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Structure and Protonation Study of the Imidazo[1,2-*a*]-Pyrimidine System in ^{1}H Nuclear Magnetic Resonance

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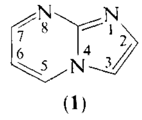
Abstract—The ^{1}H NMR spectra of imidazo[1,2-*a*]pyrimidine derivatives have been analysed to study the aromatic character and protonation behaviour of this system. By employing the 'ring current' model and calculations based on the coupled Hartree-Fock method it can be deduced that a large π-electron delocalisation exists in this heterocyclic system and affects the screening constant of the protons. Charge density schemes obtained by SCF techniques agree with the reactivity behaviour of these molecules.

A detailed study of protonation carried out by following the ^{1}H NMR spectra both in trifluoroacetic acid and in aqueous hydrochloric acid shows that the most probable site of protonation is N-1, but leaves open the possibility of a rapid exchange of one proton between N-1 and N-8.

THE CHEMICAL and spectroscopic behaviour of fused heterocycles with a bridgehead nitrogen atom has been extensively studied.[1–5] The nuclear magnetic resonance spectra of imidazo[1,2-*a*]pyridine and imidazo[1,2-*c*]-pyrimidines show that the electronic character of one ring determines the line position of the protons of the other ring mainly by a ring current effect. This has been qualitatively identified by a downfield effect on the imidazole protons due to the electronic deficient pyridine ring[1] and probably of the pyrimidine ring,[3] and an upfield effect on the pyridine or pyrimidine protons due to the electron rich imidazole ring.[1,3] Approximate ring current contributions due to the separate rings have also been determined[3] by the method of Pople[6] and with fictitious geometries.

HMO calculations have been employed[3] to determine electron densities in imidazo[1,2-*a*]pyrimidine (**1**). From



(1)

the frontier electron density electrophilic substitution on carbon is predicted to occur at position 3, while protonation should mainly occur at N-1; total π-electron density does not vary between substitution on C-2 and that on C-3, and a more basic character is attributed to N-4. Experimental evidence[3,8] suggests that protonation should occur at position 1.

We have recently reported[5] calculations of net charges with SCF methods (CNDO/2 and PPP) and ring currents obtained with the coupled Hartree-Fock perturbation theory[7] for imidazo[2,1-*b*]thiazole, employing experimental geometries for this system. In the present paper we report a ^{1}H NMR study carried out on a number of substituted imidazo[1,2-*a*]pyrimidines to test further the electronic properties and aromatic character of this condensed system in relation to the electron distribution and ring current contributions to the proton shielding constant computed by employing the experimental geometry recently determined[9] for this system. The protonation behaviour of the three nitrogen atoms will also be further tested by studying the protonation of these molecules in acidic media.

RESULTS AND DISCUSSION

The compounds analysed were numbers **1** to **10** (see Table 1). An iterative determination of the best parameters was performed whenever necessary by means of the LAOCOON 3 program.[10] The probable error on computed chemical shifts and coupling constants never exceeded 0·002 Hz, while experimental error was probably restricted to within 0·1 Hz. The results for the spectra recorded in 0·5 M chloroform-d_1 solution are reported in Table 1. For the unsubstituted compound and for **10** the values are in very good agreement with those previously reported.[3]

In the spectrum of compound **1** it can be observed that the broadening effect of the neighbouring nitrogen atom, which has a quadrupole moment, is observed on proton H-2, while sharp signals are obtained for proton H-5. An intermediate linewidth with respect to that of these protons is found for the peaks due to protons H-3, H-6 and H-7. This situation should be connected both to the fact that the nitrogen atoms producing a more pronounced broadening should be N-1 and N-8, owing to their less symmetrical chemical environment with respect to N-4, as found in the imidazo[2,1-*b*]thiazole system,[5] and that unresolved long range spin–spin coupling constants between protons in the two rings will probably be present.

The protons fall substantially into three distinct chemical shift regions: proton H-6 is found at higher field, H-2 and H-3 at intermediate field and H-5 and H-7 at lower field. The four latter protons lie near to nitrogen atoms and their relative line position should be influenced by ring current effects from the two heterocyclic rings.

To test this point we performed ring current calculations with the coupled Hartree-Fock perturbation theory[7] recently applied to heterocyclic molecules[11] and to the imidazo[2,1-*b*]thiazole system.[5] The method of calculation and the parametrisation are fully described in Ref. 11. The values obtained for compound **1** are reported in

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TABLE 1. CHEMICAL SHIFTS (δ VALUES) AND COUPLING CONSTANTS OF IMIDAZO[1,2-*a*]PYRIMIDINE DERIVATIVES RECORDED IN 0·5 M CHLOROFORM-d_1 SOLUTION

Compound	R_2	R_3	R_5	R_6	R_7	δ_2	δ_3	δ_5	δ_6	δ_7	δ_{CH_3}	J_{2-3}	J_{5-6}	J_{5-7}	J_{6-7}	Other couplings
(**1**)	H	H	H	H	H	7·784	7·709	8·743	6·917	8·521		1·43	6·75	2·07	4·10	
(**2**)	Me	H	H	H	H		7·403	8·550	6·817	8·424	2·478		6·75	2·09	4·16	$J(CH_3$—H-3) = 0·86
(**3**)	Me	Me	H	H	H			8·126	6·825	8·410	2·453		6·81	1·98	4·17	
(**4**)	Ph	H	H	H	H		7·800	8·420	6·809	8·493	2·400		6·75	2·01	4·15	
(**5**)	Ph	H	OMe	H	Me						2·504 (Me)					
							7·612		5·881		4·004 (OMe)					
(**6**)	Ph	H	H	OMe	H		7·690	7·870		8·325	3·824			2·96		
(**7**)	Ph	Me	H	H	Me						2·555		6·97			
								8·254	6·796		2·516					
(**8**)	Ph	H	Cl	H	Me		7·917		6·873		2·709					
(**9**)	Ph	Me	H	H	H			8·189	6·845	8·473	2·608		6·82	1·98	4·10	
(**10**)	Ph	H	H	H	Me		7·696	8·260	6·674		2·601		6·83			

Table 2, together with net charges on carbon and nitrogen atoms determined by the CNDO/2[12] and PPP[13] methods. Experimental geometries determined for the parent compounds[9] were employed: the fused heterocyclic system was found[9] to be planar, within the limits of experimental error. The C—H bond distances were all set equal to 1·08 Å.

The charge densities, either total from CNDO/2 or π from CNDO/2 and PPP methods, do not give satisfactory linear correlations with proton chemical shifts. Only when the proton chemical shifts δ are corrected for the ring current contribution is an almost linear correlation found with CNDO/2 total charge densities on adjacent carbons, where the largest deviation is found for proton H-2. This kind of correlation has already been found in the case of imidazo[2,1-*b*]thiazole,[5] thus confirming the importance of ring currents in determining the chemical shift of heterocyclic protons. In Fig. 1 we have also reported the values relative to pyrimidine and *N*-methylimidazole (chemical shifts are from Ref. 14). The largest deviation is observed for proton H-2 of compound **1** and seems to be linked more to the unrealistically large positive charge given for the carbon atom in this position by the CNDO/2 method than to specific anisotropy effects due to the neighbouring nitrogen atom, which should give a deviation in the opposite direction.

If we consider the difference between the proton chemical shift of a fused system and that of the corresponding proton in the single ring heterocycles, we should have a rough estimate of the ring current contribution from one ring to the protons of the other in the fused system. The set of differences between experimental chemical shifts $\Delta\delta$ is reported in Table 3, together with the corresponding differences in ring currents $\Delta\sigma_{\text{ring}}$ (values of σ_{ring} for *N*-methylimidazole are from Ref. 11 and for pyrimidine are σ(H-4) = 2·949, σ(H-5) = 2·955 ppm). The trend of the results shows that the mutual ring current contribution is qualitatively that expected from experimental results, in line with what was previously determined for imidazo[2,1-*b*]thiazole,[5] where $\Delta\delta$ and $\Delta\sigma_{\text{ring}}$ were found to be roughly correlated. On the other hand, the lack of a quantitative relationship between calculated $\Delta\sigma_{\text{ring}}$ and $\Delta\delta$ is certainly also to be attributed to the fact that the nitrogen atom in position 4 of compound **1** differs somewhat from a pyrimidine nitrogen. Nevertheless, the reliability of the calculated ring currents, even allowing for scaling factors, should be demonstrated by plots like that reported in Fig. 1 and by previously reported similar results.[5]

TABLE 2. CHARGE DENSITIES OBTAINED FROM CNDO/2 AND PPP METHODS AND SCF RING CURRENT CONTRIBUTIONS TO PROTON SHIELDING IN IMIDAZO[1,2-*a*]PYRIMIDINE

Ring position or bond	$q_{C(N)}^{CNDO}$ Total	$q_{C(N)}^{CNDO}$ π	$q_{C(N)}^{PPP}$	σ_{ring} (ppm) on proton	$P_{\mu\nu}^{PPP}$
C-2	0·0628	−0·0056	−0·0458	3·012	
C-3	−0·0473	−0·1965	−0·1835	3·178	
C-5	0·1155	0·0435	−0·0180	3·037	
C-6	−0·0757	−0·0886	−0·0355	2·773	
C-7	0·1275	0·0694	0·0019	2·774	
N-1	−0·2559	−0·2674	−0·1546		
N-4	−0·0109	0·5542	0·5279		
N-8	−0·1875	−0·1209	−0·0487		
2-3					0·6464
5-6					0·7872
6-7					0·5108

From the set of charge densities reported in Table 2 it is seen that the higher negative π-charge is predicted, by both methods, for C-3, as previously indicated by more simple calculations,[3] and as verified experimentally from the behaviour of electrophilic substitution.[15,16] The total CNDO/2 charge density also indicates a negative character for C-6, but, as discussed previously,[5] the π-electron density seems to represent better the reactivity in heteroaromatic systems.

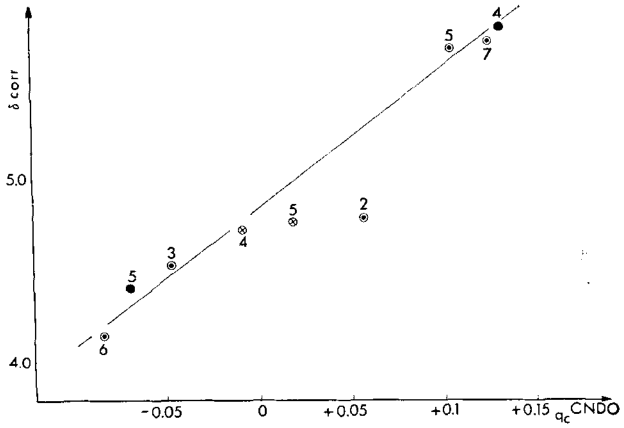

FIG. 1. Plot of ^{1}H chemical shifts corrected for ring current contribution vs total charge density on carbon given by CNDO/2 for imidazo[1,2-*a*]pyrimidine ⊙, *N*-methylimidazole ⊗ and pyrimidine ●. Numbering refers to the ring position.

TABLE 3. DIFFERENCES IN PROTON CHEMICAL SHIFT $\Delta\delta$ AND IN CALCULATED RING CURRENT EFFECT $\Delta\sigma_{ring}$ BETWEEN EQUIVALENT POSITIONS OF IMIDAZO[1,2-*a*]PYRIMIDINE AND THOSE OF *N*-METHYLIMIDAZOLE AND PYRIMIDINE

Proton	$\Delta\delta_{(ppm)}$	$\Delta\sigma_{ring}$
H-2	0·924	0·845
H-3	0·659	0·866
H-5	−0·037	0·088
H-6	−0·443	−0·183
H-7	−0·259	−0·175

An inspection of vicinal coupling constants in Table 1 shows that in the fused pyrimidine ring J_{5-6} is greater than J_{6-7}, while these constants are obviously the same and equal to 5·0 Hz in the pyrimidine molecule.[14] In view of the empirical interpretation of vicinal proton–proton coupling constants in unsaturated systems,[17] according to which they depend both on the electronegativity of the neighbouring atoms and on the π-bond order, it can be deduced that in the fused system a higher π-bond localisation should be present between carbon atoms in positions 5 and 6 than between those at 6 and 7, and higher also than that between bonded carbons in the pyrimidine molecule. Apart from the fact that this agrees with the classical uncharged structure which can be written for compound **1**, it is also confirmed by calculated π-bond orders, as can be seen from the PPP values reported in Table 2 and by comparison also with the value calculated for pyrimidine ($p_{4-5} = 0·6644$). The coupling constant J_{2-3} is very nearly the same as in *N*-methylimidazole and this is also in agreement with π-bond order arguments.

The charge density at the nitrogen atoms agrees with experimental results,[3] indicating that N-1 is the most basic in this system; in effect, the total charge density from CNDO/2 and π-electron density from both CNDO/2 and PPP show this position to be the most negative. Even so, a certain negative character is also assigned to N-8 and we therefore wonder if protonation occurs only at N-1 or also, partially, at N-8. We have thus tried to clarify this point further by running the spectra of compounds **1** to **4** in acidic solution, as shown by the results reported in Table 4. No substantial change occurs in the chemical shifts of the different protons when the protonating solvent is changed, indicating that the protonated form of **1** should be the same in the solvents employed. In trifluoroacetic acid solution the peaks are broader than in chloroform-d_1: this broadening is even higher in aqueous solution when hydrochloric acid is present in small amounts; it then reduces for intermediate ratios of compound **1** and hydrochloric acid and increases again in strong acidic solution. This behaviour is probably due to proton exchange phenomena between molecules of compound **1** and the medium, but this exchange could, in principle, also involve proton transfer between solute molecules.

The shifts of the resonance of each proton in compound **1** on adding progressive amounts of hydrochloric acid to a water solution (0·25 M) of the compound are shown in Fig. 2. The plots show only one protonation step in the same molar ratio region for all protons. This could either indicate that protonation occurs only at one site of the molecule or that in the progressive protonation the proton exchanges rapidly between different sites. This should imply that N-1 and N-8 have very similar dissociation constants.

The chemical shift differences $\Delta\delta$ reported in parentheses in Table 4 between values measured in trifluoroacetic acid solution and those in chloroform-d_1 show that the higher values are those for protons H-6 and H-7, and it seems rather unlikely that it is due only to long range effects resulting from protonation on N-1 and delocalisation of the positive charge on position 6 and 7. On the other hand, comparison with protonated pyrimidine[18] shows that the low field shift for proton H-6 is lower in compound **1** than in the parent single ring heterocycle.

This behaviour was tested by means of calculated charge densities on carbon atoms by assuming hypothetical models of differently protonated molecules. The values obtained by the CNDO/2 method are reported in Table 5. By correcting the experimental chemical shifts for the ring current contributions, as in the case of the free base (in the PPP calculation the ionisation potential of protonated nitrogen was set equal to 22·48 eV), the

TABLE 4. CHEMICAL SHIFTS (δ VALUES) AND COUPLING CONSTANTS OF PROTONATED IMIDAZO[1,2-*a*]PYRIMIDINE DERIVATIVES[a]

Compound	Solvent (conc. M)	δ_2	δ_3	δ_5	δ_6	δ_7	δ_{CH_3}	J_{2-3}	J_{5-6}	J_{5-7}	J_{6-7}	Other ccuplings
(1)	CF_3COOH	8·220	8·256	9·286	7·813	9·222		2·63	6·91	1·40	4·30	
	(0·5)	(0·436)	(0·547)	(0·543)	(0·896)	(0·701)		(1·20)	(0·16)	(−0·67)	(0·20)	
(1)	5 N HCl in H_2O[b] (0·25)	8·116	8·176	9·220	7·714	9·091		2·45	6·73	1·79	4·58	
(1)	0·5 N HCl in H_2O[b] (0·25)	8·138	8·199	9·251	7·727	9·105		2·50	6·88	1·83	4·57	
(1)	0·45 M CF_3COOH in $CDCl_3$[c] (0·25)	8·09	7·91	9·17	7·43	8·81						
(2)	CF_3COOH		7·923	9·119	7·727	9·107	2·752		7·19	1·82	4·15	$J(CH_3—H\text{-}3) = 0·52$
	(0·5)		(0·520)	(0·569)	(0·910)	(0·683)	(0·274)		(0·44)	(−0·27)	(−0·01)	(−0·34)
(3)	CF_3COOH			8·921	7·752	9·071	2·666		6·86	1·47	4·57	
	(0·5)			(0·795)	(0·927)	(0·661)	(0·213–0·266)		(0·05)	(−0·51)	(0·40)	
(4)	CF_3COOH		8·354	9·207	7·766	9·138			6·83	1·34	4·51	
	(0·5)		(0·554)	(0·787)	(0·957)	(0·645)			(0·08)	(−0·67)	(−0·36)	

[a] Values in parentheses are the differences between measurements in trifluoroacetic acid and those in chloroform-d_1.

[b] Chemical shifts were measured relative to the methyl peak of internal *t*-butyl alcohol, and translated to the TMS scale by employing $\delta_{CH_3} = 1·31$.

[c] The peaks are broad and it is difficult to determine coupling constants: chemical shifts are obtained by direct inspection of the spectrum.

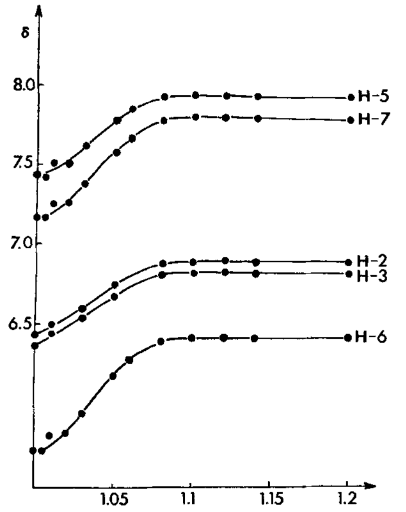

FIG. 2. Behaviour of chemical shift of protons in imidazo-[1,2-*a*]pyrimidine as a function of the molar ratio with respect to hydrochloric acid measured in water solution (0·25 M).

best correlation between corrected chemical shifts and total charge density is obtained when the molecule is considered protonated at N-1 and N-8, followed by that obtained by allowing for protonation at N-1. Allowing only for protonation at N-8, the points are randomly distributed. On the other hand, the CNDO/2 binding energy has the highest values when protonation occurs only at N-1. The trend of π-bond orders seems to support the view of protonation mainly at N-1 when compared with the behaviour of vicinal proton–proton coupling constants. From the π-bond orders calculated separately for protonation at N-1, N-8, and N-1 and N-8, it is seen in Table 5 that the trend of bond orders obtained is more coherent with experimental coupling constants for the case of protonation at N-1; p_{2-3} increases rather strongly with respect to the free base, as is observed experimentally for J_{2-3}, while p_{5-6} and p_{6-7} are near to the value ot the unprotonated molecule in agreement with the small experimental changes. It seems therefore, that the increase in aromaticity of the pyrimidine ring,[8] which should justify the preferred protonation at N-1, is not an important factor, since this should bring J_{5-6} and J_{6-7} closer together. These results may thus be considered conclusive only insofar as they exclude N-8 as the only site of protonation.

We therefore believe, that although all the evidence points to N-1 as the most probable protonation site (and, if so, this should be true in all the experimental conditions employed here), a rapid equilibrium could probably exist which distributes the proton between N-1 and N-8 according to their basicity, even if on the whole only monoprotonation of the molecule occurs, at least in the protonating conditions employed here. This possibility should also be considered in the light of the broadening of the spectra, which is observed for certain ratios of compound **1** and hydrochloric acid and which is probably connected, in these particular cases, to a slow exchange (in the NMR time scale) of a proton between the two basic nitrogen atoms.

EXPERIMENTAL

The NMR spectra were recorded on a JEOL JNM-C60-HL spectrometer in the internal lock mode. A small amount of TMS was added as internal standard and locking signal to solutions in chloroform-d_1 and in trifluoroacetic (0·5 M). Water solutions, both 0·5 M and 0·25 M (the latter being employed to follow the change in proton chemical shift at different molar ratios with respect to hydrochloric acid), contained as internal standard a small quantity of *t*-butyl acohol, the methyl peak of which, employed as reference signal, was found at 1·31 δ.

Compounds

Imidazo[1,2-a]*pyrimidine* (**1**). Bromoacetaldehyde (6·5 g) was added to a solution of 2-aminopyrimidine (5 g) in 30 ml of absolute ethanol. On refluxing the mixture, the voluminous white precipitate redissolved and yellow crystals separated. Concentration of the filtrate solution gave more crystals of the hydrobromide, m.p. 220 °C. The collected precipitate was treated with a saturated solution of sodium carbonate. The oily layer obtained was extracted with chloroform, the solvent evaporated off and the residual solid taken up with hot benzene. Colourless needles (benzene), m.p. 130 to 131 °C Lit.[19]: m.p. 131 to 133 °C.

2-Methylimidazo[*1*,*2*-a]*pyrimidine* (**2**). A solution of 2-aminopyrimidine (5 g) and α-bromopropionaldehyde (7 g) in 30 ml of absolute ethanol was refluxed for 3 h and the white precipitate collected. More crystals were obtained by addition of ether to the filtrate. The hydrobromide was dissolved in a little water and the solution saturated with KOH. The oily layer was extracted with benzene, the benzene solution was dried, the solvent evaporated off and the residual solid washed with cold ligroine (b.p. 60 to 80 °C). White needles (ligroine, b.p. 100 to 150 °C), m.p. 125 °C (Found: C, 63·24; H, 5·22; N, 31·47. $C_7H_7N_3$ requires: C, 63·14; H, 5·30; N, 31·56%).

2,3-Dimethylimidazo[*1*,*2*-a]*pyrimidine* (**3**). From 2-aminopyrimidine (5 g) and α-bromoethyl methyl ketone (7·7 g) in absolute ethanol. The aqueous solution of the hydrobromide, m.p. 315 °C, was saturated with KOH and extracted with benzene; the solvent was evaporated off and the residual solid recrystallised. Fluorescent white scales (ligroine b.p. 60 to 80 °C), m.p. 144 °C. (Found: C, 65·12; N, 6·12; N, 28·49. $C_8H_9N_3$ requires: C, 65·29; H, 6·16; N, 28·55%).

The remaining compounds were prepared as reported elsewhere.[15,16]

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TABLE 5. TOTAL CHARGE DENSITY ON CARBON OBTAINED FROM CNDO/2, RING CURRENT CONTRIBUTIONS TO PROTON SHIELDING AND π EOND ORDERS FROM PPP METHOD FOR PROTONATED IMIDAZO[1,2-*a*]PYRIMIDINE

	Protonated at N-1			Protonated at N-8			Protonated at N-1 and N-8		
Ring position or bond	CNDO q_C	σ_{ring}(ppm) on proton	$P_{\mu\nu}(\pi)$	CNDO q_C	σ_{ring}(ppm) on proton	$P_{\mu\nu}(\pi)$	CNDO q_C	σ_{ring}(ppm) on proton	$P_{\mu\nu}(\pi)$
2	0·0813	1·988		0·0875	2·531		0·1028	1·587	
3	0·0127	2·218		−0·0086	2·643		0·0410	1·729	
5	0·1521	3·101		0·2037	2·294		0·2295	2·101	
6	−0·0523	2·970		−0·0835	2·062		−0·0511	1·981	
7	0·1885	2·964		0·2203	2·064		0·2581	1·979	
2–3			0·7930			0·6811			0·8062
5–6			0·7487			0·7227			0·7063
6–7			0·5661			0·6055			0·6290

REFERENCES

1. J. P. Paolini and R. K. Robins, *J. Heterocyclic Chem.* **21,** 53 (1965).
2. W. W. Paudler and H. L. Blewitt, *J. Org. Chem.* **31,** 1295 (1966).
3. W. W. Paudler and J. E. Kuder, *J. Org. Chem.* **31,** 809 (1966).
4. P. Guerret, R. Jacquier and G. Maury, *Bull. Soc. Chim. France* 3503 (1972).
5. P. Lazzeretti, L. Marchetti, L. Pentimalli, L. Schenetti and F. Taddei, *J. Chem. Soc. Perkin Trans. II*, 1926 (1973).
6. J. A. Pople, *J. Chem. Phys.* **24,** 1111 (1956).
7. G. G. Hall and A. Hardisson, *Proc. Roy. Soc.* (*London*) *Ser. A* **268,** 328 (1962); G. G. Hall, A. Hardisson and L. M. Jackman, *Tetrahedron* **19** *Suppl. 2*, 101 (1963).
8. W. L. F. Armarego, *J. Chem. Soc.* 2778 (1965).
9. P. Domiano and L. Marchetti, *Gazz. Chim. Ital.* submitted for publication.
10. A. A. Bothner-By and S. Castellano, LAOCN 3, Mellon Institute, Pittsburg, Pennsylvania, 1966.
11. E. Corradi, P. Lazzeretti and F. Taddei, *Mol. Phys.* **26,** 41 (1973).
12. J. A. Pople and G. A. Segal, *J. Chem. Phys.* **44,** 3289 (1966).
13. R. Pariser and R. G. Parr, *J. Chem. Phys.* **21,** 466 (1953); J. A. Pople, *Trans. Faraday Soc.* **49,** 1375 (1953).
14. W. Brugel, *Nuclear Magnetic Resonance Spectra and Chemical Structure*, Vol. 1, Academic Press, New York, 1967.
15. L. Pentimalli and V. Passalacqua, *Gazz. Chim. Ital.* **100,** 110 (1970).
16. L. Pentimalli and G. Milani, *Gazz. Chim. Ital.* **100,** 1106, (1970).
17. M. A. Cooper and S. Manatt, *J. Amer. Chem. Soc.* **91,** 6325, (1969).
18. R. Wagner and W. von Philipsborn, *Helv. Chim. Acta* **53,** 299 (1970).
19. L. Almirante, A. Mugnaini, L. Polo Fritz and E. Provinciali, *Boll. Chim. Farm.* **105,** 32 (1966).