Carbon-13 Magnetic Resonance Studies of Azoles. Tautomerism, Shift Reagent Effects, and Solvent Effects[1]

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The effects of substitution, lanthanide-shift reagents, solvent changes, and tautomerism were investigated on the ^{13}C chemical shifts of pyrrole, pyrazole, imidazole, *s*- and *v*-triazole, and tetrazole. It was concluded that ^{13}C chemical shifts are of limited value to ascertain the positions of tautomeric equilibrium for rapidly interconverting azole tautomers.

Several molecules in the five-membered N-heterocycle series have been investigated by means of their ^{13}C nuclear magnetic resonance, but not in a systematic way: pyrrole as a neat liquid[3] or in acetone;[4] pyrazole in water,[5] in acetone,[4,6] and some of its N-substituted derivatives as neat liquids;[6,7] imidazole in water,[5,8] acetone,[4] and ethanol;[9] 1,2,3-triazole in acetone;[4] 1,2,4-triazole in acetone[4] or in dimethyl sulfoxide;[10] and tetrazole in dimethyl sulfoxide.[4] However, in none of these researches have the ^{13}C nmr data been used to study tautomerism. Although a great deal of work has been done on the annular tautomerism of such azoles[11] by various methods, often no definite conclusions can be reached. We will give attention here to the usefulness of ^{13}C spectroscopy in the determination of tautomeric equilibrium constants compared with ^{1}H or ^{14}N spectroscopy.

Experimental Section

Materials. The following compounds were from commercial sources and were used without further purification: pyrrole (1), *N*-methylpyrrole (2), pyrazole (3), imidazole (5), *N*-methylimidazole (6), *s*-triazole (7), and tetrazole (13). The other compounds have been described elsewhere: *N*-methylpyrazole (4) and 1,3,5-trimethylpyrazole (20);[12] 1-methyl-1,2,4-triazole (9), 1-methyl-1,3,4-triazole (8),[13] *v*-triazole (10), 1-methyl-1,2,3-triazole (12), and 1-methyl-1,2,5-triazole (11);[14] 1-methyl-1,2,3,4-tetrazole (14) and 1-methyl-1,2,3,5-tetrazole (15);[15] 3(5)-methylpyrazole (16), 3(5),5(3)-dimethylpyrazole (19), 3(5)-phenylpyrazole (21), and 3(5)-methyl-5(3)-phenylpyrazole (24);[16] 1,3-dimethylpyrazole (17) and 1,5-dimethylpyrazole (18);[17] and 1-methyl-3-phenylpvrazole (22), 1-methyl-5-phenylpyrazole (23), 1,3-dimethyl-5-phenylpyrazole (25), and 1,5-dimethyl-3-phenylpyrazole (26).[18]

Spectra. Most of the ^{13}C chemical shifts were measured with proton decoupling at natural abundance in the CW mode with a digital frequency sweep spectrometer operating at 15.08 MHz, as described earlier.[19] Some of the spectra were obtained with the same spectrometer in the Fourier-transform mode. All samples were studied at the indicated concentrations, the ^{13}C resonances of the solvents were used as internal references, and the chemical shifts were corrected to tetramethylsilane (TMS) as external reference. The shift changes produced by lanthanide shift reagents given in this paper are in parts per million, extrapolated to 1 *M* concentrations of azole and lanthanide chelate, with positive shifts upfield and negative shifts downfield. The shifts at several concentrations were linear with concentration and had linear correlation coefficients better than 0.99, except for C-4 of 1-methyl-1,2,3-triazole (12).

Results and Discussion

Resonance Assignments. The assignments were made in the usual way from data already available by intercomparison of the substances studied here, or with the aid of off-resonance decoupling experiments. However, in some cases ambiguities remained (between C-4 and C-5 of 1-methylimidazole, between C-3 and C-5 of 1-methyl-1,2,4-triazole, and between C-4 and C-5 of 1-methyl-1,2,3-triazole) and shift reagents sufficed for resolution of these. The resulting ^{13}C chemical assignments for pyrrole, pyrazole, imidazole, *s*-triazole, *v*-triazole, tetrazole, and their N-methylated derivatives in dioxane, CH_2Cl_2, or dimethyl sulfoxide are collected in Table I. Table II shows the chemical shifts of a series of C-substituted pyrazoles and their *N*-methyl derivatives in CH_2Cl_2.

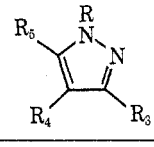
Shift Reagents and Azoles. The effects of several shift reagents on the pmr spectra of some pyrazole derivatives have been reported[20] and, for *N*-methylimidazole, the influences on both the proton[20] and the ^{14}N spectra[21] have been investigated. Our results regarding shift reagent effects on ^{13}C chemical shifts are gathered in Table III. We consider first the case of *N*-methylimidazole, for which the shifts undergone by the protons,[20] the nitrogens,[21] and the carbons are now known in the presence of europium chelates[22] (see Figure 1). It is quite clear that complexation takes place very predominantly on the pyridinic nitrogen (N-3), which is subject to a powerful contact interaction resulting in a very strong diamagnetic shift.[21] The 18-fold smaller diamagnetic shift of N-1 may reflect some direct complexation with europium chelate producing a contact interaction, or else a conjugative relay of spin density from N-3.[23] That complexation should be favored at N-3 is not surprising in view of the rather small lanthanide shifts observed for tertiary amines.[23] The upfield shift observed for one of the carbons—while the other carbons and all protons are shifted downfield—accords with the "wrong-way" shifts found for carbons in position β relative to the complexation site of open-chain[23] and acyclic[24] amines, and is also explicable by contact contributions.[23] Abnormal shifts of the α and β carbons (especially a wrong-way shift of one of the α carbons) have been reported[25] for quinoline and an important contact effect was postulated for the β carbons, which reinforces the dipolar pseudocontact factor. With this background of behavior of β carbons of amine with europium chelates, there is little doubt that the upfield-shifted ^{13}C signal of 1-methylimidazole arises from C-5,[26] and this assignment is in agreement with calculated ^{13}C chemical shifts[8] of the tautomeric N(1)-H form of imidazole. The shift changes undergone by the carbons α to the complexation site are such that the one of C-4 is more downfield (−41.6 ppm) than that of C-2 (−21.6 ppm), even though the dipolar term is expected to be about the same on both carbons, a notion which is corroborated by the fact that the C-2 and C-4 of both protons undergo nearly equal shifts. Furthermore, proton resonances seem to be much less sensitive to contact contributions[23,24,27,28] than carbon resonances. It may be that the alternate sign of spin density is transmitted across the N-3–C-4 single bond more effectively than across the C-2–N-3 π bond. In any case, the result is in accord with previous results, being positive on N-3, negative on C-4, and positive on C-5.[24]

Table I
^{13}C Chemical Shifts of Some Azoles[a]

Compd	No.	2	3	4	5	R	Dioxane[b] C-2	Dioxane[b] C-3	Dioxane[b] C-4	Dioxane[b] C-5	Dioxane[b] NCH_3	Dimethyl sulfoxide C-2	Dimethyl sulfoxide C-3	Dimethyl sulfoxide C-4	Dimethyl sulfoxide C-5	Dimethyl sulfoxide NCH_3
Pyrrole	**1**	C	C	C	C	H	117.7 (118.8)	108.0 (109.2)	108.0 (109.2)	117.7 (118.8)		116.3	106.1	106.1	116.3	
	2	C	C	C	C	CH_3	121.6 (122.6)	108.0 (109.4)	108.0 (109.4)	121.6 (122.6)	35.4 (36.9)	120.2	106.1	106.1	120.2	34.3
Pyrazole	**3**	N	C	C	C	H		(134.6)	(105.8)	(134.6)						
	4	N	C	C	C	CH_3		139.0 (139.6)	105.4 (106.2)	129.8 (130.6)	38.2 (39.2)					
Imidazole	**5**	C	N	C	C	H	(136.3)		(122.8)	(122.8)						
	6	C	N	C	C	CH_3	138.3 (138.8)		129.6 (130.1)	120.3 (121.0)	32.6 (34.0)					
s-Triazole	**7**	C(N)	N(C)	N	C	H	147.9			147.9		146.2			146.2	
	8	C	N	N	C	CH_3	144.1			144.1	30.7	143.1			143.1	29.9
	9	N	C	N	C	CH_3		152.6		144.7	36.0		150.4		143.5	34.7
v-Triazole	**10**	N	C(N)	C	N(C)	H		131.6	131.6				130.3	130.3		
	11	N	C	C	N	CH_3		134.7	134.7		41.5		133.2	133.2		
	12	N	N	C	C	CH_3			134.3	125.5	35.7			132.6	124.8	35.3
Tetrazole	**13**	N	N	N(C)	C(N)	H				143.3					142.1	
	14	N	N	N	C	CH_3				144.2	33.7				143.4	33.3
	15	N	N	C	N	CH_3			153.4		38.8			151.9		

[a] In parts per million relative to tetramethylsilane (TMS). [b] Parenthetical values are for CH_2Cl_2 as solvent.

Table II
^{13}C Chemical Shifts of Some Pyrazole Derivatives in CH_2Cl_2[a]



R_3	R_5	R	Compd	C-3	C-4	C-5	R_3	R_5	NCH_3
H	H	H	**3**	134.6	105.8	134.6			
H	H	CH_3	**4**	139.6	106.2	130.6			39.2
CH_3	H	H	**16**	144.4	105.3	135.8			
CH_3	H	CH_3	**17**	148.8	105.6	131.0	13.9		39.1
H	CH_3	CH_3	**18**	138.7	105.9	139.1		11.9	36.7
CH_3	CH_3	H	**19**	145.3	104.8	145.3	12.9	12.9	
CH_3	CH_3	CH_3	**20**	147.5	105.4	139.8	14.0	11.7	36.3
C_6H_5	H	H	**21**	150.2	103.7	134.4	C′-1 133.3 C′-2,6 129.9[b] C′-3,5 127.0[b] C′-4 129.2		
C_6H_5	H	CH_3	**22**	152.1	103.5	131.8	C′-1 134.8 C′-2,6 129.5[b] C′-3,5 126.3[b] C′-4 128.5		39.8
H	C_6H_5	CH_3	**23**	139.4	107.0	144.7		C′-1 132.2 C′-2,6 C′-3,5 129.8 C′-4	38.6
CH_3	C_6H_5	H	**24**	150.9	102.9	144.1	12.3	C′-1 133.8 C′-2,6 129.7[b] C′-3,5 126.7[b] C′-4 128.7	
CH_3	C_6H_5	CH_3	**25**	148.3	106.4	145.3	14.1	C′-1 132.2 C′-2,6 C′-3,5 129.6 C′-4	38.0
C_6H_5	CH_3	CH_3	**26**	150.6	103.2	140.9	C′-1 135.3 C′-2,6 129.2[b] C′-3,5 126.3[b] C′-4 128.2	11.9	37.0

[a] In parts per million relative to tetramethylsilane (TMS). [b] The assignments of the ortho and meta carbons are not certain and may be reversed.

The effects of praseodymium chelates on the ^{13}C chemical shifts of 1-methylimidazole (Figure 1) are "normal," in the sense that they are upfield, for both protons[20] and carbons. This difference in behavior between europium and praseodymium chelates has already been observed for other amines,[23-25] the contact contribution being surely

Table III
Lanthanide-Induced Changes in ^{13}C Shifts for Some Azoles, 1 *M* in $CDCl_3$

	1-Methylimidazole			1-Methyl-1,2,4-triazole		1-Methyl-1,2,3-triazole	
Carbon	δ, ppm (TMS)	Eu(fod)$_3$	Pr(fod)$_3$	δ, ppm (TMS)	Eu(fod)$_3$	δ, ppm (TMS)	Eu(fod)$_3$
C-2	138.7	−21.6	+80.9				
C-3				152.8	−43.0		
C-4	130.2	−41.6	+82.7			135.0	−6.6
C-5	121.0	+45.8	+17.2	144.5	−21.0	125.6	+7.4
CH_3	34.2	−4.4	+14.4	37.0	−10.2	37.4	−5.7

Table IV
^{13}C Chemical Shifts of 2.5 *M* Pyrrole (1) and *N*-Methylpyrrole (2) in Different Solvents

		Pyrrole		*N*-Methylpyrrole		
Solvent	Carbon	δ, ppm (TMS)	$\delta_{n\text{-hex}} - \delta_{solv}$	δ, ppm (TMS)	$\delta_{n\text{-hex}} - \delta_{solv}$	$\delta_{NH} - \delta(NCH_3)$
	C-2,5	117.5		121.0		−3.5
n-Hexane	C-3,4	108.1		108.7		−0.6
	NCH_3			35.1		
	C-2,5	118.2	−0.7	121.5	−0.5	−3.3
Cyclohexane	C-3,4	108.6	−0.5	109.0	−0.3	−0.4
	NCH_3			35.7	−0.6	
	C-2,5	118.9	−1.4	122.4	−1.4	−3.5
Neat liquid[a]	C-3,4	108.6	−0.5	109.4	−0.7	−0.8
	NCH_3			36.0	−0.9	
	C-2,5	118.8	−1.3	122.6	−1.6	−3.8
CH_2Cl_2	C-3,4	109.2	−1.1	109.4	−0.7	−0.2
	NCH_3			36.9	−1.8	
	C-2,5	117.7	−0.2	121.6	−0.6	−3.9
Dioxane	C-3,4	108.0	+0.1	108.0	+0.7	0.0
	NCH_3			35.4	−0.3	
	C-2,5	118.1	−0.6	122.3	−1.3	−4.2
Dimethyl-	C-3,4	107.7	+0.4	108.6	+0.1	−0.9
formamide	NCH_3			36.2	−1.1	
	C-2,5	116.3	+1.2	120.2	+0.8	−3.9
Dimethyl	C-3,4	106.1	+2.0	106.1	+2.6	0.0
sulfoxide	NCH_3			34.3	+0.8	
	C-2,5	118.0	−0.5	121.7	−0.7	−3.7
Acetone	C-3,4	107.8	+0.3	108.1	+0.6	−0.3
	NCH_3			35.4	−0.3	
	C-2,5	118.1	−0.6	122.1	−1.1	−4.0
Benzene	C-3,4	108.7	−0.6	109.2	−0.5	−0.5
	NCH_3			35.6	−0.5	

[a] Measured with 10% cyclohexane present.

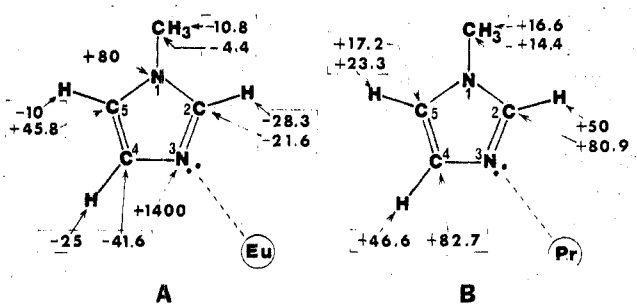


Figure 1. (A) Lanthanide-induced shifts of the proton,[20] nitrogen,[21] and carbon nuclei of 1-methylimidazole, extrapolated to an equimolar ratio of azole and europium chelate. (B) Proton[20] and carbon changes for 1-methylimidazole, extrapolated to an equimolar ratio of azole and praseodymium chelate.

smaller for praseodymium than for europium, and now we see that the shifts of C-2 and C-4, as well as the protons attached thereto, are quite similar.

With 1-methyl-1,2,3-triazole (12) and Eu(dpm)$_3$, the shifts are not as large as for the 1-methylimidazole. The upfield shift of one of the carbon signals suggests that it should be assigned to C-5 on the basis that complexation takes place predominantly on N-3. The alternative, complexation on N-2, is possibly difficult for steric reasons, as is indicated by the fact that the carbons of 1-methylpyrazole undergo only small downfield shifts with Eu(fod)$_3$.[29] The steric arrangements of N-3 in 1-methylimidazole and of N-3 in 1-methyl-1,2,3-triazole are similar, and differences in equilibrium constant for complexation will probably involve differences in nucleophilicities and charge densities on the nitrogen atoms.[30,31] From the calculated charge densities on nitrogen,[32] it is expected that N-3 of 1-methyl-1,2,3-triazole would have less affinity for Eu(fod)$_3$ and smaller shift effects.

The complex of 1-methyl-1,2,4-triazole with Eu(fod)$_3$ probably involves N-4. The carbon shifts are very similar to those of 1-methylimidazole and have been assigned to fit the same pattern. It is significant in this connection that the calculated charges on N-3 of 1-methylimidazole and N-4 of 1-methyl-1,2,4-triazole are similar.[32]

Solvent Effects. Solvent effects on ^{13}C chemical shifts have not yet been as extensively investigated as they have been on proton chemical shifts, even though, in many cases, the effects are large.[33-35,35a] Some ^{13}C solvent shifts for pyrrole and *N*-methylpyrrole are collected in Table IV, and for tetrazole and its *N*-methyl derivatives in Table V. Two important solvent effects can be expected: the influence of solvent on self-association[15] of the solute molecules, or specific solute–solvent effects.[36] If self-association is important, one should observe substantial variations with concentration. To test this, we chose to study concentration effects on the ^{13}C chemical shifts of pyrazole in CH_2Cl_2. Pyrazole is more basic than pyrrole or tetrazole and should be able to associate by hydrogen bonding. Nonetheless, the data of Table VI show only minor concentration effects, which suggests that self-association is probably not important.

Table V
^{13}C Chemical Shifts of Tetrazole and Its Two *N*-Methyl Derivatives in Different Solvents[a]

Solvent (concn, *M*)	Tetrazole (13) C-5(4)	1-Methyl-1,2,3,4-tetrazole (14) C-5	1-Methyl-1,2,3,4-tetrazole (14) NCH_3	1-Methyl-1,2,3,5-tetrazole (15) C-4	1-Methyl-1,2,3,5-tetrazole (15) NCH_3
Dioxane (0.5)	143.3	144.2	33.7	153.4	38.8
DMSO (1.7)	142.1	143.4	33.3	151.9	
DMF (2)	143.9	144.9	32.7	153.5	39.7
H_2O (0.5)	144.2	145.4	35.2		
Acetone (1.1)	143.3				

[a] In parts per million relative to tetramethylsilane (TMS).

Table VI
Concentration Effects on ^{13}C Chemical Shifts of Pyrazole[a]

Concn, *M*	C-3,5	C-4
0.5	134.62	105.82
1.0	134.63	105.82
1.5	134.62	105.79
2.0	134.64	105.79
2.5	134.64	105.79

[a] Chemical shifts given in parts per million relative to CS_2.

Pyrrole. The ^{13}C chemical shifts of this substance in various solvents are compared in Table IV with those for *n*-hexane: $\delta_{n\text{-hex}} - \delta_{solv}$. Hydrogen-bond association between the NH group of pyrrole and some of the solvents is probably not very important, because the solvent shifts are as great for the carbons of *N*-methylpyrrole as for pyrrole itself. This conclusion has already been reached from pmr measurements.[37,38]

In benzene and as neat liquids, the carbons of pyrrole and *N*-methylpyrrole are shifted downfield in a similar way, which indicates that the same kind of solute–solvent association occurs for both molecules.[36,39] In acetone, dimethylformamide, and dioxane, C-3 and C-4 of pyrrole and *N*-methylpyrrole are shifted downfield but the carbons α to the nitrogen, C-2, C-5, and CH_3N, are shifted upfield, which again indicates that similar solvent-association complexes are formed. The largest shifts are observed for dimethyl sulfoxide solutions and are all positive. With aniline,[33] the closest system for which solvent effects have been studied, the carbons α to the nitrogen are shifted downfield and the carbons β upfield in dimethyl sulfoxide-d_6 as well as in acetone-d_6. These shifts have been explained by formation of hydrogen-bonded complexes, with the solvents acting as proton acceptors.

The ^{13}C chemical shifts of 1 and 2 are more sensitive to solvent effects than proton shifts, and the variations often have opposite signs. Thus, while the protons of *N*-methylpyrrole undergo large shifts in dimethyl sulfoxide[40] (as do the carbons), these are opposite to those of the carbons to which they are linked. The protons and carbons of pyrrole and *N*-methylpyrrole are shifted in the same sense in acetone,[40] while in benzene this also occurs at positions 2 and 5, but the opposite at positions 3 and 4.[37,41] The benzene shifts have been rationalized by the ring-current effect, but the carbon shifts are all downfield, which indicates that the magnetic anisotropy from benzene is not the main factor for them. In other work,[35] the magnetic anisotropy did not seem as important an influence on the observed shift of the carbon of $CHCl_3$ in benzene as intermolecular associations. Becconsall and Hampson[34] consider that the electric reaction-field mechanism predominates in the case of CH_3I.

Tetrazole. A broad survey, as for pyrrole, cannot be carried out for tetrazole because of its low solubility, but, from the data in Table V, a trend similar to that for pyrrole seems to emerge. The shift changes of tetrazole itself, as well as those of its *N*-methyl derivatives, are upfield in dimethyl sulfoxide from the other solvents. Again, the ^{13}C and ^1H chemical shifts do not follow the same pattern.

Table VII
Shifts of Azole Carbons on Replacement of NH by NCH_3

NH and NCH_3 azole	$\Delta_i\alpha$, ppm[a]	$\Delta_i\beta$, ppm[a]	$\Delta_i\alpha + \Delta_i\beta$, ppm[a]
Pyrrole	$\Delta_{2,5} = -3.7$	$\Delta_{3,4} = -0.4$	-4.1
Pyrazole		$\Delta_4 = -0.4$	$\Delta_3 + \Delta_5 = -1$
3,5-Dimethylpyrazole		$\Delta_4 = -0.6$	$\Delta_3 + \Delta_5 = +3.3$
Imidazole	$\Delta_2 = -2.5$		$\Delta_4 + \Delta_5 = -5.5$

[a] Shifts toward lower field are taken to be negative.

Discussion

Substitution of a NH Group bv NCH_3. The chemical shift changes $\Delta_i = \delta_i(NH) - \delta_i(NCH_3)$ for each carbon, α or β to the substituted nitrogen, was desirable for the tautomerism study described later. It was at first expected that the effects would be about the same, whatever the azole, and, in order to verify this assumption, a careful study of pyrrole and *N*-methylpyrrole was made in different solvents. It can be seen (Table IV) that the changes depend somewhat on the solvent, but the shifts are always downfield when the methyl group is introduced in the molecule. The average values are -3.7 and -0.4 ppm for carbons α and β, respectively.

For the other azoles, comparisons are more difficult because of the occurrence of proton exchange between the different nitrogens, and usually only a sum of effects could be reached from comparison of the tautomeric species with the *N*-methyl derivatives. The results are summarized in Table VII, and it can be seen that, in fact, the values as well as the signs of the effects depend upon the azole, and are even different within a series of azoles (*cf.* pyrazole and 3,5-dimethylpyrazole, for which the steric hindrance may be important to the observed difference).

Methyl Group Substitution on the Carbons of Pyrazole Rings. The magnitude of the methyl-substitution effect can be gained by comparisons among the *N*-methylpyrazoles **4**, **17**, **18**, **20**, **22**, **23**, **25**, and **26**, and the following conclusions seem possible. (1) Methyl substitution at C-3 and C-5 causes a downfield shift of 8.5 to 9.2 ppm at the site of substitution. A similar effect has been described in the case of pyrrole and 2-methylpyrrole.[3] (2) Methyl substitution at C-3 leads to a small downfield shift (~ -0.5 ppm) of C-5, whereas a methyl group at position 5 gives an upfield shift (+0.9–1.5 ppm) of C-3; this shows again the difference in behavior of 1,3- and 1,5-disubstituted pyrazoles. (3) The effect of a methyl group in positions 3 or 5 on the carbon in position 4 is always a small upfield shift. (4) If two methyl groups are introduced, the effects are additive, and parallel relationships exist between the 1-methylpyrazole (**4**), 1,3-dimethylpyrazole (**17**), 1,5-dimethylpyrazole (**18**), and 1,3,5-trimethylpyrazole (**20**), as was the case for pyrrole, 1-methylpyrrole, and 2,5-dimethylpyrrole.[3]

Phenyl Group Substitution on the Pyrazole Ring. There are not enough examples to draw very general conclusions, but from compounds **4**, **17**, **18**, **22**, **23**, **25**, and **26** it is clear that the shift perturbations of the ring carbons are not the same on introducing a phenyl group in position 3 or 5. This seems to have diagnostic value in struc-

Table VIII
Correlation of ^{13}C Chemical Shifts of Azoles

Compd	No.	2	3	4	5	R	C-2 Obsd[a]	C-2 Δ[b]	C-3 Obsd[a]	C-3 Δ[b]	C-4 Obsd[a]	C-4 Δ[b]	C-5 Obsd[a]	C-5 Δ[b]
Pyrrole	1[c]	C	C	C	C	H	−15	+0.6	−4	−0.9	−4	−0.9	−15	+0.6
	2	C	C	C	C	CH_3	−17.1	−0.7	−3.5	+1.6	−3.5	+1.6	−17.1	−3.5
Pyrazole	3[c]	N	C	C	C	H			−29	−0.2	−1	+0.2	−29	−0.2
	4	N	C	C	C	CH_3			−34.5	−4.2	−0.9	+4.2	−25.3	−3.5
Imidazole	5[c]	C	N	C	C	N	−32	−0.8			−18	+0.7	−18	+0.7
	6	C	N	C	C	CH_3	−33.8	+2.5			−25.1	−0.2	−15.8	+0.7
	7[c]	C(N)	N(C)	N	C	N	−44	+0.4					−44	+0.4
s-Triazole	8	C	N	N	C	CH_3	−39.6	−3.3					−39.6	−3.3
	9	N	C	N	C	CH_3			−48.1	+2.0			−40.2	+1.5
	10[c]	N	C(N)	C	N(C)	H			−27	−0.2	−27	−0.2		
v-Triazole	11	N	C	C	N	CH_3			−30.2	+0.1	−30.2	+0.1		
	12	N	N	C	C	CH_3					−29.8	−4.9	−21.0	+0.8
	13[c]	N	N	N(C)	C(N)	H							−41	+11.5
Tetrazole	14	N	N	N	C	CH_3							−39.7	+2.0
	15	N	N	C	C	CH_3					−48.9	+1.2		

[a] Chemical shifts in parts per million upfield from the cyclopentadienate anion. [b] Deviation between experimental and observed values $\Delta = \delta_{obsd} - \delta_{calcd}$. The calculated values for R = H and R = CH_3 are obtained from different constants. [c] The experimental values are from ref 4.

tural analysis of pyrazoles. Further, the ^{13}C spectra of the phenyl groups are quite different in positions 3 or 5 when an *N*-methyl is present. All but the C′-1 carbons of a phenyl group in position 5 have about the same chemical shift, while the same carbons come into resonance with a different shift if the phenyl group is in position 3. The same sort of thing is observed in pmr spectroscopy,[43] which again shows that a phenyl group in position 5 is turned out of the plane of the pyrazole ring.

Chemical Shifts of Carbons in Azole Rings. From Table I it may be seen that a carbon resonance is shifted downfield by an adjacent *N*-methyl group, and more downfield by a pyridinic-like nitrogen. The most upfield signals are those belonging to a carbon between two carbons, and the most downfield ones are those belonging to carbons adjacent to two pyridinic-type nitrogens. Within the *N*-methyl series, replacement of a carbon by a nitrogen atom shifts the α carbons 15–30 ppm downfield. The effect on β carbons is difficult to rationalize because both positive and negative shifts are observed. In fact, this effect is not a pure β effect; a γ effect must be added; and both depend on the pathway which can or can not include nitrogen atoms. The ^{13}C chemical shifts of tautomeric azoles have been correlated[4] by a four-parameter empirical equation, $\delta_C = N_\alpha C_\alpha + N_\beta C_\beta + N_{\alpha\beta} C_{\alpha\beta} + N_{\beta\beta} C_{\beta\beta}$, where δ_C is the chemical-shift difference between a particular carbon atom in the azole and the cyclopentadienate anion (the chemical shift of the cyclopentadienate anion is 104.5 ppm from TMS), the *C*'s are the chemical-shift increments associated with structural features, and *N* is the number of nitrogen atoms with a particular structural feature. The calculated values are in reasonable agreement with the observed ones, except for tetrazole. Using a multilinear regression program,[44] slightly different values of C_α, C_β, $C_{\alpha\beta}$, and $C_{\beta\beta}$ (−15.6, −3.1, −10.1, and +5.1 ppm, respectively) are obtained with the same data, again without tetrazole. The values of C_β and $C_{\beta\beta}$ so obtained are not well fixed. The calculated and observed shifts are compared in Table VIII.

A difficulty with this approach is that it does not differentiate between pyridine-like and pyrrole-like nitrogen atoms and, of course, because of proton exchange (as for pyrazole and imidazole) each nitrogen is half pyridinic and half pyrrolic. With 1,2,3-triazole, 1,2,4-triazole, and tetrazole, the proportions of the tautomers are not equal,[11] which leads to less exact results. The same kind of treatment with the N-methylated azole derivatives, where there is no possibility of exchange, allowed for determination of eight parameters: $C_{\alpha P}$ (P = pyridine-like nitrogen), $C_{\alpha p}$ (p = pyrrole-like nitrogen), $C_{\beta P}$, $C_{\beta p}$, $C_{\alpha\beta PP}$, $C_{\alpha\beta Pp}$, $C_{\beta\beta PP}$, and $C_{\beta\beta Pp}$. The important conclusion of this analysis follow. (1) Only $C_{\alpha P}$, $C_{\alpha p}$, and $C_{\alpha\beta Pp}$ can be fixed very well and these are −19.8, −11.3, and −5.4 ppm, respectively. $C_{\alpha\beta PP}$ is almost significant, but all of the other parameters involving β carbons are not. (2) A constant of −5.1 ppm seems to be required for which we see no physical meaning. In contrast, where tautomerism was possible, the constant term amounted to only −0.5 ppm. (3) The differences between calculated and observed chemical shifts are shown in Table VIII. The agreement is not bad considering that no account has been taken of the effects of β nitrogens. The worst discrepancy (−4.9 ppm) for the *N*-methyl compounds is for C-4 of the 1,2,3-triazole (12).

Fairly regular behavior is observed for the *N*-methyl carbons. Introduction in the ring of a nitrogen α to the *N*-methyl group gives a downfield shift of −2.8 to −3.4 ppm, while the introduction of a nitrogen β gives upfield shifts of +1.9 to +2.8 ppm.

Proton *vs.* ^{13}C Chemical Shifts. Figure 2 shows a plot of the ^{13}C chemical shifts of *N*-methylazoles in dioxane against the corresponding shifts of the protons to which they are bonded for **2**, **4**, **6**, **11**,[14] **9**, **12**, **14**, **15**,[15] and **8**.[45] There is a clear trend toward linearity (correlation coefficient 0.913 with a slope of 17.74 ± 0.44 ppm).

Theoretical Charge Densities and ^{13}C Chemical Shifts. Figure 3 is a plot of the experimental ^{13}C chemical shifts of *N*-methylazoles in dioxane against the charge densities ($\pi + \sigma$) of the corresponding NH tautomers calculated by the LCAO–SCF method.[46] The correlation is not a good one (correlation coefficient 0.824), but there is clearly a trend between the ^{13}C shifts and the charges.[47,48] Furthermore, the slope of the regression line, 175 ppm/electron, is not far from the empirical relationship with slope = 160 ppm/electron reported for purine and pyrimidine nucleosides.[49] The carbons which give the worst correlation are those located between two pyridine-like nitrogen atoms (C-3 of 1,2,4-triazole and C-4 of

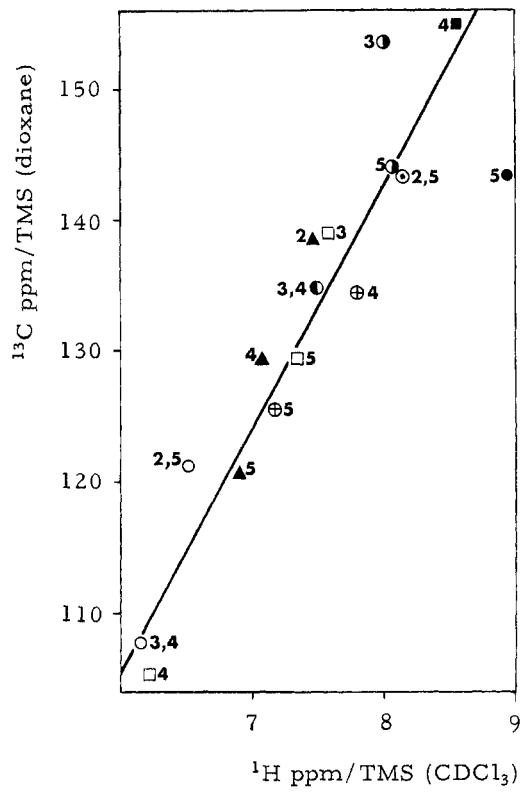


Figure 2. The ^{13}C chemical shifts of azole carbons *vs.* the chemical shifts of the directly attached protons (the numbers next to each point are the position numbers of the carbons in the ring): ○, pyrrole; □, pyrazole; ▲, imidazole; ⊕, 1,2,3,-triazole; ◐, 1,2,5-triazole; ◑, 1,2,4-triazole; ⊙, 1,3,4-triazole; ●, 1,2,3,4-tetrazole; ■, 1,2,3,5-tetrazole.

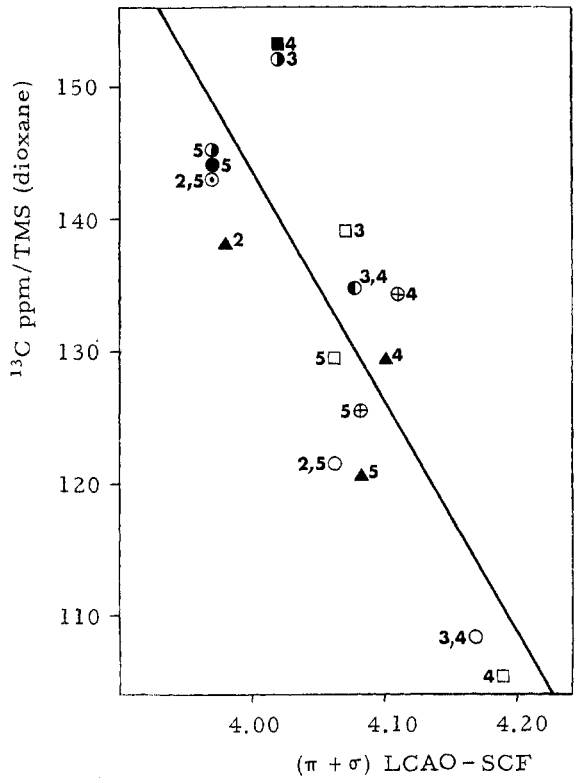


Figure 3. The ^{13}C chemical shifts of azoles relative to TMS *vs.* the (π + σ) charge densities on the carbons, calculated by the LCAO-SCF method: ○, pyrrole; □, pyrazole; ▲, imidazole; ⊕, 1,2,3-triazole; ◐, 1,2,5-triazole; ◑, 1,2,4-triazole; ⊙, 1,3,4-triazole; ●, 1,2,3,4-tetrazole; ■, 1,2,3,5-tetrazole. The numbers next to each point denote the position numbers of the carbons in the rings.

1,2,3,5-tetrazole). Similar differences were found for the C-4 atoms in the purine nucleosides.[49]

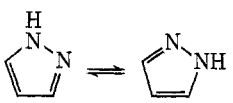
The Tautomer Problem. Proton nmr has been widely used in studies of tautomerism of azoles.[11] However, interpolation between the chemical shifts of the tautomeric species and the corresponding N-methylated derivatives is not very conclusive because the variations of chemical shifts are generally of the same magnitude as the substitution effect of an *N*-methyl group. Temperature dependances of the spectra of the tautomers provide much more definitive conclusions,[11] especially when it is possible to observe the signals of the separate tautomers and their coalescence. The interpolation method applied to ^{13}C, ^{14}N, or ^{15}N resonances seems at first likely to be useful because of the expected, much wider spread of chemical shifts. However, direct observation of ^{14}N resonances is not wholly satisfactory[32,50] because of the large line widths and possible overlappings with several nitrogen atoms; more accurate measurements of ^{14}N chemical shifts have been obtained by double resonance[26] but no quantitative conclusions have been drawn therefrom.

The ^{13}C spectra have sharp peaks and have already been used in some studies of tautomerism, for example, comparison of the ^{13}C chemical shifts of purine and benzimidazole,[9] and of histidine[8] with their respective cations. We have here chosen to analyze the tautomeric equilibrium of azoles by comparison of the shifts of the *N*-methyl derivatives with the mixture of tautomers.

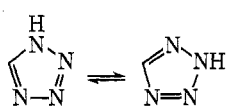
If P is the sum of the chemical shifts of tautomeric positions[51] (carbons 3 and 5 in pyrazole, or 4 and 5 in imidazole, for example), then, for a rapid equilibrium between two species A and B [*i.e.*, pyrazole (**27a, 27b**), imidazole] the equilibrium constant is

$$K_T = (P_N - P_B)/(P_A - P_N)$$

where P_N is the average experimental shift and P_A and P_B are the shifts in tautomers A and B.



27a **27b**



27A **27B**

Unfortunately, it turns out that one should correct the P_A and P_B to allow for the effect of the introduction of the methyl group, and those correction terms are both not constant and very sensitive to the azole. Furthermore, their magnitudes are great enough to prevent calculation of K_T with much confidence. This sort of situation holds for all the tautomeric azoles under study here, and it appears that only variable-temperature studies with ^{13}C nmr are likely to aid in the solution of this vexing problem. The only exception is the case of tetrazole **28a** and **28b**, for which only one carbon can be observed and for which the numerator and denominator in the equation of K_T are different enough so that the predominance of tautomer **28a** may be ascertained whatever the solvent (even in water, contrary to Charton's conclusions).[52]

Registry No. 1, 109-97-7; 2, 96-54-8; 3, 288-13-1; 4, 930-36-9; 5, 288-32-4; 6, 616-47-7; 7, 288-88-0; 8, 10570-40-8; 9, 6086-21-1; 10, 288-36-8; 11, 18922-69-5; 12, 16681-65-5; 13, 288-94-8; 14, 16681-77-9; 15, 16681-78-0; 16, 1453-58-3; 17, 694-48-4; 18, 694-31-5; 19, 67-51-6; 20, 1072-91-9; 21, 2458-26-6; 22, 3463-26-1; 23, 3463-27-2; 24, 3440-06-0; 25, 10250-58-5; 26, 10250-60-9.

References and Notes

(1) This work is the 11th publication in the series "Nmr Studies of Heterocyclic Compounds." For previous papers in this series, see ref 50. The part of this research done at the California Institute of Technology was supported by the National Science Foundation.
(2) (a) Université des Sciences et Techniques du Languedoc. (b) California Institute of Technology. (c) Presently at the Université des Sciences et Techniques du Languedoc.
(3) T. F. Page, Jr., T. Alger, and D. M. Grant, *J. Amer. Chem. Soc.*, **87**, 5333 (1965).
(4) F. J. Weigert and J. D. Roberts, *J. Amer. Chem. Soc.*, **90**, 3543 (1968).
(5) R. J. Pugmire and D. M. Grant, *J. Amer. Chem. Soc.*, **90**, 4232 (1968).
(6) R. G. Rees and M. J. Green, *J. Chem. Soc. B*, 387 (1968).
(7) K.-H. Spohn and E. Breitmaier, *Chimia*, **25**, 365 (1971).
(8) W. F. Reynolds, I. R. Peat, M. H. Freedman, and J. R. Lyerla, Jr., *J. Amer. Chem. Soc.*, **95**, 328 (1973).
(9) R. J. Pugmire and D. M. Grant, *J. Amer. Chem. Soc.*, **93**, 1880 (1971).
(10) G. P. Kreishman, J. T. Witkowski, R. K. Robins, and M. P. Schweizer, *J. Amer. Chem. Soc.*, **94**, 5894 (1972).
(11) For a general survey see J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, "Heteroaromatic Tautomerism," Academic Press, New York, N. Y., in press.
(12) J. Elguero, R. Jacquier, and H. C. N. Tien Duc, *Bull. Soc. Chim. Fr.*, 3727 (1966).
(13) R. Jacquier, M.-L. Roumestant, and P. Viallefont, *Bull. Soc. Chim. Fr.*, 2630 (1967).
(14) J. Elguero, E. Gonzalez, and R. Jacquier, *Bull. Soc. Chim. Fr.*, 2998 (1967).
(15) G. B. Barlin and T. J. Batterham, *J. Chem. Soc. B*, 516 (1967).
(16) J. Elguero and R. Jacquier, *Bull. Soc. Chim. Fr.*, 2832 (1966).
(17) J. Elguero, R. Jacquier, G. Tarrago, and H. C. N. Tien Duc, *Bull. Soc. Chim. Fr.*, 293 (1966).
(18) J.-L. Aubagnac, J. Elguero, and R. Jacquier, *Bull. Soc. Chim. Fr.*, 3306 (1969).
(19) F. J. Weigert and J. D. Roberts, *J. Amer. Chem. Soc.*, **90**, 3543 (1968).
(20) R.-M. Claramunt, J. Elguero, and R. Jacquier, *Org. Magn. Resonance*, **3**, 595 (1971).
(21) M. Witanowski, L. Stefaniak, H. Januszewski, and Z. W. Wolkowski, *Tetrahedron Lett.*, 1653 (1971).
(22) The magnitudes of the effects between the different nuclei are not strictly comparable because different chelates in different solvents have been used: Eu(dpm)$_3$ in CCl_4 for ^{1}H and ^{14}N spectra and Eu(fod)$_3$ in $CHCl_3$ for the ^{13}C resonance.
(23) (a) C. Marzin, D. Leibfritz, G. E. Hawkes, and J. D. Roberts, *Proc. Nat. Acad. Sci. U. S.*, **70**, 562 (1973), and references cited therein. (b) Very recently, similar contact contributions have been evaluated and compared in the case of the ^{13}C spectra of isoquinoline complexed to various shift reagents: O. A. Gansow, P. A. Loeffler, R. E. Davis, M. R. Willcott, III, and R. E. Lenkinski, *J. Amer. Chem. Soc.*, **95**, 3389, 3390 (1973).
(24) G. E. Hawkes, C. Marzin, S. R. Johns, and J. D. Roberts, *J. Amer. Chem. Soc.*, **95**, 1661 (1973).
(25) A. A. Chalmers and K. G. R. Pachler, *Tetrahedron Lett.*, 4033 (1972).
(26) The reverse assignment of the resonances of C-4 and C-5 has been made by H. Saitô, Y. Tanaka, and S. Nagata, *J. Amer. Chem. Soc.*, **95**, 324 (1973). However, see also R. J. Pugmire, D. M. Grant, L. B. Townsend, and R. K. Robins, *J. Amer. Chem. Soc.*, **95**, 2791 (1973).
(27) G. E. Hawkes, D. Leibfritz, D. W. Roberts, and J. D. Roberts, *J. Amer. Chem. Soc.*, **95**, 1659 (1973).
(28) Contact effects have been invoked for protons of π systems with Eu(dpm)$_3$ to explain deviations of the shifts from those predicted by dipolar interactions: B. F. G. Johnson, J. Lewis, P. McArdle, and J. R. Norton, *Chem. Commun.*, 535 (1972).
(29) Quantitative values were not obtained because of poor solubility.
(30) C. Beauté, Z. W. Wolkowski, and N. Thoai, *Tetrahedron Lett.*, 817 (1971).
(31) L. Ernst and A. Mannschreck, *Tetrahedron Lett.*, 3023 (1971).
(32) M. Witanowski, L. Stefaniak, H. Januszewski, Z. Grabowski, and G. A. Webb, *Tetrahedron*, **28**, 637 (1972).
(33) G. L. Nelson, G. C. Levy, and J. D. Cargioli, *J. Amer. Chem. Soc.*, **94**, 3089 (1972).
(34) J. K. Becconsall and P. Hampson, *Mol. Phys.*, **10**, 21 (1965).
(35) R. L. Lichter and J. D. Roberts, *J. Phys. Chem.*, **74**, 912 (1970).
(35a) Note Added in Proof. Two important recent additional publications on solvent effects and ^{13}C chemical shifts are M. R. Bacon and G. E. Maciel, *J. Amer. Chem. Soc.*, **95**, 2413 (1973), and H. H. Mantsch and I. C. P. Smith, *Can. J. Chem.*, **51**, 1384 (1973). The latter paper covers effects related to those described here.
(36) M. G. Reinecke, H. W. Johnson, and J. F. Sebastian, *J. Amer. Chem. Soc.*, **91**, 3817 (1969).
(37) J. Ronayne and D. H. Williams, *J. Chem. Soc. B*, 805 (1967).
(38) H. Anderson, *Can. J. Chem.*, **43**, 2387 (1965).
(39) T. Ledaal, *Tetrahedron Lett.*, 1683 (1968).
(40) N. Lumbroso-Bader, M.-T. Chenon, and J. Bouquant, *J. Chim. Phys.*, **67**, 1829 (1970).
(41) The situation, however, is rendered somewhat complex by the fact that the proton shifts in benzene are compared with those in CCl_4,[37] which probably cannot be considered an inert solvent.[42]
(42) K. M. Baker and R. G. Wilson, *J. Chem. Soc. B*, 236 (1970).
(43) L. G. Tensmeyer and C. Ainsworth, *J. Org. Chem.*, **31**, 1878 (1966).
(44) J. W. ApSimon, J. Elguero, A. Fruchier, D. Mathieu, and R. Phan Tan Luu, *Can. J. Chem.*, submitted for publication.
(45) R. A. Olofson and R. V. Kendall, *J. Org. Chem.*, **35**, 2246 (1970).
(46) M. Roche and J. Pujol, *J. Chim. Phys.*, **68**, 465 (1971).
(47) The use of the EHT method does not improve the correlation: M. Roche, Thesis, Marseille, France, 1970.
(48) A more elaborate approach is in progress at the Université de Provence, Marseille, France, with Mr. M. Radjmann.
(49) A. Jones, D. M. Grant, M. W. Winkley, and R. K. Robins, *J. Amer. Chem. Soc.*, **92**, 4079 (1970).
(50) M. Witanowski, L. Stefaniak, H. Januszewski, and J. Elguero, *J. Chim. Phys.*, **70**, 697 (1973).
(51) Nontautomeric positions, such as C-4 in pyrazole, are not sufficiently affected by the tautomerism to be helpful in the analysis.
(52) M. Charton, *J. Chem. Soc. B*, 1240 (1969).

Carbon-13 Nuclear Magnetic Resonance Spectra of Tetraalkylammonium Tetraalkylborides

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Chemical shifts in carbon-13 nuclear magnetic resonance spectra of tetraalkylammonium ions, tetraalkylboride ions, and trialkylboranes correlate linearly with calculated chemical shifts of the corresponding isoelectronic hydrocarbons. Additive substituent effects on chemical shifts for charged and neutral nitrogen and charged and neutral boron also are reported. Aromatic solvent induced shifts of tetraalkylammonium tetraalkylborides in parts per million are smaller in carbon-13 nmr spectra than in proton nmr spectra.

As part of a broad investigation of the properties of tetraalkylammonium tetraalkylborides we have obtained carbon-13 nmr spectra of some tetraalkylammonium halides and tetraalkylborides, as well as some trialkylboranes. Because the effects of substituents on carbon-13 chemical shifts are largely additive,[1,2] it is usually possible to predict new ^{13}C nmr spectra from previous spectra of similar compounds. In this paper we report correlations of ^{13}C chemical shifts which may be used to predict chemical shifts of tetraalkylammonium ions, tetraalkylboride ions, and trialkylboranes. An extensive correlation of primary, secondary, and tertiary amine ^{13}C chemical shifts is already available.[3]

Experimental Section

Tetraethylammonium iodide (Eastman) was dried at 50° for 5 hr at 10^{-5} Torr. Other tetraalkylammonium salts and trialkylboranes were obtained and purified as described elsewhere.[4]