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NMR SPECTRA AND π-ELECTRON DENSITIES OF SOME IMIDAZO(1,2-a) PYRIDINES

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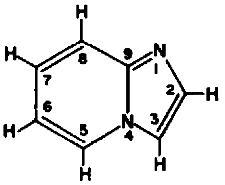
Abstract—As part of an extensive investigation of ten-π-electron nitrogen heterocyclic compounds, imidazo(1,2-a)pyridine and several of its mono- and dialkylated derivatives were prepared. The NMR spectra of these compounds were analyzed and a qualitative correlation between the proton chemical shifts and the π-electron densities of the carbon atoms bearing these protons is discussed.

In the course of studies on the chemistry of ten-π-electron systems containing bridgehead nitrogens, we have examined the NMR spectra of imidazo(1,2-a)pyridine and several of its mono- and dialkylated derivatives.

In this paper we wish to report the analyses of these spectra, as well as some correlations between π-electron densities and the chemical shifts of the various protons.

In order to permit a complete analysis of the spectrum of imidazo(1,2-a)pyridine (I) it is necessary to establish the chemical shifts of the six different protons.[1] This cannot be done with any degree of certainty without taking recourse to comparison with derivatives of I.



I

Chemical shifts

The most prominent peaks in the spectrum of I are two doublets, which by first-order analysis are ascribable to H_2 and H_3. These peaks are indeed absent in the 2,3-dimethyl derivative.

A decision as to which of these peaks is due to H_2 and H_3, respectively, can be arrived at by inspection of an expanded spectrum of I. The more shielded "doublet" (456 c/s)[2] shows secondary splitting ($J_{35} = 0{\cdot}7$ c/s) which is also present in the 2-methyl and 2-ethyl compounds but is absent in the 5-methyl compound; thus the 460 c/s peak is ascribable to H_2.

The most deshielded proton appears as two apparent triplets centered at 483 c/s. These triplets are absent in the 5-methyl and 5,7-dimethyl compounds. Consequently, these peaks are due to H_5.

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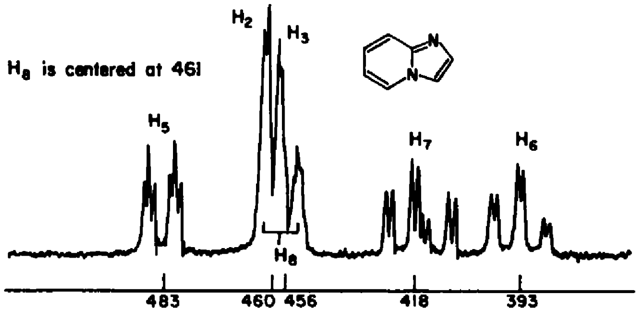
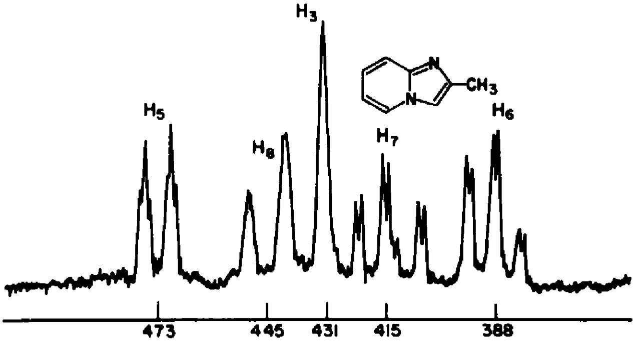
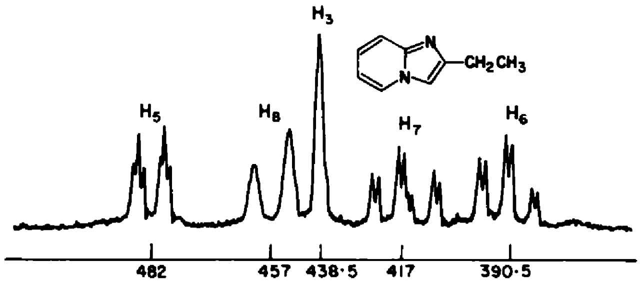
[1] The protons are labelled as indicated in structure I.

[2] The line positions are given in c/s downfield from TMS, all measurements were performed at 60 MC/s.







A poorly defined triplet integrating for 1/2 proton appears to be the counterpart of a similar triplet covered by H_2 (which integrates to 1 1/2 protons). These two triplets are centered at 461 c/s. Both of these triplets are clearly visible in the 2-methyl and 2-ethyl compounds, where the H_2 interference has been removed. In the 2,3-dimethyl compound, one of the H_5 triplets is covered by one of the H_8 triplets. The 8-methyl compound is devoid of these triplets; thus, H_8 is assigned to these peaks. This leaves H_7 and H_6 to be assigned. The two remaining multiplets, centered at 418 c/s and 393 c/s, respectively, are clearly part of an ABXY system.[3] These same multiplets are present in the 2-methyl, 2-ethyl and in the 2,3-dimethyl compounds, showing the absence of any significant coupling between the five-ring protons and H_7 and/or H_6.

The assignment of the multiplet centered at 418 c/s to H_7 and that at 393 c/s to H_6 will become evident as the coupling constants are evaluated in the next paragraph.

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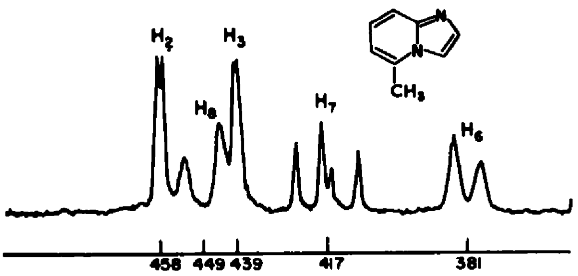
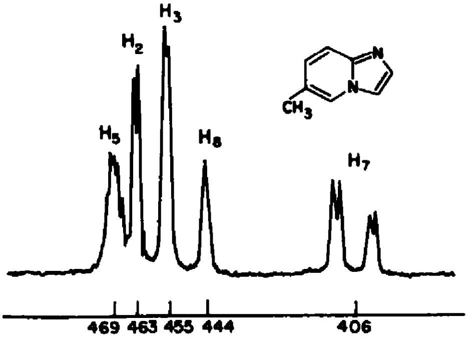
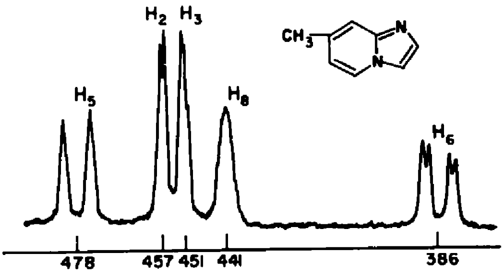
[3] Two excellent examples of such an ABXY system are found in indazole and in quinoline (P. J. Black and M. L. Heffernan, *Austr. J. Chem.* 16, 1051 (1963); *Ibid* 17, 558 (1964).







Coupling constants

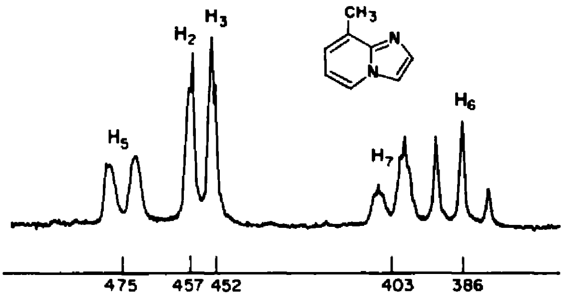
The J_{23} coupling constant of 1·2 c/s is self-evident from the spectra of the compounds unsubstituted in the five-membered ring.

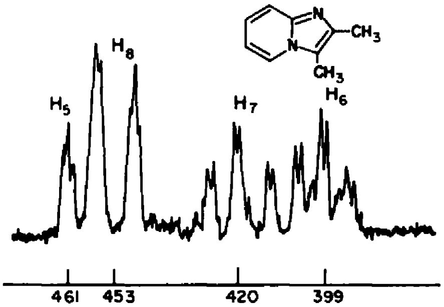
The secondary splitting of H_3 due to H_5 (0·5 c/s) is clearly shown by an expanded spectrum of the H_3 proton of those compounds having no substituents in either position 3 or 5 of the imidazo(1,2-a)pyridine. Unfortunately, the H_5 proton peaks are too complicated to permit the assignment of J_{35} from them.

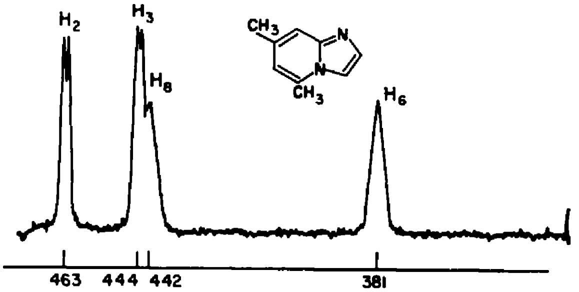
The absence of any coupling between H_2 and H_3 is demonstrated by the identity of the H_3 splitting patterns of the unsubstituted compound with those of the 2-methyl, 2-ethyl and 2,3-dimethyl compounds.

The coupling between H_6 and H_5 ($J = 6·5 - 7·2$ c/s) is obtainable from second-order splitting rules,* and at the same time identifies H_6 as resonating at 393 c/s. The J_{78} coupling constant ($J = 9·0 - 9·4$ c/s) is equally readily identifiable from first-order splitting rules as applied to the various spectra. This coupling constant also identifies H_7 as resonating at 418 c/s. The spin-spin coupling between protons H_7 and

* An argument similar to that used for obtaining J_{58} can be used.

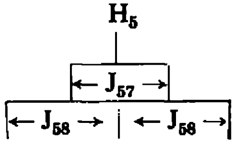






H_6 follows readily from an analysis of the H_7 and H_6 multiplets. Coupling constants J_{57} and J_{68} are identifiable by a comparison of the spectra of the unsubstituted compound with the 6-methyl and 7-methyl compounds, respectively.

The long range H_5-H_8 coupling requires more vigorous discussion. It is obtained from an expanded NMR spectrum of the protons in the six-membered ring. The analysis of one of the two triplets is as follows:



A similar spectrum (for one branch of the triplet) is obtained for H_8. The H_5-H_3 coupling is not discernable on this expanded rather broad peak.

Analysis of the various methyl compounds confirms and further elaborates the coupling constant assignments.

It is of some interest that the methyl groups in positions 2, 3, 6, 7 and 8 are coupled to one of the ring protons, as evidenced by their doublet nature.

The methyl group in the 2-methyl compounds (144 c/s) is coupled to H_3 and not to H_8 since the methyl groups in the 2,3-dimethyl compound are singlets.

The methyl group in the 6-methyl compound is split into a doublet ($J = 1{\cdot}1$ c/s). That the coupling is due to H_5 and not to H_7 is evidenced by the fact that H_7 is only a doublet with each member split into another doublet due to H_7-H_5 coupling.

The splitting of the methyl group in the 7-methyl compounds ($J = 0{\cdot}8$ c/s) is not due to H_6 since H_6 is doublet ($J_{56} = 7{\cdot}2$) with each member of the doublet further split by H_8 ($J = 1{\cdot}4$ c/s). H_8 is a complicated multiplet suggesting that it is indeed coupled to the methyl group.

The methyl group in the 8-methyl compound is present as a doublet ($J = 1{\cdot}0$ c/s). This grouping is in all likelihood coupled to H_7 since H_7 is a complicated multiplet.

The methyl positions in the 5,7-dimethyl compound (133 and 139 c/s, respectively) are obtainable by comparing them with the methyl group-ring proton couplings in the 5- and the 7-methyl compounds (resonating at 134 and 132 c/s, respectively). The 7-methyl group in both the mono- and the disubstituted compounds is split into doublets ($J = 0{\cdot}8$ c/s). The 5-methyl group is not split in either the mono- or the disubstituted compounds.

The various chemical shift values, as well as coupling constants, are listed in Table 1.

COMPARISON OF CHEMICAL SHIFTS WITH π-ELECTRON DENSITIES

The inadequacy of the ring-current model to predict NMR spectra has been repeatedly established.[4] It became of interest to compare the chemical shift positions of the different protons of the various imidazo(1,2-a)pyridines with the π-electron densities which we had calculated for purposes to be discussed in a forthcoming paper.

As will become clear in the following discussion, there is a certain semi-quantitative relationship between the proton chemical shifts and the π-electron densities on the carbon bearing the respective protons.[5]

One might anticipate that the proton attached to the lowest π-electron-density carbon would be the most deshielded proton of a given ring, in any polynuclear aromatic system, while the highest π-electron-denisty carbon would tend to yield the most shielded proton.

The five-membered ring protons

The lowest π-electron density of the two protons in the five-membered ring is always found at H_2. The chemical shift position of this proton is accordingly found at a higher deshielded position than the H_3 proton in all compounds tested (Table 2). This relationship holds for π-electron densities calculated by the conjugation model, as well as hetero-model[8] LCAO method for the methylimidazo(1,2-a)-pyridines.

The six-membered ring protons

The correlation of the protons in the six-membered ring with the π-electron densities of the carbon atoms bearing these protons is, unfortunately, not as complete. The H_8 proton does not fit the correlation satisfactorily. However, if one does not

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[4] W. G. Schneider, H. J. Bernstein and J. A. Pople, *J. Amer. Chem. Soc.* **80**, 3497 (1958).

[5] A related study on azulene has been published (cf. Ref. 4).

TABLE 1. SUMMARY OF CHEMICAL SHIFTS AND COUPLING CONSTANTS OF IMIDAZO(1,2-a)PYRIDINES*

Chem. shifts (c/s)	Parent	2-methyl	5-methyl	6-methyl	7-methyl	8-methyl	2-ethyl	2,3-dimethyl	5,7-dimethyl
H_7	418	415	417	406	—	403	417	420	—
H_6	393	388	381	—	386	386	390·5	399	381
H_5	483	473	—	469	478	475	482	461	—
H_8	461	445	449	444	441	—	451	453	442
H_2	460	—	458	463	457	457	—	—	463
H_3	456	431	439	455	451	452	438·5	—	444
Substituent position		144(CH_3)	134(CH_3)	119(CH_3)	132(CH_3)	151(CH_3)	81(CH_3) 117(—CH_2—)	141(2-CH_3) 130(3-CH_3)	139(5-CH_3) 133(7-CH_3)
coupling consts. (c/s)									
J_{76}	6·6	6·6	7·0	—	—	6·7	6·6	6·6	—
J_{78}	9·0	9·0	9·0	9·2	—	—	9·0	9·4	—
J_{56}	6·8	6·8	—	—	7·2	6·5	6·8	7·2	—
J_{57}	1·3	1·4	—	1·6	—	1·4	1·4	1·3	—
J_{68}	1·3	1·3	1·2	—	1·4	—	1·3	1·4	—
J_{23}	1·2	—	1·2	1·2	1·2	1·2	—	—	1·2
J_{35}	0·7	0·7	—	0·5	0·5	0·7	0·7	—	—
J_{58}	1·3	0·0	—	0·0	0·0	—	0·0	0·0	—
J_{83}	0·0	--	0·0	0·0	0·0	—	—	—	0·0
$J_{6Me,5}$	—	—	—	1·1	—	—	—	—	—
$J_{8Me,7}$	—	—	—	—	—	1·0	—	—	—
$J_{7Me,8}$	—	—	—	—	0·8	—	—	—	0·8
$J_{7Me,6}$	—	—	—	—	0·0	—	—	—	0·0
$J_{2Me,3}$	—	0·8	—	—	—	—	—	—	—
$J_{5Me,6}$	—	—	0·0	—	—	—	—	—	0·0

* Protons are labelled as in structure I. The coupling between the methyl protons and the ring protons are indicated $J_{\text{methyl position, ring proton number}}$.

TABLE 2. π-ELECTRON DENSITY CORRELATION WITH THE CHEMICAL SHIFT POSITIONS OF THE FIVE-MEMBERED RING PROTONS

Substituent	H_2(c/s)	qr(conj)	qr(hetero)	H_3(c/s)	qr(conj)	qr(hetero)
2-methyl	—	—	—	431	1·142	1·174
5-methyl	458	1·039	1·041	441	1·113	1·115
6-methyl	463	1·037	1·038	455	1·114	1·115
7-methyl	452	1·039	1·041	447	1·115	1·119
8-methyl	457	1·037	1·038	452	1·112	1·112
5,7-dimethyl	445	1·041	1·046	426	1·115	1·121

consider this proton in the correlation, the order of increasing deshielding *vs* decreasing π-electron densities holds quite well.

The conjugation model calculations are in complete agreement with the above comments, while the π-electron density calculations obtained from the hetero-model method do not agree for the 6-methyl and the 8-methyl derivatives. It is, of course, not possible to assign any quantitative significance to these correlations.

Chemical shift differences due to electron density changes

It is well known[6] that replacement of a hydrogen in an aromatic ring by a methyl group causes an increase in the shielding of the proton on the carbon *ortho* to the substituted one.

We considered it reasonable that a correlation should exist between the change of the π-electron densities of this proton and its change in the chemical shift positions. Since we are dealing with changes only, rather than absolute values, this correlation would be expected to hold fairly rigidly.*

A comparison of the electron density changes of the *ortho* carbon atoms, all of which are numerically of the order of 0·015–0·085 for both the hetero-model and the conjugation model calculations, correlates well with increasing shielding of the protons on the *ortho* carbon atoms (7–25 c/s).

The protons on the carbon *para* to the methylated position are found at a higher field (5–19 c/s) which again agrees well with the π-electron density change on the corresponding carbon atom (0·01–0·08).

These correlations are readily discernible from Table 3.

SUMMARY

These results show that there is indeed a qualitative relationship between chemical shift positions in the NMR spectra and the π-electron densities on the carbon atoms bearing the protons under examination. While it is clear that the correlations are only of a qualitative nature, it is hoped that an expansion of these studies to other ten-π-electron nitrogen heterocyclics will extend these correlations. A recent paper by M. P. Schweizer, S. I. Chan, G. K. Helmkamp and P. O. Iso (*J. Amer. Chem. Soc.* **86**, 696 (1964)) discusses such a quantitative correlation between the excess charge densities in purine and the chemical shifts of the aromatic protons in this molecule. We are currently investigating the application of these calculations to our compounds.

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* The effect due to diamagnetic anisotropy changes in these nonalternant hydrocarbons should be less pronounced than that due to variation of the local charge densities (cf. Ref. 6, p. 256).

[6] J. A. Pople, W. G. Schneider and H. J. Bernstein, *High-resolution Nuclear Magnetic Resonance* p. 258, McGraw-Hill, New York (1959).

TABLE 3[7]. THE EFFECT OF METHYL GROUPS ON THE *ortho* AND *para* HYDROGEN ATOMS

2-methyl	Δqr- (conj.)	Δqr- (hetero)	c/s(subst.)	Δc/s	7-methyl	Δqr- (conj.)	Δqr- (hetero)	c/s(subst.)	Δc/s
ΔH_3	0·030	0·062	431	25·0	ΔH_8	0·012	0·052	436	16·0
					ΔH_6	0·096	0·024	382	11·0
5-methyl					8-methyl				
ΔH_6	0·028	0·055	382	11·0	ΔH_7	0·028	0·054	403	15·0
ΔH_8	0·012	0·035	451	12·0	ΔH_5	0·009	0·036	475	8·0
6-methyl					5,7-dimethyl				
ΔH_7	0·014	0·026	406	12·0	ΔH_6	0·040	0·081	381	12·0
ΔH_5	0·029	0·057	469	14·0	ΔH_8	0·045	0·085	477	19·0

EXPERIMENTAL

Syntheses of imidazo(1,2-a)*pyridines*. The imidazo(1,2-a)pyridines were prepared by the reaction of a properly substituted 2-aminopyridine with an α-halo-carbonyl compound by the procedure described by A. M. Roe, *J. Chem. Soc.* 2195 (1963).

Nuclear magnetic resonance spectra. The NMR spectra were obtained with a Varian A-60 Spectrometer (TMS as internal standard) and line positions were checked by the side-band technique. The spectra reported are for $CDCl_3$ solutions of approximately equal concentrations (50% vol/vol). No corrections to infinite dilution were applied since only relative shift changes were of importance and the bulk susceptibility of the various imidazo(1,2-a)pyridines was assumed to be the same.

LCAO calculations. The matrices for the calculations were solved with the aid of a program written by Dr. W. Brooks of the Ohio University Chemistry Department. The program employs the Jacobi method for the solution of the determinants. The parameters employed[8] are as follows:

(a) Auxiliary inductive parameters $C_{\alpha\dot{N}} = 0{\cdot}10$, $C_{\alpha\ddot{N}} = 0{\cdot}05$
(b) $h_{\dot{N}} = 0{\cdot}5$, $k_{C—X} = 0{\cdot}80$
(c) $h_{\ddot{N}} = 1{\cdot}5$, $k_{C—X} = 1{\cdot}00$
(d) The C_9 coulomb integral: $C_9 = \alpha_0 + 0{\cdot}06\beta_0$
(e) Conjugation model ($\equiv C—X—Z = C—C\equiv H_3$)
h_C and $h_X = -0{\cdot}1$, $k_{C—X} = 0{\cdot}80$
(f) Hetero model: $h_X = 4{\cdot}00$, $k_{C—X} = 0{\cdot}45$ (X = methyl group)

The justification for the use of the above parameter values, which are based on UV spectral correlations, will be discussed in a forthcoming paper. The complete π-electron density data for the various compounds is listed below.

π-ELECTRON DENSITIES (CONJUGATION MODEL)

Compound	Position number 1	2	3	4	5	6	7	8	9
Parent	1·462	1·036	1·112	1·482	0·947	1·022	0·976	1·017	0·954
2-Methyl	1·476	0·989	1·142	1·482	0·950	1·023	0·972	1·017	0·956
5-Methyl	1·467	1·039	1·113	1·491	0·898	1·050	0·967	1·035	0·954
6-Methyl	1·463	1·037	1·114	0·976	0·976	0·979	0·983	1·014	0·960
7-Methyl	1·469	1·039	1·115	1·487	0·945	1·034	0·925	1·043	0·953
8-Methyl	1·459	1·037	1·112	1·482	0·966	1·020	0·997	0·969	0·966
2,3-Dimethyl	1·479	1·017	1·092	1·489	0·951	1·024	0·976	1·017	0·961
5,7-Dimethyl	1·474	1·041	1·116	1·496	0·896	1·063	0·923	1·061	0·953

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[7] A positive value of Δqr indicates an electron density greater than that of the parent at the specified position. A positive value of Δc/s indicates a change to a chemical shift value numerically smaller than that of the parent compound.

[8] The basic set of parameters are those suggested by A. Streitwieser, Jr., *Molecular Orbital Theory, for Organic Chemists* p. 135, J. Wiley, New York (1961).

π-ELECTRON DENSITIES (HETERO MODEL) (*Contd.*)

	Position number								
Compound	1	2	3	4	5	6	7	8	9
2-Methyl	1·462	0·938	1·174	1·483	0·952	1·024	0·974	1·018	0·959
5-Methyl	1·472	1·041	1·115	1·496	0·840	1·077	0·964	1·051	0·954
6-Methyl	1·465	1·038	1·115	1·482	1·004	0·932	0·995	1·012	0·965
7-Methyl	1·476	1·041	1·119	1·491	0·941	1·046	0·875	1·068	0·952
8-Methyl	1·458	1·038	1·112	1·482	0·983	1·018	1·023	0·917	0·977
2,3-Dimethyl	1·491	0·999	1·073	1·494	0·958	1·026	0·984	1·017	0·972
5,7-Dimethyl	1·485	1·046	1·121	1·505	0·835	1·103	0·870	1·101	0·952

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We would also like to thank Dr. W. Brooks of this Department for making the computer program available to us.