, 14, 15



11, 20, 21, 22

A previous report [4] has shown that hydroxyl and methoxyl substituents in the six-membered ring of azoloazines produce only minor perturbations of the chemical shift values in the five-membered ring.

IV. Conclusions.

Nitrogen substitution patterns in azaindolizines have been systematically studied and a highly correlated set of data has been derived. These data demonstrate that nitrogen substitution in the five-membered ring produces larger cross-ring effects than are observed in the five-membered ring when subsitution occurs in the six-membered ring. Within the six-membered ring, the *para*-effect is constant ($\sim \pm 1$ ppm except for the anomaly at the bridgehead carbon). The *meta*-effect appears to fall into two groups of different but comparable magnitudes (5.7 to 6.8 ppm and 3.3 to 4.7 ppm). The *ortho*-substituent is more complex and is expressed by a range of chemical shifts that group by magnitudes into two ranges (26.3 to 31.7 and 9.7 to 16.5 ppm) if the anomalous effect at 8a (4.7 ppm) is not included. Within the five-membered ring, one observes a highly regular chemical shift pattern which reflects an attenuated perturbation from nitrogen substitution in the six-membered ring.

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