^{14}N and ^{2}H Quadrupole Double Resonance in Substituted Imidazoles

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The ^{14}N and ^{2}H quadrupole resonance frequencies have been measured for fifteen substituted imidazoles at room temperature by means of double-resonance techniques. The variations in the ^{14}N quadrupole parameters of the amino nitrogen atom, N(1), are primarily determined by the hydrogen-bonding environment. Two interchanges of the ^{14}N electric field gradient components are inferred to occur; the first involves the x and y axes when gaseous imidazole condenses to form a solid, and the second involves the y and z axes when $|e^2qQ/h|$ (^{14}N) falls below 1.35 MHz, as in several imidazolium salts. Much smaller variations in the ^{14}N quadrupole parameters of the imino nitrogen atom, N(3), are observed and their behaviour may be interpreted by assuming that an interchange between the x and y axes of the ^{14}N electric field gradient tensor has occurred, relative to gaseous imidazole, in all the solids studied.

The use of ^{14}N quadrupole double resonance spectroscopy to probe the charge distribution about imidazole nitrogen sites has been illustrated by Ashby and his collaborators in their work with metal-co-ordinated imidazole.[1,2] They showed that the data for the imino site N(3) reflected the effects of σ charge withdrawal by co-ordination to the metal ion and could provide insight into the prominent role apparently played by imidazole, as a metal ligand, in many biological processes involving the amino acid histidine.[3,4]

In the studies reported here, a series of substituted imidazoles has been investigated by ^{14}N and ^{2}H quadrupole double resonance spectroscopy. The compounds studied were selected so as to give the widest possible range of substituents at all carbon positions; the chief limitation was the short spin lattice relaxation times often encountered at room temperature. The nitrogen quadrupole resonance data for these compounds show complex features, due largely to the effects of hydrogen bonding on both π and σ electrons in the imidazole ring. They indicate a solid-state thione form for 2-mercaptoimidazole and demonstrate the close equivalence of the two nitrogen sites in the imidazolium cation.

Experimental

Imidazole (B.D.H.) and benzimidazole (B.D.H.) were used without further purification. All the imidazole derivatives were prepared at Smith Kline & French Research Laboratories. 4,5-Dimethylimidazolium formate was prepared from 4,5-dimethylimidazole and one equivalent of formic acid and recrystallized from propan-2-ol; m.p. 115—119 °C. Deuteriated samples were prepared by recrystallization from pure D_2O. Chemical compositions were checked by C, H, and N analysis.

Quadrupole double resonance spectra were obtained, at room temperature, by techniques described elsewhere.[5-7] The peak frequencies were largely independent of the r.f. voltage to the Q coil at the levels used in this work ($V_Q \leqslant 80$ V peak-to-peak); at higher values high-frequency shifts and changes in line shape were observed, *e.g.* in 4-ethoxycarbonyl-4-methylimidazole, the ν_z frequency for N(3) shifted from 326 kHz at 80 V to 343 kHz at 250 V. Zeeman studies in magnetic fields ranging from 0.1 to 3 mT were extensively used to separate 'solid-effect' satellites from level-crossing signals [6] in the ^{14}N spectra, and to assign ν_x, ν_y resonances in the ^{2}H spectra. In one case, that of imidazolium hydrogen maleate (which has already been discussed [8]), the ^{14}N signals at room temperature were detected entirely by the 'solid effect,' even in zero field, and as a consequence were all doublets, with a splitting of about 50 kHz. Although no shifts of ^{14}N lines were ever observed in these Zeeman studies, presumably owing to the low gyromagnetic ratio of ^{14}N, deuteron ν_x resonances were seen to shift to higher frequencies and ν_y to lower ones, as predicted theoretically [5,6] (although the magnitude of the former were always appreciably larger than that of the latter). When Zeeman fields higher than 1 mT were used to study the deuteron, strong distortion of the ^{2}H lines was observed, because they invariably overlapped the proton dipolar absorption edge, in spite of the low r.f. irradiation fields used (V_Q varied between 0.35 and 2.1 V peak-to-peak).

Chlorine quadrupole resonance frequencies were measured in 4-chloroimidazole with a 'Decca' super-regenerative oscillator spectrometer.

Results

^{14}N and ^{2}H quadrupole double resonance data in the substituted imidazoles (1)—(14), (16), and (17) at room temperature are listed in Table 1. Both spectra at 77 K have been previously published for imidazole.[1,9] Our results agree with the assignments of these authors and support their arguments against the results of an earlier investigation.[10] The resolution of separate N(1) and N(3) signals in all solid imidazoles and their small temperature dependence (in imidazole) provides no evidence for appreciable proton transfer, at least up to room temperature.[11]

A typical ^{14}N quadrupole double resonance spectrum is shown in Figure 1 for 2-methylimidazole; the residence time in high field (τ_P) was 5 s and in the Q-coil (τ_Q) 0.5 s. The spectrum was swept in frequency steps of 2 kHz with $V_Q =$ 80 V; the prominent step near 130 kHz is the beginning of the dipolar absorption region.[6] The detection and assignment of resonances due to N(1)H groups were generally straightforward, as the spectrum indicates; three resonance lines were normally detected whose frequencies were related according to $\nu_x = \nu_y + \nu_z$, once the proton satellites had been separated from the central quadrupole resonance line (detected presumably by level crossing [6]) by studies in low Zeeman fields, as described in an earlier publication.[7] In the 4-methyl derivatives we found invariably that the lines were split. The possibility of proton transfer renders 4-substituted imidazoles tautomerically equivalent (Figure 2) and it is feasible that we might have been dealing with a crystalline mixture of both tautomers, particularly in the case of 4-methylimidazole for

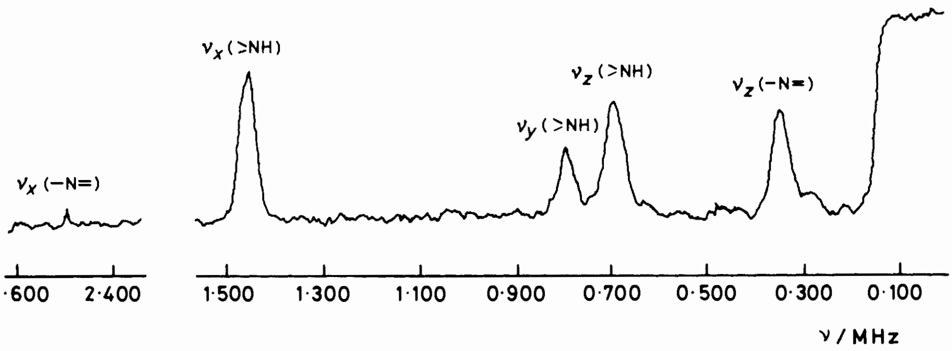


Figure 1. ^{14}N Quadrupole double resonance spectrum of 2-methylimidazole at 290 K: τ_P 5 s, τ_Q 0.5 s, 2 kHz step, V_Q 80 V peak-to-peak

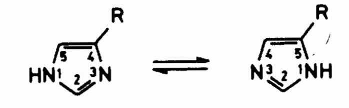
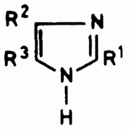
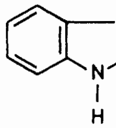


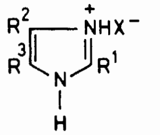
Figure 2. Tautomeric equivalence in substituted imidazoles



	R^1	R^2	R^3
(1)	H	H	H (solid)
(2)	H	Me	H
(3)	Me	H	H
(4)	H	Me	Me
(5)	Me	Me	H
(6)	H	Br	H
(7)	H	Cl	H
(8)	H	NO_2	H
(9)	H	NO_2	Me
(10)	H	NO_2	Br
(11)	H	CO_2Et	Me
(12)	H	p-$BrC_6H_4NHOC(:O)$	H
(13)	H	p-$O_2NC_6H_4$	H
(14)	SH	H	H



(15)



(16) X = HCO_2, R^1 = H, $R^2 = R^3 = CH_3$
(17) X = $HO_2CCH{=}CHCO_2$ (*cis*), $R^1 = R^2 = R^3$ = H

which two lines of very different intensities were detected in the high-frequency region (ν_x region) of the amino group absorption, a feature difficult to understand in terms of crystallographically inequivalent sites. To our knowledge, the only *X*-ray study of this compound was done on a supercooled melt[12] and is not clear on this point. In the case of 2,4-dimethylimidazole and 4-chloroimidazole it is not possible to conclude from the ^{14}N spectra whether the splitting is caused by the presence of a tautomeric mixture or by crystallographic inequivalence and there are no *X*-ray data to support either. On the basis of other evidence,[3,13] however, electron-withdrawing substituents such as halogens, the nitro group, *etc.*, seem to favour the 4-tautomer and electron-donating substituents favour the 5. In Table 1 imidazole derivatives have been named accordingly. Finally, three sets of resonance lines were found for 4,5-dimethylimidazole, suggesting the occurrence of three inequivalent crystallographic sites, since prototropic tautomerism is not observable here, because the two tautomers have identical structures.

The detection and interpretation of resonances from N(3) sites in these compounds presented special problems, because we were unable to detect ν_y signals. This situation was not surprising in view of the lower signal-to-noise ratio of the corresponding ν_x signals relative to those of NH (Figure 1) due presumably to the weaker ^{1}H–^{14}N dipolar coupling, but rendered detection of the ν_z resonances with accuracy absolutely essential. The latter often occurred at very low frequencies, as a result of the low asymmetry parameters which seem to be characteristic of imino sites in imidazole rings. In these circumstances, their frequencies were expected to overlap the dipolar absorption edge, which often extended up to 200 kHz under normal operating conditions; this enhances continuous coupling effects[6] and helps to explain the unexpectedly high sensitivity of detection of these signals. Another reason is the presence of strong proton satellites, which became obvious once Zeeman studies were carried out to allow accurate measurement of the quadrupole resonance frequency. However, because of the dipolar absorption edge, such studies proved to be tedious and care was needed to distinguish between true ν_z signals and those which were subharmonics of stronger, higher frequency lines (such as ν_x) or harmonics and half-harmonics of the proton Larmor frequency in the low Zeeman fields used. In many cases, r.f. irradiation field intensities were needed which were much lower than those normally used to detect −N= signals. Figure 3 illustrates this procedure for the resolution of the low-frequency line in the spectrum of Figure 1. It is interesting to note that the fact that proton satellites were observed at all for dico-ordinated nitrogen sites is almost certainly an indication of weak N–H · · · N hydrogen bonding in many of these compounds, as is found in the crystal structure analyses of imidazole,[14,15] benzimidazole,[16] 4-methylimidazole,[12] and 2-methyl-4-nitroimidazole.[17] Finally, as a result of the low sensitivity of detection of ν_x signals for these sites, it was not always possible to resolve clearly the aforementioned multiple splitting of lines. In such cases it was thought more accurate to report an average value in Table 1.

In 4,5-dimethylimidazolium formate, imidazolium hydrogen maleate,[8] and 2-mercaptoimidazole, no signals attributed to imino groups, −N=, were detected. This confirmed protonation of the imidazole ring in the two former compounds, leading to a structure of type (I) for the cation, and indicated a solid-state thione form (II) for the third. Nitrogen spectra from two of the nitro derivatives showed more resonance lines than could be assigned to NH and −N= sites. They were therefore attributed to NO_2 ^{14}N nuclei. As these groups are

Table 1. ^{14}N and ^{2}H Quadrupole double resonance data in substituted imidazoles, at 291 K ^{a}

		^{14}N					^{2}H				
Compound	Site	ν_x/MHz	ν_y/MHz	ν_z/MHz	e^2qQ/h/MHz	η	Site	ν_x/kHz	ν_y/kHz	e^2qQ/h/kHz	η
Imidazole (1)	N(1)	1.367	0.721	0.647	1.391	0.930	NH	124.3	111.2	157.0	0.167
	N(3)	2.511		0.192	3.220	0.119	CH	135.7	129.7	176.9	0.068
4-Methylimidazole (2)	N(1)	1.356	0.700(5)	0.666(10)	1.364(7)	0.977(19)	NH	126.1	111.7	158.5	0.182
		1.324		0.666(10)	1.321(6)	1.008(20)		123.5	110.2	155.8	0.171
	N(3)	2.471(10) ^{b}		0.252 ^{b}	3.127(13) ^{b}	0.161 ^{b}	CH	139.2	131.6 ^{b}	180.5	0.084
								136.4	131.6 ^{b}	178.7	0.054
2-Methylimidazole (3)	N(1)	1.461	0.782	0.680	1.495	0.910	NH	120.2	106.9	151.4	0.176
	N(3)	2.503		0.329	3.118	0.211					
4,5-Dimethylimidazole (4)	N(1)	1.443	0.856	0.585	1.534	0.763	NH	125.1	112.6	158.5	0.158
		1.402	0.780	0.625	1.453	0.861		123.8	108.8 ^{b}	155.1	0.194
		1.374	0.749	0.625	1.415	0.883		120.3	108.8 ^{b}	152.7	0.151
	N(3)	2.464 ^{b}		0.214 ^{b}	3.143 ^{b}	0.136 ^{b}	CH	140.7	132.1 ^{b}	181.9	0.095
								139.4		181.0	0.081
2,4-Dimethylimidazole (5)	N(1)	1.592	1.042	0.549	1.757	0.625	NH	130.0	115.3	163.5	0.180
		1.511	0.844	0.671	1.567	0.856		118.2	106.1	149.5	0.162
	N(3)	2.529(8)		0.302	3.171(11)	0.191					
		2.507(8)		0.346	3.112(11)	0.222					
	or			or							
		2.529(8)		0.346	3.141(10)	0.220					
		2.507(8)		0.302	3.141(11)	0.192					
4-Bromoimidazole (6)	N(1)	1.359	0.701	0.653	1.377	0.949	NH	125.8	113.3	159.4	0.157
	N(3)	2.591		0.421(4)	3.174(3)	0.265(3)					
4-Chloroimidazole (7)	N(1)	1.442	0.782	0.660	1.483	0.890	NH	131.0	117.7	165.8	0.160
		1.380	0.717	0.660	1.440	0.943		129.7	115.8	163.7	0.170
							or		or		
	N(3)	2.564 ^{b}		0.443	3.123	0.284		131.0	115.8	164.5	0.185
		2.564 ^{b}		0.410	3.145	0.261		129.7	117.7	164.9	0.146
4-Nitroimidazole (8)	N(1)	1.303	0.762	0.541	1.377	0.786	NH	127.1	114.2(5)	160.9(3)	0.160(6)
	N(3)	2.621		0.368	3.249	0.277					
	NO_2	1.022	(0.752)	0.272	1.181	0.461					
5-Methyl-4-nitro-imidazole (9)	N(1)	1.424	0.793	0.633	1.477	0.857	NH	139.8	128.3	178.7	0.129
	N(3)	2.670		0.242(10)	3.399(5)	0.142(6)					
	NO_2	1.020	(0.764)	(0.256)	(1.189)	(0.431)					
5-Bromo-4-nitro-imidazole (10)	N(1)	1.569	0.870	0.695	1.629	0.854					
	N(3)	2.609		0.336	3.255	0.207					
4-Ethoxycarbonyl-5-methylimidazole (11)	N(1)	1.363	0.702	0.659	1.378	0.957	NH	125.0	114.1	159.4	0.137
	N(3)	2.596		0.326	3.244	0.201	CH	141.2	135.0	184.1	0.067
4-Imidazolylcarboxy-*p*-bromoanilide (12)	N(1)	1.265	0.818	0.445	1.390	0.640					
	NH	2.880		0.583	3.451	0.338					
	N(3)	2.578		0.226	3.287	0.138					
4-(*p*-Nitrophenyl)-imidazole (13)	N(1)	1.526	1.189	0.343	1.806	0.380					
	N(3)	2.753		0.170	3.557	0.096					
2-Mercaptoimidazole (14)	N(1) [N(3)]	1.841	1.206	0.629	2.035	0.618					
Benzimidazole (15)	N(1)	1.863	1.167	0.694	2.021	0.687	NH	133.2	121.4	169.7	0.139
	N(3)	2.573		0.422	3.149	0.268	CH	136.8	131.1	178.6	0.064
4,5-Dimethyl-imidazolium formate (16)	N(1) [N(3)]	1.230	0.900	0.326	1.423	0.458	NH	111.0	99.3	140.2	0.167
	N(3) [N(1)]	1.216	0.873	0.340	1.395	0.488		100.9	87.8	125.8	0.208

^{a} Concerning the ambiguity of 4(5)-substitution, the compounds are named according to their most likely structures from literature data. ^{b} Average values.

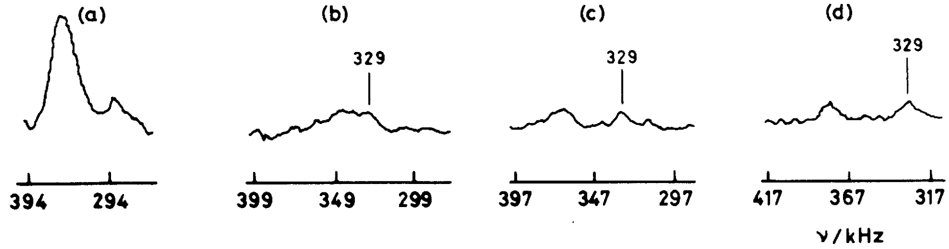
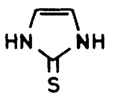


Figure 3. Resolution of the low frequency ν_z absorption line for N(3) in 2-methylimidazole: τ_P 8 s, τ_Q 0.5 s, (a) V_Q 80 V peak-to-peak, 2 kHz step; (b) *H* 0 G, 1 kHz step, V_Q 10 V peak-to-peak; (c) *H ca.* 7 G, 1 kHz step, V_Q 10 V peak-to-peak; (d) *H ca.* 10 G, 1 kHz step, V_Q 10 V peak-to-peak (1 G = 10^{-4} T)

(I)



(II)

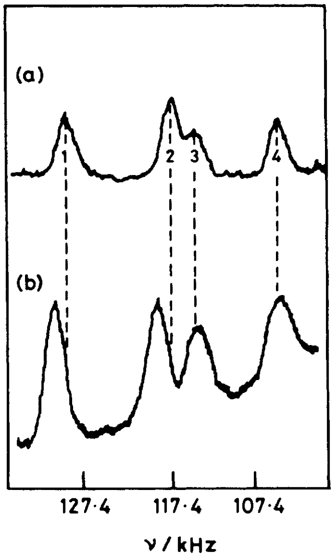


Figure 4. ^2H Quadrupole double resonance spectra of 2,4-dimethylimidazole at 291 K: (a) in zero magnetic field and (b) in a magnetic field of 0.8 mT at the Q coil

not directly bonded to protons (although their oxygen atoms may be involved in short hydrogen-bond contacts) the intensities of the lines detected were very weak and this meant that they could not always be reproduced. When this was the case, quadrupole data referring to these groups are listed in parentheses in Table 1. In two cases [compounds (10) and (13)] no $^{14}NO_2$ signals could be detected and the assignments reported in Table 1 must therefore be in some doubt.

Deuteron Spectra.—For ^2H, only the two higher frequency signals are usually found and correct assignment of the ν_x and ν_y lines was therefore essential. In many cases only two lines were detected and the assignments were obvious. Occasionally, the spectra were more complicated. For instance, the splitting of resonances which had already been observed in ^{14}N spectra for some of these compounds was confirmed in their ^2H results; ν_x and ν_y lines were then assigned by careful Zeeman studies, as Figure 4 illustrates: lines 1 and 2 are clearly ν_x while 3 and 4 are ν_y. Other compounds, including imidazole, showed more signals that those expected from the N–D deuterons. They occurred in pairs (with the ν_x, ν_y lines assigned as before) and could be easily distinguished from N–D deuteron signals as the corresponding ^2H quadrupole coupling constants and asymmetry parameters were more typical of C–D deuteron sites [18] with sp^2 hybridization at the carbon atom.[19] We believe that these signals originate from hydrogen–deuterium exchange at the C(2) ring position. Deuteriation of these compounds was achieved by dissolution in 100% D_2O and slow evaporation *in vacuo* at room temperature for at least two or three days. Hydrogen–deuterium exchange at C(2) in imidazole and some of its derivatives is known to occur in short periods of time at high temperatures (>100 °C) but is slower at room temperature.[13] It is therefore likely that at least partial exchange occurred at C(2) under the deuteriation conditions used in this work. Furthermore, the same reaction at C(4) and C(5) is much slower and no C–D signals were ever detected in derivatives with C(2) substituents.

Table 2. ^{35}Cl Quadrupole resonance frequencies in 4-chloroimidazole

T/K	ν/MHz
297	34.760
	34.196
77	35.488
	35.279

Protonation of the imidazole ring in 4,5-dimethyl imidazolium formate, already apparent from the ^{14}N data, was further confirmed by the detection of four ^2H resonance lines.

In four compounds we failed altogether to find any deuteron spectra, either as a result of their poor solubility in D_2O or of short ^1H spin–lattice relaxation times, or both.

Chlorine Spectra.—The ^{35}Cl quadrupole resonance frequencies detected in 4-chloroimidazole are listed in Table 2. They confirm the multiplicity of lines already observed in the nitrogen and deuteron double resonance spectra of this compound.

Discussion

The ^{14}N quadrupole interaction is defined by means of a symmetric, traceless, second-rank tensor, which is usually discussed in terms of the three principal components q_{xx}, q_{yy}, and q_{zz} of the second derivative of the electrostatic potential ($q_{zz} = d^2V/dz^2$ *etc.*) defined according to the convention (1)

$$|q_{zz}| \geqslant |q_{yy}| \geqslant |q_{xx}| \qquad (1)$$

and their direction cosines with respect to axes fixed in the molecule. In a powder, generally the magnitudes of these components are deduced from experiment, and rarely their sign and orientation; they are expressed in terms of the quadrupole coupling constant e^2qQ/h (in Hz) where $q = q_{zz}$ is the principal component of largest magnitude, Q is the nuclear electric quadrupole moment, and the asymmetry parameter η is defined by equation (2) bearing in mind that

$$\eta = (q_{xx} - q_{yy})/q_{zz} \qquad (2)$$

Laplace's equation (3) is assumed to hold. For ^{14}N, their

$$q_{xx} + q_{yy} + q_{zz} = 0 \qquad (3)$$

values are governed largely by the $2p$ electron distribution; in gaseous imidazole,[21] for example, the maximum principal component, q_{zz}, lies close to the inferred directions of the lone-pair orbitals at both nitrogen sites, that is perpendicular to the molecular plane for N(1) ($2p_\pi$) and in plane, bisecting the CNC angle, for N(3) ($2p_\sigma$). Since $Q(^{14}N)$ is positive (*ca.* $1.7 \times 10^{-30}m^2$) and q_{zz} for one electron in a $2p_z$ orbital is negative, the quadrupole coupling constant e^2qQ/h is negative at both nuclear sites.

In the solid state phase, however, hydrogen bonding may occur both at N(1) and N(3), so that not only the magnitudes of the quadrupole parameters are likely to change but also their orientations. It has already been proposed that this occurs in imidazole [9,21,22] for which both crystallographic data

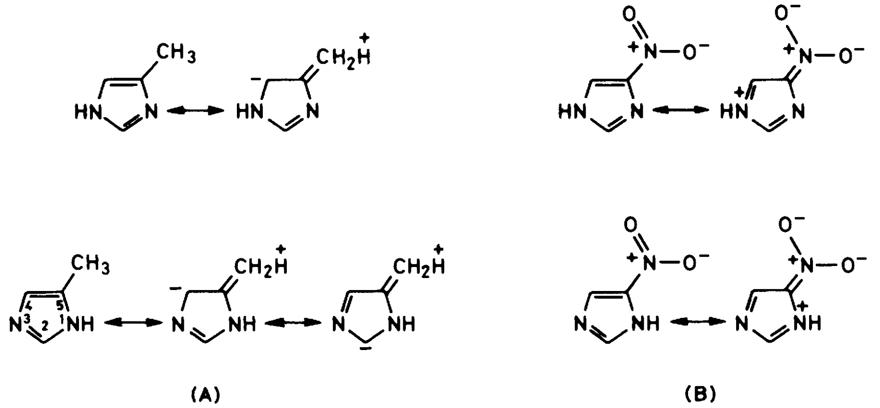


Figure 5. Mesomeric effect from electron-donating (A) and electron-withdrawing (B) 4-substituents on the π-electron charge distribution of the imidazole ring

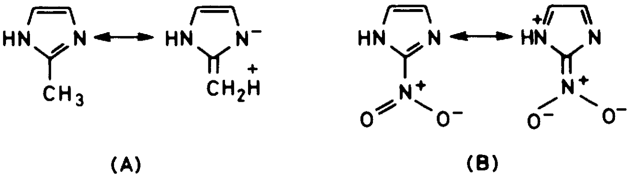


Figure 6. Mesomeric effect from electron-donating (A) and electron-withdrawing (B) 2-substituents on the π-electron charge distribution of the imidazole ring

and theoretical calculations of the quadrupole coupling tensor have been published,[14,15,20,22-24] but little information of this kind is available for substituted imidazoles. The quadrupole coupling constants also depend on temperature, but the changes for imidazole itself are not large [1,9] and their effects will be neglected for the other compounds discussed in this paper.

Perhaps the most striking aspect of Table 1 is the large variation in the ^{14}N(1)H quadrupole coupling constants in contrast to those of the imino-sites N(3). One possible explanation lies in the selectivity of mesomeric effects: N(1) sites have potentially two delocalizable π-electrons and so will be more sensitive to changes in the π-electron distribution resulting from substitution by electron-donating or electron-withdrawing groups, whereas imino-sites N(3) will only show such effects directly when π-electron donating groups are substituted at C(2), as illustrated in Figures 5 and 6. Inductive effects, on the other hand, which are known to decrease with distance, might have been expected to shed some light on the problem of prototropic tautomerism (Figure 2); unfortunately, their influence is difficult to distinguish from that of hydrogen bonding, which this discussion will show to have a very significant effect on the quadrupole parameters.

It is first necessary to establish the most probable orientation of the ^{14}N e.f.g. axes at both kinds of nitrogen atom in the substituted imidazoles in the solid state. Microwave studies of gaseous imidazole [21] have located the principal z-axis of the imino (−N=) or N(3) e.f.g. tensor in the plane of the molecule with $e^2q_{zz}Q/h$ negative and having a deviation of only 4° from the direction of the $\widehat{CNC}$ bisector ($\widehat{CNC}$ = 104.5°); the principal y-axis lies perpendicular to the plane [subject to the usual conventions of equation (1) with $q_{zz} = q$). Theoretical calculations are in general agreement with the orientation of q_{zz} but some authors place q_{yy} perpendicular [22,23] and others parallel [24] to the molecular plane. The lack of unanimity doubtless arises from the low value of η which means that q_{xx} and q_{yy} are of comparable magnitude and therefore difficult to distinguish both experimentally and theoretically, a feature that also makes it difficult to infer their relative orientation in the molecule in the crystal.

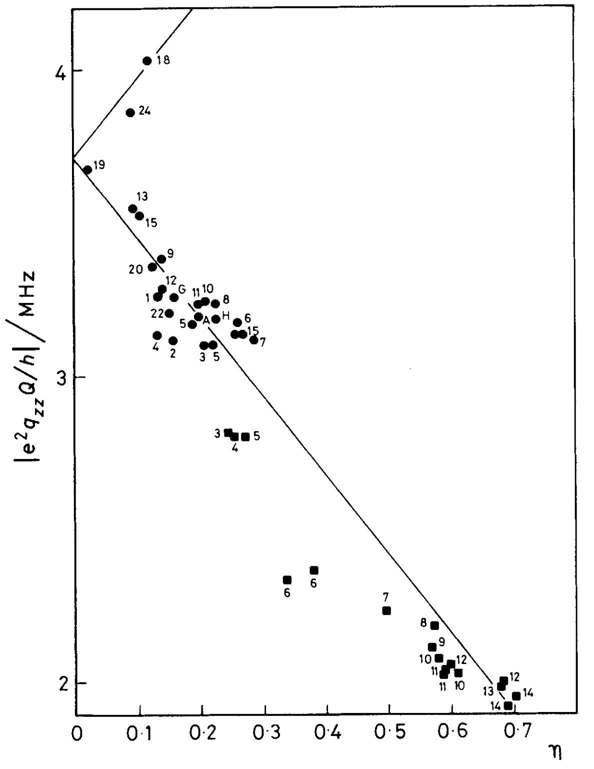
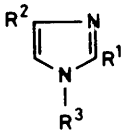


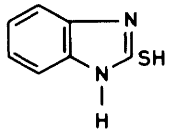
Figure 7. Correlation of $|e^2qQ/h|$ with η for the imino site [N(3)] in substituted imidazoles. The numbered points correspond to compounds in Table 1 or the text (●) or to those mentioned in ref. 1 (■)

Hydrogen-bonding to the amino nitrogen atom in a neighbouring molecule is known to occur,[14,15] one effect of which is to reduce the value of the ^{14}N quadrupole coupling constant relative to that in the gas. It is then difficult to understand the nuclear quadrupole resonance data for 1-benzylimidazole (e^2qQ/h = 3.679 MHz, η = 0.022),[1] in which hydrogen bonding to the imino-nitrogen atom is impossible, unless it is assumed that the x and the y axes of the ^{14}N e.f.g. tensor in imidazole interchange on passing from the gas to the solid state. Figure 7 illustrates this point by means of a plot of



	R^1	R^2	R^3
(18)	H	H	H (gaseous)
(19)	H	H	$PhCH_2$
(20)	H	$HO_2CCH(NH_2)CH_2$	H (L-histidine)
(21)	H	$HO_2CCH(NH_2)CH_2$	H (hydrochloride monohydrate)
(22)	H	$NaO_2CCH{=}CH$	H
(23)	H	$HO_2CCH{=}CH$	H (monohydrate)
(24)	H	H	Ac
(25)	Me	H	Me

(26) (gaseous)
(27) (solid)



(28)

$|e^2qQ/h|$ against η for all the compounds listed in Table 1, together with additional points for gaseous imidazole (18),[21] 1-benzylimidazole (19),[1] L-histidine (20),[1] sodium urocanate (22),[9] 1-acetylimidazole (24),[25] and the N(7) nuclei in the five-membered rings of hypoxanthine (H), guanine (G), and adenine (A) taken from the following paper.[26]

The reflection implied at the $\eta = 0$ axis when $|e^2qQ/h| \sim 3.7$ MHz suggests that q_{xx} and q_{yy} have interchanged directions so that substituted imidazoles with imino-quadrupole coupling constants less than this should in the solid state have the orientation shown in Figure 8, in which the x and y axes of the ^{14}N quadrupole tensor have been interchanged with respect to those deduced from the analyses of the microwave spectrum of gaseous imidazole.[21] The curve which has been drawn in Figure 7 to connect these points also passes close to those for a number of imidazole complexes, for which the orientation of Figure 8 has also been postulated.[1] In these latter compounds $(e^2qQ/h)^{-1}$ shows a good correlation [1] with η, to which many of the substituted imidazoles adhere. Such a correlation has been attributed [1] to changes in the N(3) $2p_\sigma$ donor orbital population due to varying degrees of co-ordination to the metal atom; since q_{zz} has been inferred to lie close to the direction of this orbital, its value is very susceptible to the $2p_\sigma$ atomic population. In the case of the substituted imidazoles, these arguments would lead to populations varying over a relatively small range from 1.92 in compound (13) in Table 1 to 1.88 in compounds (3), (5), and (7), due presumably to substituent effects and the differing strengths of hydrogen bonding. The N–D quadrupole coupling constants [27–29] strongly support the existence of hydrogen bonding to N(1) in many of the compounds in Table 1, although it is not generally possible to tell whether such association occurs with the imino-nitrogen atom of the ring or suitable atoms in the substituents.

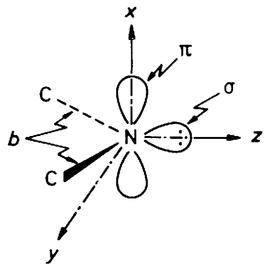


Figure 8. Proposed orientation of the ^{14}N electric field gradient tensor for the imino site N(3) in imidazole and many of its substituted derivatives in the solid state

For the e.f.g. tensor of the amino ($\rangle$NH) nitrogen nucleus, N(1), in gaseous imidazole [21] ($e^2q_{zz}Q/h$) lies perpendicular to the molecular plane and is negative, with q_{yy} making an angle of 17° with the N–H bond towards the imino nitrogen atom; again the theoretical estimates differ on the position of the two smaller principal components, two [23,24] placing q_{yy} correctly and the other [22] interchanging the directions of q_{xx} and q_{yy}. In the solid state, the situation is much more uncertain, as becomes apparent when we plot (Figure 9) $|e^2q_{zz}Q/h|$, the N(1) experimental quadrupole coupling constant taken from Table 1, against $|e^2q_{yy}Q/h|$ obtained from the relation (4).

$$q_{yy} = -(q_{zz}/2)(1 + \eta) \qquad (4)$$

Additional points have been inserted for imidazolium hydrogen maleate (17),[8] gaseous (26) [30] and solid pyrrole (27),[25,31] gaseous imidazole (18),[21] sodium urocanate (22),[9] L-histidine hydrochloride monohydrate (21),[9] urocanic acid monohydrate (23),[9] and 1-acetylimidazole (24) [25] and the NH groups in the five-membered rings of several solid nucleotide bases and their salts,[26] including hypoxanthine (H), adenine (A) and its dihydrobromide (AB), and guanine (G), and the data (closed squares) for twelve imidazole complexes ([3]—[14]),* 1-benzylimidazole (19), L-histidine (20), and imidazolium nitrate [15], and iodide [16], taken from Ashby *et al.*'s paper.[1] Most of the results fall within a series of three bands which have been inserted in Figure 9, the bands themselves crossing near the region in which $|e^2q_{yy}Q/h| = |e^2q_{zz}Q/h| =$ *ca.* 1.3 MHz. It may be inferred that compounds with quadrupole coupling constants greater than this value should have q_{zz} perpendicular to the molecular plane, with e^2qQ/h negative; below, q_{zz} lies somewhere in the molecular plane, and according to convention e^2qQ/h becomes positive. This re-orientation has been emphasized in the diagram by re-plotting the results for 4-nitroimidazole (8′), 4,5-dimethylimidazolium formate (16′), imidazolium hydrogen maleate (17′), di-imidazole(pyrocatecholato)zinc [8′], imidazolium nitrate [15′], and one of the NH groups in L-histidine hydrochloride monohydrate (21′) and urocanic acid monohydrate (23′) with q_{yy} and q_{zz} interchanged.

The problem now is to decide on the orientation of the in-plane components in the solid state. They are known for gaseous imidazole and pyrrole, but the results for these two molecules, (18) and (26) occupy rather an ambiguous position in Figure 9, lying in between the two principal correlation bands. Too much significance should not be attached to these graphical plots; they depend for their validity on a rough constancy of the ^{14}N e.f.g. axes within the bonding framework, a generalization which on occasions may be a serious approximation, as in gaseous imidazole where q_{yy} deviates by 17° from the N–H direction. However, the bands drawn in Figure 9 relate the quadrupole parameters of 36 imidazole derivatives, and the few more rigorous calculations of the full e.f.g. tensor that have been made, for imidazole and 1-methylimidazole,[24] support the general constancy in orientation of the e.f.g. axes.

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* Compounds with numbers in square brackets are numbered as in ref. 1; their formulae are not displayed.

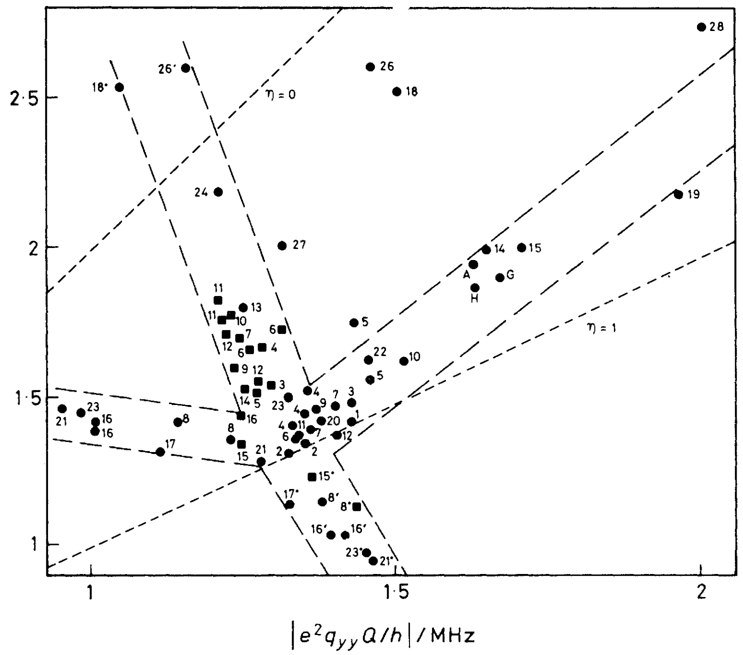


Figure 9. Correlation of $|e^2q_{zz}Q/h|$ with $|e^2q_{yy}Q/h|$ for N(1) in imidazoles. The numbered points correspond to compounds in Table 1 in the text (●) to those mentioned in ref. 1 (■). The dotted lines correspond to the loci of all points for which $\eta = 0$ (upper) and $\eta = 1$ (lower)

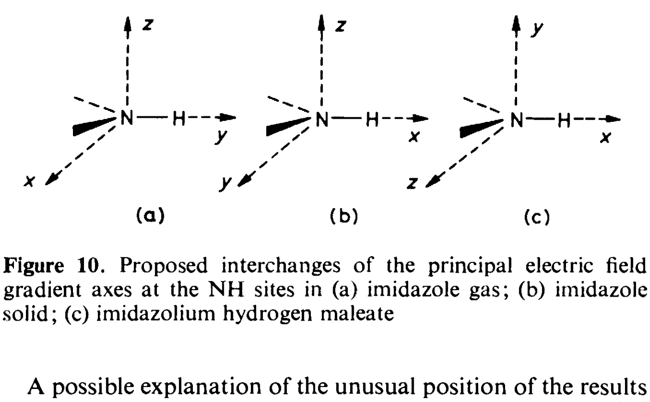


Figure 10. Proposed interchanges of the principal electric field gradient axes at the NH sites in (a) imidazole gas; (b) imidazole solid; (c) imidazolium hydrogen maleate

A possible explanation of the unusual position of the results for gaseous imidazole and pyrrole comes from recent calculations for a trimeric imidazole unit in which the three rings have been placed in the same relative orientation and distance apart as is found in the crystal;[32] for the central molecule in the trimer, the orientations of the x and y axes of the ^{14}N(1) e.f.g. tensor are found to be interchanged with respect to those in the monomer. In Figure 9, this would correspond to reflecting points 18 and 26 in the line $\eta = 0$, giving the new positions marked 18′ and 26′ in that Figure, which now lie within the left-hand band containing results for twelve imidazole complexes. The general trend for this group of molecules is for e^2qQ/h to decrease with increasing strength of hydrogen bonding, as evinced by the N–H stretching frequencies[1] and hydrogen-bond distances.[2,33] Assuming this interchange to have occurred in solid imidazole, we then have the general e.f.g. orientations shown in Figure 10 for molecules whose points in Figure 9 lie above the $\eta = 0$ line [Figure 10(a)], for those lying between the $\eta = 0$ and $\eta = 1$ lines [Figure 10(b)], and for those lying below the $\eta = 1$ line [Figure 10(c)]. These correlations relate the quadrupole parameters of 41 imidazole derivatives.

To interpret these correlations, we are obliged, in the almost complete absence of *ab initio* calculations for these molecules, to use the rough model of Townes and Dailey[31] which relates the principal e.f.g. components to the p-orbital populations at the nitrogen atom. The absolute values of such populations have little significance, but their trends within a related series of molecules of known e.f.g. orientation may nevertheless be of some use.[34] For NH in the axial orientation of Figure 10(a), the theory gives[31] equations (5)—(7) in which (e^2q_0Q/h)

$$q_{xx} = q_0[-(\sigma/2)(1 - \cot^2\theta) - \pi/2 + (b/2)(2 - \cot^2\theta)] \quad (5)$$

$$q_{yy} = q_0[\sigma(1 - \cot^2\theta) - \pi/2 + b(\cot^2\theta - \tfrac{1}{2})] \quad (6)$$

$$q_{zz} = q_0[-(\sigma/2)(1 - \cot^2\theta) + \pi - (b/2)(1 + \cot^2\theta)] \quad (7)$$

is the nitrogen $2p$ atomic quadrupole coupling constant (about − 9 MHz[1,25]), σ and b are the N–H and N–C orbital populations (the latter are assumed to be identical), π is that of the p_π lone-pair orbital, and 2θ is the CNC angle. Since the latter is very similar at both N(1) and N(3) (107 and 105° respectively[15]), it is convenient to take $2\theta = 106°$, in which case $\cot^2\theta = ca.\ 3/5$ and equations (5)—(7) become equations (8)—(10) which are applicable to both amino and

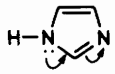
$$q_{xx} = q_0(-\sigma/5 - \pi/2 + 7b/10) \quad (8)$$

$$q_{yy} = q_0(2\sigma/5 - \pi/2 + b/10) \quad (9)$$

$$q_{zz} = q_0(-\sigma/5 + \pi - 4b/5) \quad (10)$$

imino sites provided that due attention is paid to the different relative orientation of the e.f.g. tensors and the different significance of σ in the two cases.

To return to the NH group, these equations reproduce *some* of the features of more reliable *ab initio* calculations;[24] *e.g.* the sign of e^2qQ/h is predicted to be negative in imidazole and 1-methylimidazole [in which π is likely to be greater than $(\sigma + 4b)/5$], and in 1-methylimidazole both e^2qQ/h and η might be expected to increase relative to imidazole owing



(III)

partly to a drop in σ. The correlations implied in Figure 9 suggest that e^2qQ/h remains negative for all magnitudes greater than 1.35 MHz and that the behaviour of the NH electrons depends primarily on the hydrogen bonding to this group. The band on the left-hand side of Figure 9, of approximate slope +6, is governed by the behaviour of N(1) towards various strengths of hydrogen bonding, from none at all for gaseous imidazole (18) and 1-acetylimidazole (24) to species such as O, N, or I^- in which the strength of the interactions differs from one molecule to the next. The right-hand band, of approximate slope −1.6, relates the quadrupole parameters of substituted imidazole rings hydrogen bonded, usually to each other, by N–H · · · N hydrogen bonds; the principal variations from one molecule to the next are then caused by substituent effects and other factors. The evidence for these generalisations will now be discussed.

As regards the left-hand band, Ashby *et al*[1] have already noted the general relationship between N–H stretching frequency and hydrogen-bond length There is an inferred connection with the positive charge on the imidazole ring; points [10] and [11] in Figure 9, for example, belong to the neutral complexes $Zn(im)_2Br_2$ and $Zn(im)_2I_2$ (im = imidazole); adding a proton at N(3) reduces e^2qQ/h drastically, as in the iodide (point 30); replacing I^- by a stronger hydrogen-bonding species such as NO_3^-, HCO_2^-, or the hydrogen maleate ion[33] is sufficient to produce an interchange in the *y* and *z* axes of the N(1) e.f.g. tensor, so that below $|e^2qQ/h|$ = 1.35 MHz, we find compounds mostly with positively charged imidazole rings and an N(1) e.f.g. orientation shown in Figure 10(c). Above this value, the band has a slope of about +6, which from equations (8)—(10) and the orientation of Figure 10(b) corresponds to the relationship (11) between the changes in orbital populations. Hydrogen bonding changes σ

$$\Delta\pi = ca. - \Delta\sigma/4 + 4\Delta b/3 \qquad (11)$$

which from equations (8)–(10) affects both q_{zz} and q_{yy} to equal extents but in opposite directions [note that *x* and *y* have to interchange to conform with the orientation of Figure 10(b)]; changes in π and *b* must therefore be significant and probably of the same sign according to equation (11) decreasing with increasing strength of hydrogen bonding The variations of *b*, however, are likely to be smaller than those in σ.[29] Now many of the compounds in this group are imidazole complexes, in which N(3) is adjacent to an electron acceptor and N(1) is expected to be hydrogen bonded to an electron donor;[2] the resulting asymmetry in the electron potential will favour the π electron migration shown in structure (III) and the quadrupole resonance results show that the σ charge migrates in the same direction. Below $|e^2qQ/h|$ = *ca.* 1.35 MHz, the *y* and *z* directions interchange, and the slope of the band changes since these two components have differing coefficients in π and *b*. The new slope of +3 (assuming e^2qQ/h is now positive) implies that equation (12) holds, and

$$\Delta\pi = ca. \Delta\sigma/9 + 6\Delta b/7 \qquad (12)$$

similar trends occur, with changes in π even more closely equal to those in *b*, and both smaller than those in σ. This region of Figure 9 contains mostly salts of the imidazolium ion, which is still polarizable if hydrogen bonding to the two NH groups is sufficiently different in strength. These relationships may be used to make the tentative assignments of the ^{14}N and ^{2}H quadrupole data for 4,5-dimethylimidazolium formate shown in Table 3. The similarity in charge distribution between hydrogen-bonded protonated and unprotonated imidazole rings is noteworthy.[15]

Table 3. ^{14}N and ^{2}H Quadrupole resonance data in 4,5-dimethylimidazole and its cation at 291 K

	^{14}N		^{2}H	
	e^2qQ/h / MHz	η	e^2qQ/h / kHz	η
4,5-Dimethylimidazole (4)	1.467[a]	0.837[a]	155.4[a]	0.168[a]
4,5-Dimethylimidazolium formate (16)	1.395 1.423	0.488 0.458	125.8 140.2	0.208 0.167

[a] Average values.

In contrast, the right-hand band in Figure 9, which contains mostly results from substituted imidazoles, has a slope of approximately −1.6 for a limited region above $|e^2qQ/h|$ = *ca* 1.35 MHz, implying the relationship (13). At least three of

$$\Delta\pi = ca. 3\Delta\sigma - 2\Delta b \qquad (13)$$

the compounds in this group, imidazole,[15] 4-methylimidazole,[12] and benzimidazole,[16] are known to contain chains of imidazole rings linked by N–H · · · N hydrogen bonds. If such bonding is present in all, then the electronic effects observed in this group may be mostly ascribed to the effect of substituents on the NH group in a roughly constant hydrogen-bonding environment. If changes in σ are small, equation (13) shows that changes in π are larger than those in *b*, and indeed may have the opposite sign. The effect of *C*-substituents is, in general, small except for NO_2, which, in at least one compound, 4-nitroimidazole (8), withdraws so much $2p_\pi$ charge from N(1) (Figure 5) that the *y* and *z* directions of the e.f.g. tensor appear to interchange (Figure 9). This effect is not observed in 4-nitro-5-bromoimidazole (point 10) presumably because the bulky Br substituen reduces the conjugation by forcing the NO_2 group out of planarity with the ring. A high ^{14}N quadrupole coupling constant is also found in benzimidazole, owing possibly to the weaker hydrogen bonding,[16,35] but more probably to an increase in p_π density in the imidazole ring at the expense of that in the benzene ring, an effect also observed in ^{14}N magnetic resonance studies.[36] The positions of the points for 2-mercaptoimidazole (14) and 2-mercaptobenzimidazole (28), which have thione structures,[37] may also be due to a high $2p_\pi$ charge density on the nitrogen atom.

An apparent exception to these generalisations is afforded by the molecule of 4-(*p*-nitrophenyl)imidazole (point 13), a substituted imidazole which nevertheless lies in the left-hand band in Figure 9. Its position would be explained if the N(1) group in the imidazole ring were hydrogen bonded to the nitro substituent in the benzene ring rather than to N(3) in an adjacent imidazole ring.

The sensitivity of the N(1) quadrupole parameters to hydrogen bonding is such as to conceal any obvious effects of tautomerism in the imidazole ring (Figure 2) except possibly for the case of 4-methylimidazole already discussed There is, indeed, little obvious dependence apparent in the effects of substituents on their position of substitution, except for N(1) and possibly C(2); with respect to the latter, there are clear differences between the quadrupole parameters of 4- and 2-methylimidazole and 4,5- and 2,4-dimethylimidazole, where in both cases the 2-substituent increases both $|q_{yy}|$ and $|q_{zz}|$, presumably by increasing the π-electron population at nitrogen [equations (11) and (13)]. In agreement with this conclusion, 2-methylimidazole is more basic than 4-methylimidazole, but with other substituents there is no clear distinction between the effects of electron-withdrawing and electron-releasing substituents as is found in pK_a studies;[3,38] for example, 4-methyl- and 4-bromo-imidazole have almost the same quadrupole parameters at room temperature but very different basicities.[38]

At the N(3) position, changes in the population of the σ donor orbital due to complexing have already been discussed by Ashby *et al.*[1] As regards the substituted imidazoles, they show few differences in their quadrupole parameters, except possibly in two cases (Figure 7). In the first, that of 1-benzylimidazole,[19] blocking hydrogen bonding does increase $|e^2qQ/h|$ as expected, perhaps sufficiently to interchange the directions of q_{xx} and q_{yy} from those in Figure 8, as seems to occur in 1-acetylimidazole (24). The position of 4-(*p*-nitrophenyl)imidazole (13) is similarly explained if, as we have previously suggested, N(1) hydrogen bonds to the NO_2 group of the 4-substituent rather than to N(3) in another imidazole ring The most notable feature of all these results is the relatively small variation (<0.7 MHz) in q_{yy} relative to q_{xx} for all the solid compounds plotted in Figure 7, which is presumably connected with the direction of q_{yy} roughly perpendicular to the lobes of both the σ lone pair and p_π orbitals (Figure 8). As one atomic population rises, the other falls, leading to a rough constancy in q_{yy}. More detailed analyses must await a better knowledge of the solid-state molecular wavefunctions.

Acknowledgements

We thank the British Council for a research grant to one of us (M. L. S. G.) and Queen Elizabeth College, the S.E.R.C. and the University of London Central Research Fund for grants towards the purchase of equipment. We thank Mr. W. Tertiuk (Smith Kline & French Research Ltd.) for assistance with purification and synthesis of samples, Dr. G. R. Wellman (Smith Kline & French Laboratories, Philadelphia) for a sample of 4,5-dimethylimidazole, and Miss M.-I. Pousão-Smith for assistance with the diagrams.

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Received 9*th August* 1982; *Paper* 2/1385