Protonation and phase effects on the NMR chemical shifts of imidazoles and pyrazoles: experimental results and GIAO calculations†

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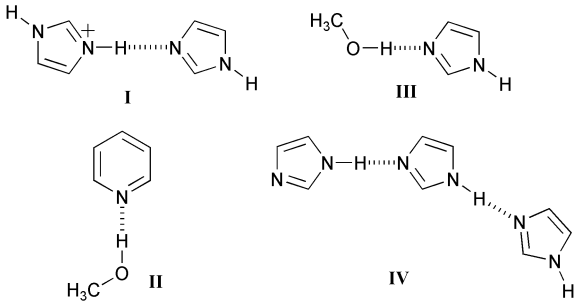
The effects produced on ^{1}H, ^{13}C and ^{15}N chemical shifts by protonation and by hydrogen-bonding solvents on five azoles have been determined experimentally. The following compounds have been studied: imidazole, 4,5-dimethylimidazole, pyrazole, 3,5-dimethylpyrazole and 4,5-dihydro-3-methyl-2*H*-benz[*g*]indazole. Phase effects on the ^{13}C chemical shifts of the C-4 atom of pyrazole are discussed based both on empirical models and on GIAO calculations of absolute shieldings in different complexes. The special case of the chemical shifts of pyrazoles in the solid state, where they form multiple N–H···N hydrogen bonds, has also been studied theoretically.

Introduction

This paper aims to provide a description of protonation and phase effects on the NMR chemical shifts of simple imidazoles and pyrazoles. We will divide this paper into four sections: (*i*) study by ^{13}C and ^{15}N NMR CPMAS of some pyrazolium and imidazolium cations $[B–H]^+$; (*ii*) study by ^{1}H NMR in solution and by ^{13}C and ^{15}N NMR in the solid state of some hemi-protonated pyrazolium cations $[B–H···B]^+$ with special emphasis on distinguishing them from an equimolar mixture of $[B–H]^+ + B$; (*iii*) study by ^{13}C NMR in solution of solvent effects in neutral N–H pyrazoles, especially hydrogen bond effects and extension of these effects to the solid state considered as a "peculiar solvent" and (*iv*) GIAO calculations on model compounds in an attempt to provide an explanation to the observations reported in sections (*i*)–(*iii*).

The most popular method to calculate absolute shieldings σ and, through them, chemical shifts δ, is Ditchfield's GIAO [gauge independent (or invariant or including) atomic orbital] method.[1–3] In what concerns aromatic heterocycles, such as imidazoles and pyrazoles, there are 75 references concerning GIAO applications, including some NICS (nuclear independent chemical shifts).[4] An examination of these 75 papers reveals that these GIAO calculations involved almost exclusively isolated molecules, that is in the gas phase. The exceptions are two publications reporting the calculation of nonspecific solvent effects,[5,6] another one on the effect of coordination with metals,[7] and two more on the consequences of dimerisation or higher order associations.[8,9] Three publications concern the study of specific solvent effects produced by hydrogen bonds (HBs). We have represented in Scheme 1 these examples: protonated imidazole dimer **I**,[10] pyridine solvated by methanol **II**,[11] and hydrogen-bonded imidazoles **III** and **IV**.[12]



Scheme 1

In the present paper, we wish to report some experimental studies by solution and solid state NMR related to the structure of azole cations and to the effect of hydrogen bonds on the chemical shifts of azoles. We consider protonation and deprotonation as the terminal step of HBs,[13] thus we will discuss some examples of protonated diazoles (imidazoles, pyrazoles) and some azole anions:

$$B: + H–A \rightleftharpoons B···H–A \rightleftharpoons B^{+}–H···A^{-} \rightleftharpoons B–H + A^{-}$$

To provide a theoretical basis for the observed effects, GIAO/DFT calculations will be carried out on different model compounds. Theoretical calculations of absolute shieldings of charged heteroaromatic compounds (cations) are relatively more common,[13–16] although no examples of diazolium (imidazolium, pyrazolium) cations have been reported.

Experimental

Chemistry

Melting points were determined on a microscope hot stage apparatus and are uncorrected. Mass spectra were obtained

† Electronic supplementary information (ESI) available: absolute and relative shieldings calculated at the B3LYP/6-311++G**//B3LYP/6-311++G** level for compounds **V** to **XXI** as well as pyrazole and 3,5-dimethylpyrazole dimers, trimers and tetramers (420 shieldings). See http://www.rsc.org/suppdata/nj/b2/b210251j/

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with a Shimadzu QP-5000 spectrometer at 60 eV using the EI mode. Imidazole(**1**), pyrazole (**3**) and 3,5-dimethylpyrazole (**4**) were commercial reagent grade and were used as received.

4,5-Dimethylimidazole (2). 2 was prepared according to Bredereck.[17] Instead of **2** we isolated its formate **6c**. To obtain compound **2**, a solution of **6c** in 2 N NaOH was extracted with chloroform. Yield 90%. The compound was purified washing it with ether–hexane–chloroform (a few drops) or by sublimation. M.p. 119.3 °C (by DSC, sample prepared in Ar atmosphere). Lit. m.p. 117 °C.[17]

4,5-Dihydro-3-methyl-2*H*-benz[*g*]indazole (15). We have described the NMR properties of this compound in solution[18] but not its synthesis. An equimolar mixture of 2-acetyl-1-tetralone and hydrazine hydrate was heated in ethanol for 4 h. By evaporation, compound **15** was obtained, m.p. 142–143 °C (dichloromethane–hexane), yield 90%. Calcd for $C_{12}H_{12}N_2$: C 78.23, H 6.57, N 15.21; found: C 78.48, H 6.61, N 15.04. ^{1}H NMR ($CDCl_3$, δ, J/Hz): 9.67 (1H, v br, NH), 7.73 (1H, dd, H6', $J_{5'6'} = 7.5$), 7.23 (1H, dd, H3', $J_{3'4'} = 7.2$), 7.21 (1H, ddd, H5', $J_{3'5'} = 2.1$), 7.18 (1H, ddd, H4', $J_{4'5'} = 6.5$, $J_{4'6'} = 1.5$), 2.94 (t, 2H, $^2J = 7.3$, CH_2-8'), 2.67 (t, 2H, CH_2-7'), 2.26 (s, 3H, CH_3).

4,5-Dihydro-3-methyl-1*H*,2*H*-benz[*g*]indazolium chloride (16). This compound has been prepared in two ways. (1) Compound **15** was dissolved in ethanol and concentrated hydrochloric acid was added until precipitation of a white solid, m.p. > 294–295 °C (ethanol–dichloromethane), yield 97%. (2) Following the method described in ref. 18 (2-acetyl-1-tetralone, ethanol, some drops of concentrated hydrochloric acid and hydrazine hydrate) the same compound was obtained. Calcd for $C_{12}H_{13}N_2Cl$: C 65.31, H 5.94, N 12.69; found: C 65.19, H 5.80, N 12.72. ^{1}H NMR ($CDCl_3$, δ, J/Hz): 14.94 (2H, v br, NH), 8.20 (1H, dd, H6', $J_{5'6'} = 7.7$), 7.30–7.38 (3H, m, H3', H4', H5'), 3.03 (t, 2H, $^2J = 7.5$, CH_2-8'), 2.74 (t, 2H, CH_2-7'), 2.52 (s, 3H, CH_3).

4,5-Dihydro-3-methyl-1*H*-benz[*g*]indazole-4,5-dihydro-3-methyl-1*H*,12*H*-benz[*g*]indazolium chloride (14).[19]. This compound has been prepared in two ways. (1) Compound **15** was dissolved in ethanol and concentrated hydrochloric acid was added in a 2:1 stoichiometry, then the solution was evaporated to dryness. (2) Equimolar quantities of **15** and **16** were dissolved in ethanol, the solution was stirred 30 min at r.t. and then evaporated, m.p. 184.5–185.5 °C (dec.). Calcd for $C_{24}H_{25}N_4Cl$: C 71.18, H 6.22, N 13.84; found: C 70.90, H 6.32, N 13.70. Crystallisation of these samples in ethanol–dichloromethane only afforded crystals of **16**. ^{1}H NMR ($CDCl_3$, δ, J/Hz): 11.61 (2H, NH), 11.19 (1H, NH), 7.97 (2H, m. H6'), 7.27–7.30 (6H, m, H3', H4', H5'), 2.98 (4H, CH_2-8'), 2.68 (4H, CH_2-7'), 2.41 (6H, CH_3).

Salt stoichiometries

To determine the stoichiometry of the different salts, that is, if they are salts (XH^+ Y^-) or hemi-salts [$(XHX)^+$ Y^-], the compounds have been analyzed: all of them are true salts. **5a**: anal. calcd for $C_3H_5N_2Cl$: C, 34.47; H, 4.82; N, 26.80; found: C, 34.17; H, 4.56; N, 26.51. **5b**: anal. calcd for $C_5H_5F_3N_2O_2$: C, 32.98; H, 2.77; N, 15.38; found: C, 32.96; H, 2.64; N, 15.39. **6a**: anal. calcd for $C_5H_9N_2Cl$: C, 45.29; H, 6.84; N, 21.13; found: C, 45.03; H, 6.48; N, 20.86. **6b**: anal. calcd for $C_7H_9F_3N_2O_2$: C, 40.01; H, 4.32; N, 13.33; found: C, 40.22; H, 4.37; N, 13.54. **7b**: anal. calcd for $C_5H_5F_3N_2O_2$: C, 32.98; H, 2.77; N, 15.38; found: C, 32.94; H, 2.83; N, 15.42. **7c**: anal. calcd for $C_3H_5N_2Br$: C, 24.18; H, 3.38; N, 18.80; found: C, 24.06; H, 3.23; N, 18.76. **8a**: anal. calcd for $C_5H_9N_2Cl$: C, 45.29; H, 6.84; N, 21.13; found: C, 45.32; H, 6.50; N, 21.23.

NMR spectroscopy

^{1}H NMR (400.13 MHz), ^{13}C NMR (100.62 MHz) and ^{15}N NMR (40.56) spectra in solution were obtained using a Bruker DRX-400 instrument. Chemical shifts (δ) in ppm are referred to external Me_4Si for ^{1}H and ^{13}C and to external NO_2CH_3 for ^{15}N NMR spectra. Solid state ^{13}C and ^{15}N CPMAS NMR spectra were recorded using a Bruker AC-200 instrument (50.32 and 20.28 MHz) and standard CP pulse sequences were employed.[12]

Ab initio calculations

The optimisation of the structures of all compounds discussed in this paper was carried out at the B3LYP/6-311++G** level[20,21] using the facilities of the Gaussian 98 set of programs.[22] In all cases, the minimum nature of the geometries has been confirmed by frequency calculations at the same level. Absolute shielding σ were calculated, at the same level, over these geometries within the GIAO approximation.[1,2]

We have already used DFT calculations for hydrogen-bonded systems, obtaining accurate results for geometries and energies[13,23] as well as for shieldings.[3,12,24,25] For more information about modern GIAO methods refer to the work of Pulay and for the GIAO-DFT approach to that of Cheeseman.[26] At the level of theory used in this paper, one cannot expect to reproduce the experimental findings, only to find linear correlations between experimental values and calculated ones, of the type $\delta_{exp} = a + b\,\delta_{calc}$. Higher levels of calculation are necessary to calculate absolute shieldings σ.[3,26]

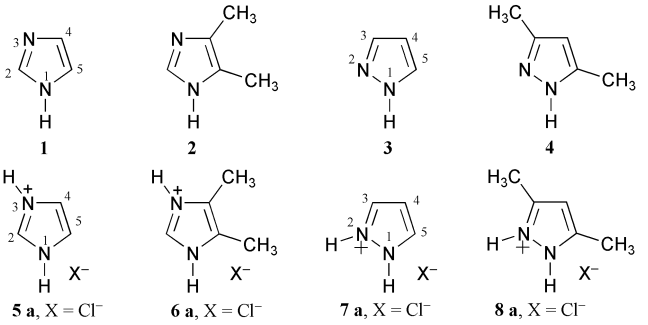
Results and discussion

Protonation of a base B having a lone pair normally affords the cation $[B–H]^+$ but in some cases this hydrogen cation binds to another B molecule to form a $[B–H\cdots B]^+$ structure, such as **I** in the case of B being imidazole.[10,27]

Pyrazolium and imidazolium cations

If a solution of azole is dissolved in a medium containing a strong acid and the solvent evaporated an azolium salt is obtained in most cases. In this way, using hydrochloric, hydrobromic and trifluoroacetic acids, the compounds reported in Scheme 2 have been prepared (compound **6c** was fortuitously obtained while trying to prepare **2**). Their ^{13}C chemical shifts obtained in the solid state by the CPMAS technique, together with some data in solution from the literature, useful for assignment, are reported in Table 1.

The differences with the *N*-methyl quaternary salts can be due to the effect of the substituents on the nitrogen atoms but the differences between the trifluoroacetate salts in the solid state and the spectra of the azoles in sulfuric acid are phase effects, which in some cases are important. A reasonable



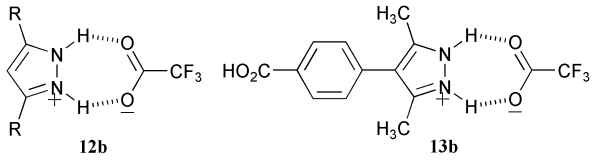
Scheme 2

Table 1 ^{13}C chemical shifts of azolium cations **5–11** ($\Delta\delta = \delta_{CPMAS} - \delta_{SO_4H_2}$)

Azolium	Medium	C-2	C-3	C-4	C-5	C-Me groups
5a	CPMAS	136.2	–	121.6	116.8	–
5b[a]	CPMAS	135.6	–	118.8	118.8	–
5[b]	SO_4H_2	132.1	–	118.3	118.3	–
$\Delta\delta$ (**5a**)	(Cl^-)	4.1	–	3.3	−1.5	–
$\Delta\delta$ (**5b**)	($CF_3CO_2^-$)	3.5	–	0.5	0.5	–
9[c]	DMSO-d_6	137.0	–	123.4	123.4	–
6a	CPMAS	130.8	–	123.9	123.9	8.6
6b[d]	CPMAS	–	–	–	–	–
6c	CPMAS	132.8	–	124.1	124.1	8.9
6[e]	SO_4H_2	129.4	–	124.4	124.4	6.9
$\Delta\delta$ (**6a**)	(Cl^-)	1.4	–	−0.5	−0.5	1.7
$\Delta\delta$ (**6c**)	(HCO_2^-)	3.4	–	−0.3	−0.3	2.0
7a[f]	CPMAS	–	–	–	–	–
7b[g]	CPMAS	–	133.7	106.3	133.7	–
7c	CPMAS	–	138.0 (br)	110.0	138.0 (br)	–
7[b]	SO_4H_2	–	133.8	107.7	133.8	–
$\Delta\delta$ (**7b**)	($CF_3CO_2^-$)	–	−0.1	−1.4	−0.1	–
$\Delta\delta$ (**7c**)	(Br^-)	–	4.2	2.3	4.2	–
10[h]	DMSO-d_6	–	137.2	106.6	137.2	–
8a	CPMAS	–	147.5	106.5	142.7	11.7
8b[i]	CPMAS	–	145.7	105.4	145.7	10.1
8[b]	SO_4H_2	–	146.5	106.8	146.5	9.2
$\Delta\delta$ (**8a**)	(Cl^-)	–	1.0	−0.3	−3.8	2.5
$\Delta\delta$ (**8b**)	($CF_3CO_2^-$)	–	−0.8	−1.4	−0.8	0.9
11[j]	DMSO-d_6	–	145.2	107.0	145.2	11.8
13[k]	CF_3CO_2H	–	142.2	118.2	142.2	10.2
13b[l]	CPMAS	–	142.3	117.1	142.3	10.2

[a] $CF_3CO_2^-$ at 118.3 (CF_3) and 164.1 ppm (C=O). [b] From ref. 28. [c] 1,3-Dimethylimidazolium iodide (Scheme 3).[29] [d] We never succeeded in obtaining this compound as a solid. [e] This work. [f] This compound is too hygroscopic to record its CPMAS spectrum. [g] $CF_3CO_2^-$ at 118.4 (CF_3) and 162.7 ppm (C=O). [h] 1,2-Dimethylpyrazolium iodide **10** (Scheme 3).[29] [i] $CF_3CO_2^-$ at 118.1 (CF_3) and 163.0 ppm (C=O). [j] 1,2,3,5-Tetramethylpyrazolium iodide **11** (Scheme 3).[30] [k] $CF_3CO_2^-$ at 115.6 (CF_3) and 163.2 ppm (C=O).[31] [l] $CF_3CO_2^-$ at 114.3 (CF_3) and 159.6 and 163.2 ppm (C=O).[31]

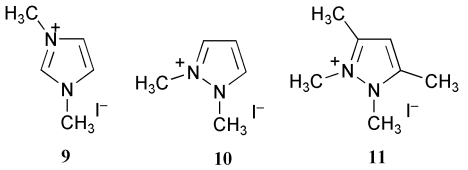
explanation is that the trifluoroacetates of pyrazolium have the chelated structure **12b**. We have described such a compound, **13b**, determined its X-ray structure and measured its ^{13}C NMR chemical shifts (see Table 1).[31]



12b **13b**

In the case of 4,5-dimethylimidazole, we have also studied the formate salt **6c** (Scheme 2). The analogy with the trifluoroacetate **6b** shows that compound **6c** is also an imidazolium salt (B^+–H···A^-) and not an imidazole/formic acid complex (B···H–A).

Only two compounds show two chemical shifts for "equivalent" positions: **5a** (imidazolium chloride) where C-4 and C-5 are different and **8a** (3,5-dimethylpyrazolium chloride) where



9 **10** **11**

Scheme 3

Table 2 ^{13}C chemical shifts of the neutral compounds and protonation effects (ppm) in the solid state

Azole	C-2	C-3	C-4	C-5	C-Me groups
Imidazole **1**[a]	136.3	–	126.8	115.3	–
ΔP ($CF_3CO_2^-$)	−0.7	–	−8.0	+3.5	–
4,5-Dimethylimidazole **2**[b]	131.3	–	131.3	122.2	6.3, 7.8, 10.8
ΔP (Cl^-)	−0.5	–	−7.4	1.7	2.5, 1.0, −2.0
Pyrazole **3**[a]	–	138.7	107.0	128.8	–
ΔP ($CF_3CO_2^-$)	–	−5.0	−0.7	4.9	–
3,5-Dimethylpyrazole **4**[c]	–	147.5	104.8	139.3	10.5 (Me_5), 12.8 (Me_3)
ΔP ($CF_3CO_2^-$)	–	−1.8	0.6	6.4	−0.4 (Me_5), −2.7 (Me_3

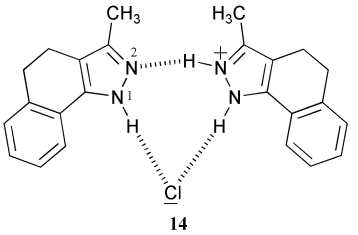
[a] From ref. 33. [b] This work. [c] At low temperature to avoid SSPT.[34]

C-3 and C-5 are also non-equivalent. The crystal structure of these two salts is not known but the NMR observation does not mean necessarily that there are two different molecules in the unit cell.

The interest to have chemical shifts determined in the solid state (Table 1, CPMAS) is that they can be directly compared with those of the neutral molecules because, in general, annular tautomerism is suppressed in the solid.[32] In Table 2 are reported the protonation effects ($\Delta P = \delta_{azolium} - \delta_{azole}$). The most noticeable effects are those observed on C-4 of imidazoles (about −8 ppm) and on C-5 of pyrazoles (about +6 ppm). C-5 of imidazoles is erratic while C-3 of pyrazoles is about −3 ppm. We will discuss these effects in the corresponding section dealing with GIAO calculations.

Hemi-protonated pyrazolium cations

A survey of the Cambridge Structural Database (September 2001 release) shows that 22 X-ray structures of pyrazolium salts have been published.[35] One of the most interesting structures was that reported by Bertolasi, Gilli and coworkers in 1999.[19] It corresponds to the hemi-hydrochloride salt **14**. It can be considered as a tetrahydroindazole derivative or a naphthopyrazole, but for all structural purposes, it is a 3,4,5-trisubstituted pyrazole. It is formed by a pyrazole and a pyrazolium salt, and although the central hydrogen appears localised, it could be a possible candidate for SSPT (solid state proton transfer).[34,36]



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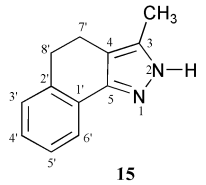
Our attempts to obtain a good single crystal of this product (which was obtained by the authors trying to prepare the neutral compound **15** with some drops of concentrated hydrochloric acid as a catalyst),[16] failed. The crystals we obtained had a unit cell that was different (monoclinic, $a = 7$, $b = 17$, $c = 9$ Å, $\beta = 107°$); probably they correspond to the usual dimer chloride structure **16** $([B–H]^+\ Cl^-)_2$.[31]

We have carried out an NMR study in solution and in the solid state of the free base **15** (a 2*H*-tautomer), the hemi-hydrochloride **14** and the chloride **16** (that we have represented as a dimer by analogy to other such salts):[37] the results are reported in Table 3.

Table 3 ^{13}C and ^{15}N NMR chemical shifts of the pyrazoles **14–16** (shifts relative to TMS and nitromethane, respectively)

Cpd	Solvent	C-Me	C-4	C-Ar	Me	N-1	N-2
15[a]	$CDCl_3$	137.55	113.43	145.81	9.90		
15[b]	$CDCl_3$	137.57[c]	113.75	146.13[c]	10.02	N.o.[d]	N.o.[d]
15[e]	CPMAS	137.9	111.4	147.2	6.9	−108.2	−171.3
14[f]	$CDCl_3$	139.68	114.56	143.51	9.87	N.o.	N.o.
14[g]	CPMAS	139.6	112.8	140.4	10.9	−192[h]	−130.1
							−172.5
ΔP[i]	CPMAS	1.7	1.1	−6.8	4.0	−18.7	−81.8
16[j]	$CDCl_3$	140.58	114.93	142.46	10.02	−187.4	−187.4
16[k]	CPMAS	140.4	113.0	140.4	10.6	−182.5	−193.6
ΔP[i]	CPMAS	2.5	1.6	−6.8	3.7	−11.2	−85.4

[a] From ref. 18 (the assignment of C-Me and C-Ar carbons is based on two-dimensional experiments). [b] Other carbons: 136.62 (C2′), 129.37 (C1′), 128.34 (C3′, $^1J = 159.7$), 127.39 (C4′, $^1J = 159.9$, $^3J = 7.8$), 126.72 (C5′, $^1J = 160.0$, $^3J = 7.5$), 121.94 (C6′, $^1J = 157.1$), 29.78 (C8′, $^1J = 127.5$), 18.54 (C7′, $^1J = 128.9$) and (Me, $^1J = 127.6$). [c] Very broad due to 1*H*/2*H* tautomerism. [d] Too broad to be observed. [e] Other carbons: 135.0 (C2′), 131.2 (C1′), 127.3 (C3′), 126.0 (C4′), 125.2 (C5′), 121.7 (C6′) 28.2 (C8′), 18.8 (C7′). [f] Other carbons: 137.10 (C2′), 129.50 (C3′, $^1J = 160.6$, $^3J = 7.8$), 128.48 (C4′, $^1J = 157.4$), 127.34 (C5′, $^1J = 161.5$, $^3J = 6.6$), 125.25 (C1′), 124.09 (C6′, $^1J = 160.6$), 29.07 (C8′, $^1J = 127.5$), 17.87 (C7′, $^1J = 129.8$) and (Me, $^1J = 129.1$). [g] Other carbons: 136.9 (C2′), 131.6 and 130.7 (C3′), 127.8 (C4′), 125.6 (C5′), 125.5 and 123.4 (C1′), 123.2 and 121.3 (C6′), 29.6 and 27.0 (C8′), 16.5 (C7′). [h] Very broad. [i] $\Delta P = \delta_{azolium} - \delta_{azole}$. [j] Other carbons: 137.42 (C2′), 130.70 (C3′, $^1J = 160.9$, $^3J = 7.6$), 128.57 (C4′, $^1J = 160.9$), 127.79 (C5′, $^1J = 162.6$, $^3J = 7.2$), 125.26 (C6′, $^1J = 162.6$), 123.22 (C1′), 28.71 (C8′, $^1J = 128.3$), 17.53 (C7′, $^1J = 130.7$) and (Me, $^1J = 130.4$). [k] Other carbons: 137.0 (C2′), 130.5 (C3′, C4′), 128.0 (C5′), 123.0 (C6′), 121.7 (C1′), 26.8 (C8′), 16.1 (C7′).



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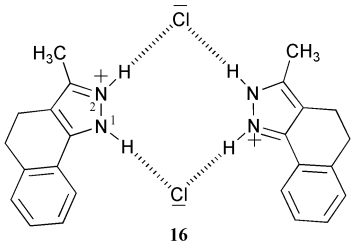

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^1H NMR studies at very low temperatures

We have reported in the experimental that for the hemi-chloride **14**, two NH signals are observed in ^1H NMR ($CDCl_3$): one corresponding to a proton at 11.19 ppm and another corresponding to two protons at 11.61 ppm, probably because **14** in solution behaves as an equimolar mixture of **15** and **16**.

In connection with this structure, we report here the result obtained by ^1H NMR at 200 MHz when a mixture of [$^{15}N_2$]-3,5-dimethylpyrazole **4**[38] (2 equiv.) and trifluoroacetic acid (1 equiv.) was recorded in a Freon (a 2:1 mixture of $CDClF_2$–CDF_3) at 120 K (−153 °C). Two NH signals are observed (Fig. 1), one at 14.37 ppm corresponding to two protons with the appearance of a doublet ($^1J = 100$ Hz) and the other at 18.30 ppm corresponding to one proton, a triplet with

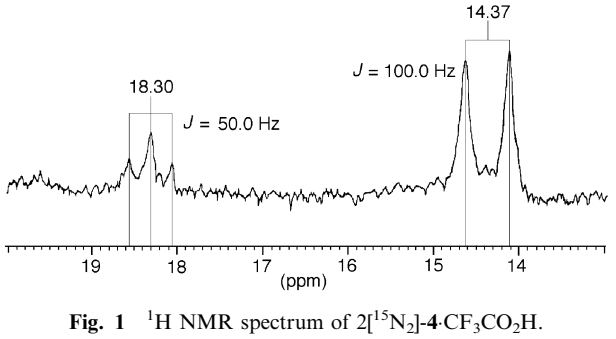
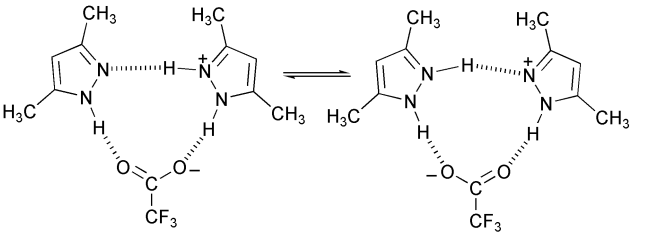


Fig. 1 ^1H NMR spectrum of 2[$^{15}N_2$]-**4**·CF_3CO_2H.



Scheme 4

$^1J = 50$ Hz. The signal at ~14.4 ppm corresponds to the protons linked to the trifluoroacetate anion, since both nitrogen atoms are labelled with ^{15}N, the coupling of 100 Hz is normal for one $^1J(^1H–^{15}N)$.[39] The signal at ~18.3 ppm is due to the proton between a pyrazole and a pyrazolium and the observed triplet corresponds to the average signal of a proton linked to a pyrazolium ring; this leads to a value of 50 Hz. In solution, the proton transfer (Scheme 4) between both nitrogen atoms is very fast on the NMR time scale, even at this temperature.

Phase effects on the ^{13}C chemical shift of C-4 of NH-pyrazoles

We have observed that the signal of C-4 in NH-pyrazoles, which is unaffected by tautomerism, is sensitive to solvents. The shift is particularly clear in spectra recorded with the CPMAS technique. In Table 4 we have gathered the results we obtained for five pyrazoles: pyrazole (**3**), 3,5-dimethylpyrazole (**4**), 3(5)-phenyl-5(3)-methylpyrazole (**17**), 3,5-di-*tert*-butylpyrazole (**18**) and 3,5-diphenylpyrazole (**19**). These compounds are either commercial or have been described by us in previous publications.[40–42]

By plotting the chemical shift of C-4 for pyrazoles **4**, **17**, **18** and **19** (*Y* variables) against those of pyrazole **3** itself, Fig. 2 is obtained. In general, the chemical shifts are proportional, showing that the phenomenon is very general (the square correlation coefficients are 0.997 for **4**, 0.999 for **17** and 0.94 for **16**). In the case of diphenylpyrazole **19**, $r^2 = 0.84$, this could be related to conformational differences of the *C*-phenyl rings in different solvents. The intercepts correspond to the effect of the substituents at positions 3 and 5 on δC-4 while the slopes (always < 1, on average 0.683) indicate that the 3,5-disubstituted pyrazoles are less sensitive to phase effects than pyrazole itself.

We will consider now only pyrazole (**3**). For this compound we have determined other values of δC-4 that are reported in Table 5. Attempts to analyze these chemical shifts using non-specific solvent parameters (Reichardt's E_T^N or Catalán's SPP^N)[43,44] failed ($r^2 < 0.1$). Then, we tried the biparametric model of Catalán (SA, solvent acidity and SB, solvent basicity),[45] which he recommends for specific contributions but the squared correlation coefficient, $r^2 = 0.2$, is very low proving that the changes in δC-4 probably reflect specific effects (see the discussion concerning GIAO calculations). It is possible that a range of 2 ppm (between MeOH and HMPA) is too narrow for empirical modelling.

Table 4 ^{13}C chemical shift of the C-4 carbon atom in NH-pyrazoles (concentration 0.19 mmol per 0.75 mL)

Pyrazole	HMPA-d_{18}	DMSO-d_6	$CDCl_3$	CPMAS	Melted
3	103.89	104.81	105.49	107.2	103.21
4	102.67	103.30	103.74	104.8	–
17	101.06	101.27	102.03	102.8	–
18	95.49	96.26	96.91	98.4	–
19	99.89	99.77	100.17	101.9	–

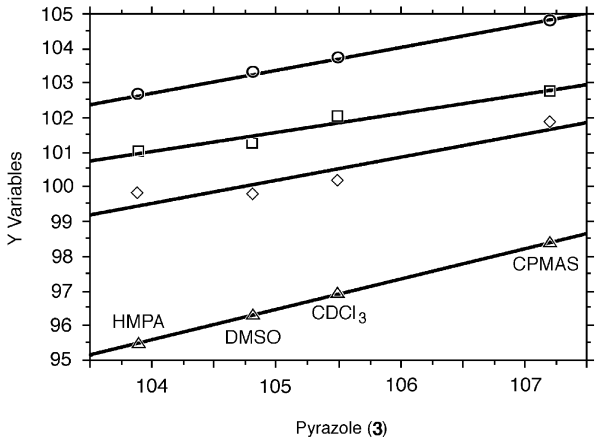


Fig. 2 ^{13}C chemical shifts of the C-4 of NH-pyrazoles: 3,5-dimethylpyrazole (**4**, ○), 3(5)-methyl-5(3)-phenylpyrazole (**17**, □), 3,5-di-*tert*-butylpyrazole (**18**, △), 3,5-diphenylpyrazole (**19**, ◇).

Ab initio calculations

The failure of the empirical approach, both mono- and biparametric, prompted us to calculate the properties of some complexes that can be models of the observed solvent effects. We selected a number of general situations that are represented in Scheme 5.

The HBAs and HBDs we have studied are, respectively, on one side :NH_3, :NCH, :OH_2, :O=CH_2 and, on the other, HF, HCl, HCN, HOH and HC≡CH. In the case of water as donor, the minimum structure does not correspond to **VII** but to **XI**, where water is acting both as an HBD and a HBA. Some special situations like **IX** and **X**, the complexes with two water molecules, **XII** and **XVII**, and the hemi-salt **XXII**, have also been calculated. This results in a very large number of absolute shieldings (isotropic NMR chemical shifts) that can be transformed into δ chemical shifts through the use of the usual references (TMS for ^{1}H and ^{13}C and nitromethane for ^{15}N).[3] At the same time the interaction energies $E_i = E_{complex} - E_{separated\ molecules}$ are also obtained.

As an illustration of these calculations we have represented the histograms corresponding to the calculated chemical shifts of carbon C-2 of imidazole (Fig. 3) and C-4 of pyrazole (Fig. 4). In both cases, the hydrogen-bonded solvents mimic the protonation and deprotonation, but in opposite directions in both diazoles. In the case of ^{15}N shieldings, the appearance is more visible due to the sensitivity of this nucleus (Fig. 5).

Discussion of calculated values. A statistical approach to a large collection of values should start with the correlation matrix. All variables that are highly correlated ($r^2 > 0.99$) correspond to pairs of values that are physically related (as measured by the probability value, *P*) *regardless if a plausible explanation can be found.* A first approach would be an internal discussion of the calculated values. For instance, the effect on the most basic centre, $\Delta\sigma$N ($\sigma_{complex} - \sigma_{heterocycle}$; pyrazole N-2 **VII**, imidazole N-3 **XV**, pyridine N-1 **XX**) is linearly related to E_i:

$$\textbf{VII}: \Delta\sigma\text{N(ppm)} = -(0.53 \pm 0.01)\cdot E_i(\text{kJ mol}^{-1}),\quad n = 4,\ r^2 = 0.999 \quad (1)$$

$$\textbf{XV}: \Delta\sigma\text{N(ppm)} = -(0.32 \pm 0.02)\cdot E_i(\text{kJ mol}^{-1}),\quad n = 4,\ r^2 = 0.992 \quad (2)$$

$$\textbf{XX}: \Delta\sigma\text{N(ppm)} = -(0.67 \pm 0.02)\cdot E_i(\text{kJ mol}^{-1}),\quad n = 4,\ r^2 = 0.996 \quad (3)$$

The important physical meaning of these relationships is that the stronger the complex, the more deshielded the basic nitrogen atom. At the limit, a total proton transfer will result in the pyrazolium **XIV,** the imidazolium **XIX**, and pyridinium **XXI** ions. Adding these points, which are far removed from the hydrogen-bonded systems, results in a parabolic relationship, eqns. (4)–(6). The region of the parabola that corresponds to the hydrogen-bonded species can be assimilated to a straight line [eqns. (1)–(3)].

$$\textbf{VII, XIV}: 1/\Delta\sigma\text{N(ppm)} = -(0.50 \pm 0.02)\cdot 1/E_i(\text{kJ mol}^{-1}),\quad n = 5,\ r^2 = 0.998 \quad (4)$$

$$\textbf{XV, XIX}: 1/\Delta\sigma\text{N(ppm)} = -(0.88 \pm 0.03)\cdot 1/E_i(\text{kJ mol}^{-1}),\quad n = 5,\ r^2 = 0.994 \quad (5)$$

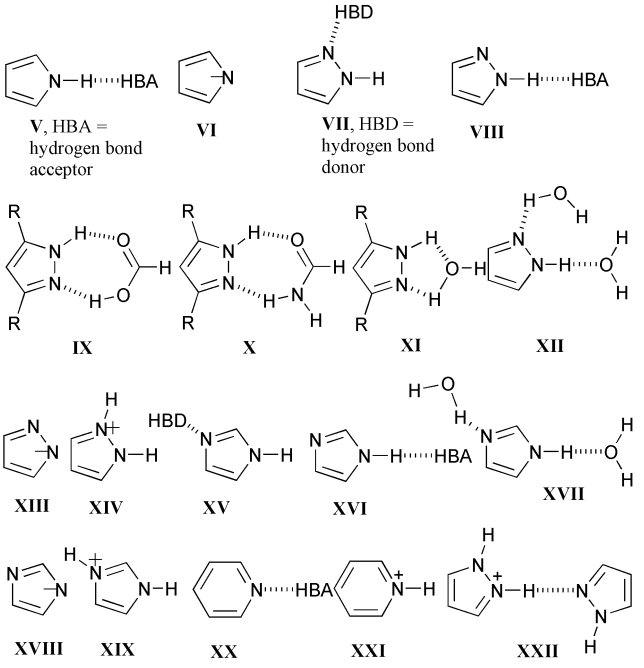
$$\textbf{XX, XXI}: 1/\Delta\sigma\text{N(ppm)} = -(0.36 \pm 0.01)\cdot 1/E_i(\text{kJ mol}^{-1}),\quad n = 5,\ r^2 = 0.998 \quad (6)$$

The slopes of eqns. (4)–(6) are proportional to the aromaticity index REPE [resonance energy per π-electron: pyridine (0.58) > pyrazole (0.55) > imidazole (0.42)].[46] Using $1/(E_i\cdot\text{REPE})$, all of the 15 points fall on a single line. The same happens for $\Delta\sigma$N-1 and E_i for HBA groups. Thus, in the case

Table 5 ^{13}C chemical shift of the C-4 atom in pyrazole **3** itself (concentration 0.19 mmol per 0.75 mL)

Solvent	C-4	E_T^N	SPP^N	SA	SB
DMSO	104.81	0.444	1.000	0.647	0.072
Water	104.17	1.000	0.962	0.025	1.062
HMPA	103.89	0.315	0.932	0.813	0.000
Acetone	104.90	0.355	0.881	0.475	0.000
CH_2Cl_2	105.81	0.309	0.876	0.057	0.040
Methanol	105.88[a]	0.762	0.857	0.545	0.605
Ethanol	104.96	0.654	0.853	0.658	0.400
Formamide	104.66	0.799	0.833	0.414	0.549
$CHCl_3$	105.49	0.259	0.786	0.071	0.047
Acetic acid	104.94	0.648	0.781	0.390	0.689

[a] 106.3 ppm at 178 K.[12]



Scheme 5

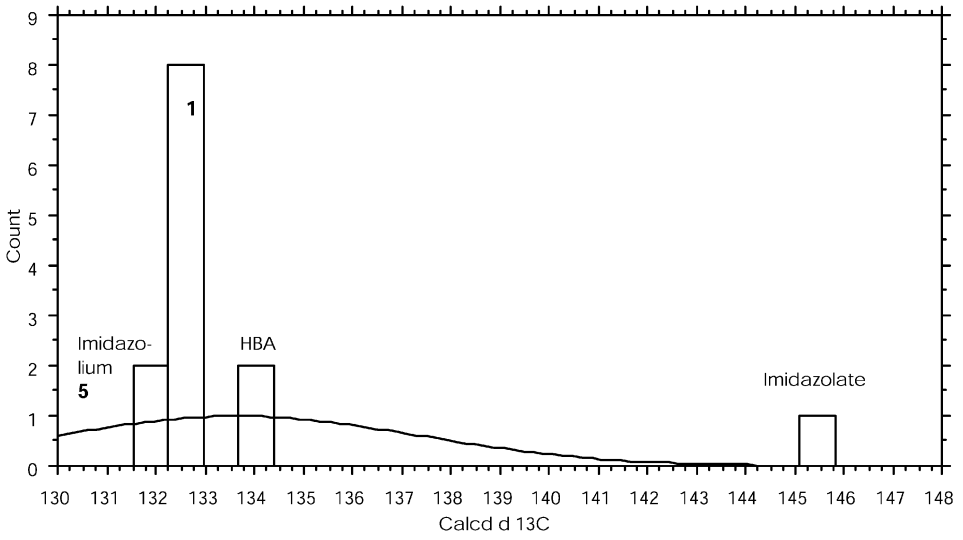


Fig. 3 ^{13}C chemical shifts of imidazole C-2.

of pyrrole:

$$\mathbf{V}\text{: } \Delta\sigma\mathrm{N(ppm)} = -(0.55 \pm 0.04)\cdot E_i(\mathrm{kJ\ mol^{-1}}),\quad n = 4, r^2 = 0.986 \qquad (7)$$

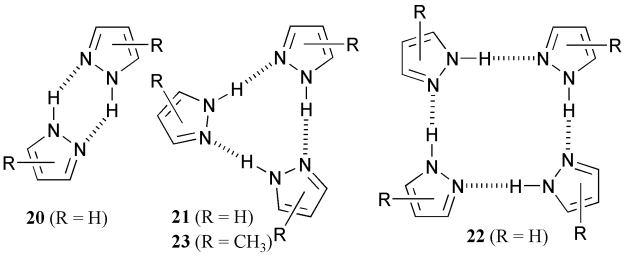
Similar equations were found with pyrazoles **VIII** and imidazoles **XVI**.

The ^{13}C chemical shifts are less sensitive and the correlations less good. For instance, for pyrazole C-4, eqn. (8) is obtained (note the change in sign of E_i between HBA and HBD):

$$\mathbf{VII}, \mathbf{VIII}\text{: } \Delta\delta^{13}\mathrm{C(C\text{-}4,\ ppm)} = -(0.12 \pm 0.02)\cdot E_i(\mathrm{kJ\ mol^{-1}}),\quad n = 8, r^2 = 0.90 \qquad (8)$$

Although the correlation is rather poor, nevertheless, the stronger the complex, the greater the deshielding produced by an HBD solvent and the greater the shielding produced by an HBA solvent.

We have also calculated the absolute shieldings of the dimer **20**, trimer **21** and tetramer **22** of pyrazole **3** (R = H) and the trimer **23** of 3,5-dimethylpyrazole **4** (R = 3,5-dimethyl). Pyrazole itself crystallises forming chains (catemers) while **4** crystallises forming a trimer. Dimers and tetramers are found for other pyrazoles.[47] A representation of the relative shieldings, $\Delta\delta$ (n-mer − monomer), *vs.* n ($n = 1$ for the monomer to $n = 4$ for the tetramer) is given in Fig. 6.



There is a smooth variation of all signals with different signs and relative importance. Expectedly, the effects on ^{15}N are much larger (about ten times) than those on ^{13}C. All signals follow a bi-logarithmic variation, for instance, for the carbon at position 4:

$$\mathrm{Ln}\Delta\delta^{13}\mathrm{C(C\text{-}4,\ ppm)} = -(2.31 \pm 0.04) + (1.42 \pm 0.05)\mathrm{Ln}n,\quad n = 4, r^2 = 0.998 \qquad (9)$$

Discussion of experimental *vs.* calculated values: anions, cations and hydrogen-bonded complexes. We report in Table 6

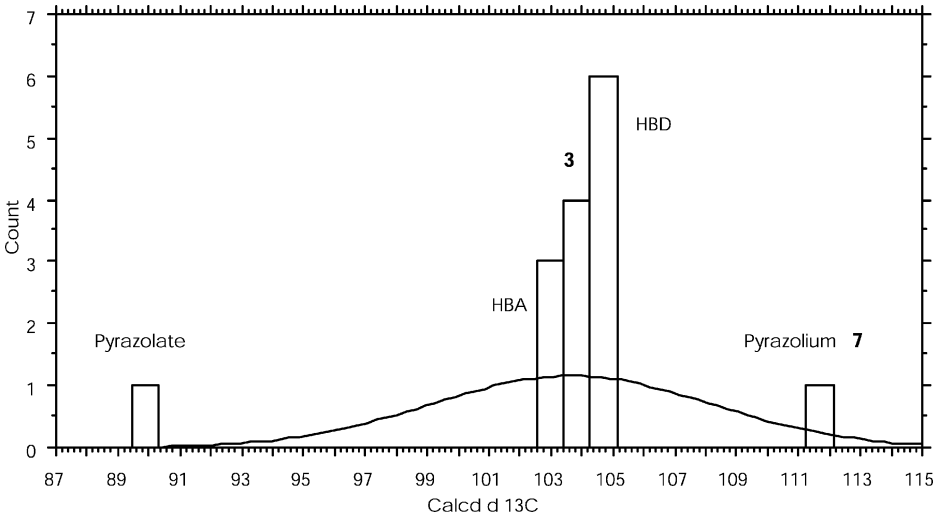


Fig. 4 ^{13}C chemical shifts of pyrazole C-4.

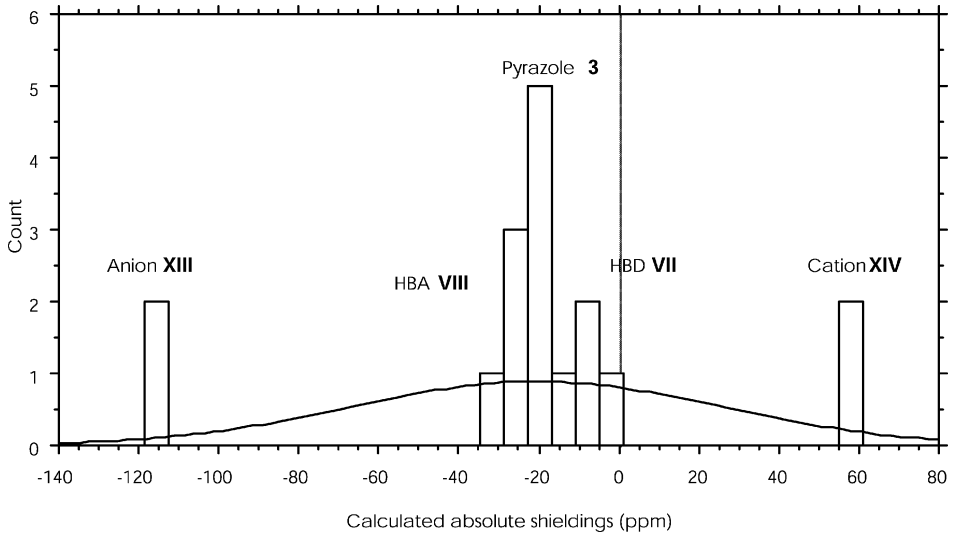


Fig. 5 Average ^{15}N shieldings of pyrazole N-1 and N-2.

some experimental values corresponding to structures **V** to **XX** (Scheme 5) that will be useful for the following discussion.

The calculated absolute shieldings (σ) were transformed into chemical shifts (δ) (both in ppm) by using eqns. (10) and (11):

$$\delta^{13}C_{calc} = 184.75 - \sigma^{13}C \quad (10)$$

$$\delta^{15}N_{calc} = -167.54 - \sigma^{15}N \quad (11)$$

The value of −184.75 ppm corresponds to the shielding of TMS calculated at the same theoretical level[24] while the value of −167.54 ppm has been empirically adjusted (the σ^{15}N of nitromethane gas at the same level is −154.43 ppm but the shift to bulk nitromethane is not known).[3]

Then, the experimental data were adjusted to the calculated values leading to eqns. (12–14). In eqn. (13) the point corresponding to N-3 of imidazole in methanol at low temperature (−143.4 ppm)[12] was excluded (fitted −124.2 ppm). In eqn. (14), ^{xx}Y means both ^{13}C and ^{15}N.

$$\delta^{13}C_{exp} = (0.951 \pm 0.002)\cdot\delta^{13}C_{calc},\ n = 59,\ r^2 = 1.000 \quad (12)$$

$$\delta^{15}N_{exp} = (0.901 \pm 0.007)\cdot\delta^{15}N_{calc},\ n = 26,\ r^2 = 0.999 \quad (13)$$

$$\delta^{xx}Y_{exp} = (0.929 \pm 0.004)\cdot\delta^{xx}Y_{calc},\ n = 85,\ r^2 = 0.998 \quad (14)$$

These equations include solvent effects as well as protonated species (cations) and anions. We soon discovered that the calculated values for anions **VI**, **XIII** and **XVIII** strongly deviated when the experimental results were obtained in THF but were normal when measured in DMSO. Therefore, we calculated

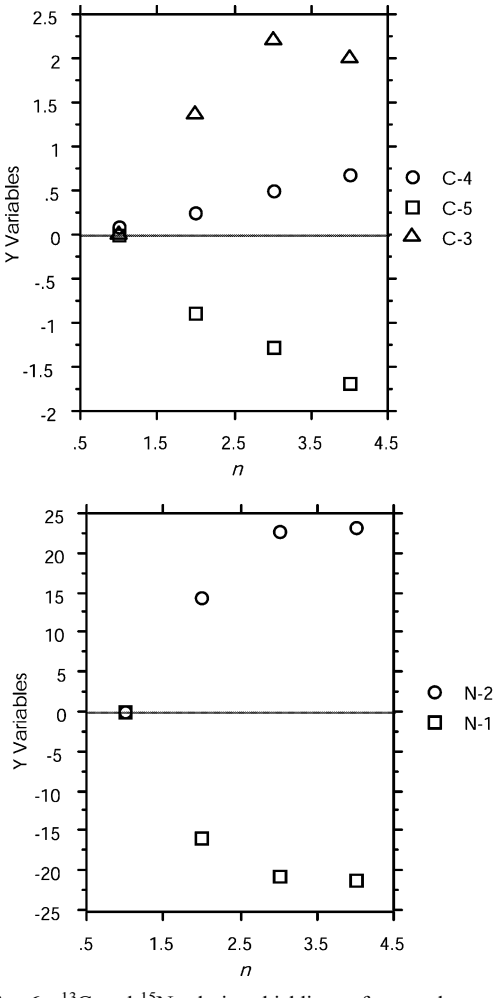


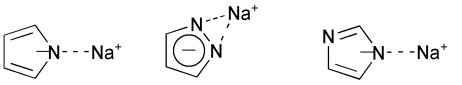
Fig. 6 ^{13}C and ^{15}N relative shieldings of pyrazole n-mers.

Table 6 ^{13}C and ^{15}N chemical shifts of different azoles (if not otherwise indicated, values are from this work)

Cpd	Solvent	Pos. 1	Pos. 2	Pos. 3	Pos. 4	Pos. 5
Pyrrole[a]	THF-d_8	−234.05	118.04	108.12	108.12	118.04
Pyrrolate anion[a]	THF-d_8	−155.9	127.44	106.15	106.15	127.44
Imidazole **1**	Water	–	135.25	–	120.95	120.95
Imidazolate **XVIII**	DMSO-d_6	−133.8	–	−133.8	–	–
Imidazolium **XIX**	SO_4H_2	−212.7	–	−212.7	–	–
Pyrazole **3**	Water	–	–	134.19	104.17	134.19
Pyrazole **3**	Methanol	–	–	140.17	105.88	129.58
Pyrazole **3**	Acetic acid	–	–	133.17	104.94	133.17
Pyrazole **3**	Formamide	–	–	N.o.[b]	104.66	N.o.[b]
3,5-dmpz **4**	Methanol	–	–	150.13[c]	104.97	141.14[c]
Pyrazolate **XIII**	THF-d_8	−78.4	−78.4	–	–	–
Pyrazolium **XIV**	SO_4H_2	−194.2	−194.2	–	–	–
Pyridine	Hexane	−59.21	149.30	122.60	134.39	–
Pyridine	Water	−79.04	147.45	123.34	136.30	–
Pyridinium **XXI**[d e]	SO_4H_2	−186.7	142.5	129.0	148.4	–

[a] ^{13}C closely related to those reported by Stothers[48] and by Breitmaier and Voelter.[49] [b] Probably due to a slow prototropic rate. [c] Blocked prototropy. [d] ^{13}C data from Breitmaier and Voelter, pyridinium cation in water.[49] [e] The ^{15}N chemical shift of **XXI** in CF_3CO_2H is −184.26 ppm.[50]

the absolute shieldings for the anion·Na^+ complexes (**XXIII**, **XXIV** and **XXV**) and used these values [after transforming them into δ by means of eqns. (10) and (11)] for the regressions in eqns. (12)–(14).



XXIII **XXIV** **XXV**

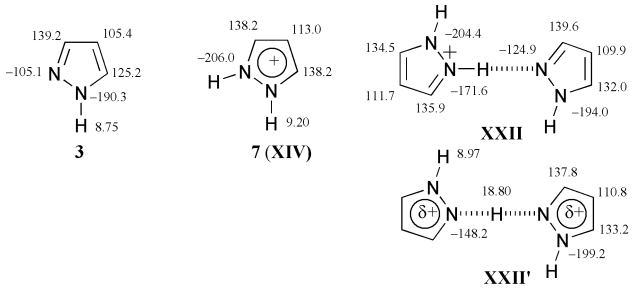
The calculated values agree fairly well with the protonation effects. For instance, C-4 of imidazoles (about −8 ppm both experimentally—solid state—and calculated) and C-5 of pyrazoles (about +6 ppm experimental—solid state—and +13 ppm calculated). Eqns. (12) and (13) allow to predict a large number of ^{13}C (91) and ^{15}N chemical shifts (72), including specific solvent effects by HBAs and HBDs.

The hemi-salts deserve a special discussion. The shielding values for compounds **3** and **7** as well as for model **XXII** have been transformed into δ values by means of the above equations (and similar ones for the ^1H NMR data) and are reported in Scheme 6. Although we have represented **XXII'** with the proton in the middle it is not a transition state but the average of two symmetrical **XXII** structures.

The values for **XXII** are almost exactly the mean between **3** and **7**, the exception being the nitrogen atoms involved in the HB (average: −155.6 instead of −142.7 ppm) and the very deshielded H atom of the HB. The signal of the N–H···N proton of the trifluoroacetate of 3,5-dimethylpyrazolium·3,5-dimethylpyrazole (see Fig. 1 and Scheme 4) appears at 18.30 ppm, in very good agreement with the calculated value for **XXII** (the signal at 14.37 ppm is hydrogen-bonded to a trifluoroacetate anion). Since the protons for compound **13** appear, in $CDCl_3$, at 11.61 (2H) and 11.19 ppm (1H) we concluded that its structure in solution corresponds to a mixture of **3** (**15**) and **7** (**16**) and not to **XXII** (**14**).

In the solid state, the ^{13}C chemical shifts of **14** (Table 3) are intermediate between those of **15** and **16** but not a superposition of both, thus, it is a new structure. This structure has a high symmetry, which is inconsistent with a static **XXII** (no ^{13}C signal is splitted); our conclusion is that this compound shows SSPT on the time scale of ^{13}C NMR although the proton appears localised in X-ray crystallography. Three nitrogen signals are observed in ^{15}N CPMAS NMR: one at −192 ppm (very broad) and two others at −130.1 and −172.5 ppm (Table 3). The signal at −192 ppm corresponds to the average of two N-1 signals (**XXII'**, calculated −199.2 ppm); the N-2 signals, expected for **XXII** at −125 (neutral)/−172 (cation) are observed at −130.1 and −172.5 ppm. Our tentative conclusion is that compound **14** in the solid state shows a slow proton transfer that produces a coalescence of signals that are close (carbons and N-1 atoms) but not of those that have very different chemical shifts (N-2 atoms).

We have calculated (at a lower level, GIAO/B3LYP/6-31G*) the compound shown in Scheme 4 and Fig. 1, [**4**H^+**4**]$CF_3CO_2^-$, with the proton in the middle of the two pyrazole rings. Considering that for TMS at this level corresponds to $\sigma^1H = 32.18$ and $\sigma^{13}C = 189.69$ ppm,[24] and through the relationship $\delta_{exp} = (0.91 \pm 0.01)\delta_{calc}$, one finds for the trifluoroacetate anion 121.2 (CF_3) and 159.8 ppm (CO_2^-), which agree well with the values of Table 1. For the protons, the values are 22.9 (experimental 18.3, one proton) and 16.8 ppm (experimental 14.4, two protons).



3 **7 (XIV)** **XXII** **XXII'**

Scheme 6

Discussion of experimental *vs.* calculated values: pyrazole dimers, trimers and tetramers. As we have mentioned previously, we have calculated the absolute shieldings of dimer **20**, trimer **21,** tetramer **22** and trimer **23**. It is now possible to compare these calculations with the experimental data. The best results are obtained when solid state results and solution results (obtained in different solvents to slow down the prototropy)[51,52] are compared with the absolute shieldings calculated for the trimer. Using eqns. (10) and (11) to transform σ into δ, the following equation is obtained, where both nuclei are considered in the same equation:

$$\delta^{xx}Y_{exp} = (0.912 \pm 0.009)\cdot\delta^{xx}Y_{calc},\ n = 26,\ r^2 = 0.997 \quad (15)$$

The worse point is N-2 of pyrazole **3** (expt −81.9 in THF,[51] fitted −89.1 ppm). In methanol this signal appears at −100.2 ppm.[12]

Conclusions

The main conclusions of the present study are the following 1. For the molecules or complexes reported in this study, the absolute shieldings calculated at the GIAO/B3LYP/6-311++G** level provide a correct picture of the most important effects like protonation, deprotonation, formation of hemi-salts, *etc.* 2. Solvent effects on ^{13}C NMR signals are too feeble to be properly described by supermolecules although complexes containing two water molecules represent fairly well the situation in solvents like methanol. 3. The dynamic situation of the hemi-trifluoroacetate of 3,5-dimethylpyrazole (Scheme 4) has been clarified. 4. By a combination of NMR data in the solid state and GIAO calculations, the existence of a proton transfer in hemi-salt **14** (SSPT) has been established. This is an important result because SSPT remains an infrequent phenomenon.

Acknowledgements

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References

1 F. London, *J. Phys. Radium*, 1937, **8**, 397.
2 R. Ditchfield, *Mol. Phys.*, 1974, **27**, 789.
3 I. Alkorta and J. Elguero, *Struct. Chem.*, 2002, **13**, 97.
4 P. v. R. Schleyer, C. Maerker, A. Dransfeld, H. Jiao and N. J. R. v. Hommes, *J. Am. Chem. Soc.*, 1996, **118**, 6317.
5 M. Jaszunski, K. V. Mikkelsen, A. Rizzo and M. Witanowski, *J. Phys. Chem. A*, 2000, **104**, 1466.
6 M. N. Manalo, A. C. de Dios and R. Cammi, *J. Phys. Chem. A*, 2000, **104**, 9600.
7 R. W. Schurko and R. E. Wasylishen, *J. Phys. Chem. A*, 2000, **104**, 3410.
8 E. Megiel, T. Kasprzycka-Guttman, A. Jagielska and L. Wroblewska, *J. Mol. Struct.*, 2001, **569**, 111.

9 E. Kleinpeter and A. Koch, *J. Phys. Org. Chem.*, 2001, **14**, 566.
10 M. J. Potrzebowski, M. Cypryk, M. Michalska, A. E. Koziol, S. Kazmierski, W. Ciesielski and J. Klinowski, *J. Phys. Chem. B*, 1998, **102**, 4488.
11 J. C. Facelli, *Chem. Phys. Lett.*, 2000, **322**, 91.
12 R. M. Claramunt, C. López, D. Sanz, I. Alkorta and J. Elguero, *Heterocycles*, 2001, **55**, 2109.
13 I. Alkorta, I. Rozas, O. Mó, M. Yáñez and J. Elguero, *J. Phys. Chem. A*, 2001, **105**, 7481.
14 D. B. Chesnut and L. D. Quin, *J. Am. Chem. Soc.*, 1994, **116**, 9638.
15 W. Bocian, J. Jazwinski, O. Staszewska, J. W. Wiench, L. Stefaniak and G. A. Webb, *Khim. Geterotsikl. Soedin.*, 1996, 1581.
16 J. W. Wiench, L. Stefaniak, E. Grech and G. A. Webb, *Bull. Pol. Acad. Sci., Chem.*, 1999, **47**, 67.
17 H. Bredereck and G. Theilig, *Chem. Ber.*, 1952, **86**, 88.
18 C. López, R. M. Claramunt, S. Trofimenko and J. Elguero, *Can. J. Chem.*, 1993, **71**, 678.
19 V. Bertolasi, P. Gilli, V. Ferreti, G. Gilli and C. Fernández-Castaño, *Acta Crystallogr., Sect. B*, 1999, **55**, 985–993.
20 6–311++G**: R. Ditchfield, W. J. Hehre and J. A. Pople, *J. Chem. Phys.*, 1971, **54**, 724–728; M. J. Frisch, J. A. Pople, R. Krishnam and J. S. Binkley, *J. Chem. Phys.*, 1984, **80**, 3265–3269.
21 B3LYP: A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648; C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B*, 1988, **37**, 785; A. D. Becke, *Phys. Rev. A*, 1988, **38**, 3098; B. Miehlich, A. Savin, H. Stoll and H. Preuss, *Chem. Phys. Lett.*, 1989, **157**, 200.
22 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle and J. A. Pople, *Gaussian 98*, Gaussian, Inc., Pittsburgh, PA, 1998.
23 C. Foces-Foces, A. Echevarría, N. Jagerovic, I. Alkorta, J. Elguero, U. Langer, O. Klein, M. Minguet-Bonvehí and H.-H. Limbach, *J. Am. Chem. Soc.*, 2001, **123**, 7896; I. Alkorta, I. Rozas and J. Elguero, *J. Phys. Chem. A*, 2001, **105**, 10462; I. Alkorta and J. Elguero, *J. Org. Chem.*, 2002, **67**, 1515; I. Alkorta and J. Elguero, *J. Am. Chem. Soc.*, 2002, **124**, 1488; E. Espinosa, I. Alkorta, J. Elguero and E. Molins, *J. Chem. Phys.*, 2002, **117**, 5529.
24 I. Alkorta and J. Elguero, *Struct. Chem.*, 1998, **9**, 187.
25 R. M. Claramunt, C. López, M. A. García, M. D. Otero, M. R. Torres, E. Pinilla, S. H. Alarcón, I. Alkorta and J. Elguero, *New J. Chem.*, 2001, **25**, 1061; I. Alkorta, I. Rozas and J. Elguero, *Tetrahedron*, 2001, **57**, 6043; N. Jagerovic, M. L. Jimeno, I. Alkorta, J. Elguero and R. M. Claramunt, *Tetrahedron*, 2002, **58**, 9089.
26 K. Wolinski, J. F. Hinton and P. Pulay, *J. Am. Chem. Soc.*, 1990, **112**, 8251; B. Wang, U. Fleischer, J. F. Hinton and P. Pulay, *J. Comput. Chem.*, 2001, **22**, 1887; B. Wang, J. F. Hinton and P. Pulay, *J. Comput. Chem.*, 2002, **23**, 492; J. R. Cheeseman, G. R. Trucks, T. A. Keith and M. J. Frisch, *J. Chem. Phys.*, 1996, **104**, 5497; P. J. Stephens, C. S. Ashvar, F. J. Devlin, J. R. Cheeseman and M. J. Frisch, *Mol. Phys.*, 1996, **89**, 579; K. B. Wiberg, J. D. Hammer, K. W. Zilm, J. R. Cheeseman and T. A. Keith, *J. Phys. Chem. A*, 1998, **102**, 8766.
27 A. Quick and D. J. Williams, *Can. J. Chem.*, 1976, **54**, 2465.
28 J. Elguero, M. L. Jimeno and G. I. Yranzo, *Magn. Reson. Chem.*, 1990, **28**, 807.
29 R. M. Claramunt, D. Sanz, G. Boyer, J. Catalán, J. L. G. de Paz and J. Elguero, *Magn. Reson. Chem.*, 1993, **31**, 791.
30 J. P. Fayet, M. C. Vertut, A. Fruchier, E. M. Tjiou and J. Elguero, *Org. Magn. Reson.*, 1978, **11**, 234.
31 C. Foces-Foces, C. Cativiela, M. M. Zurbano, I. Sobrados, N. Jagerovic and J. Elguero, *J. Chem. Crystallogr.*, 1996, **26**, 579.
32 J. Elguero, A. R. Katritzky and O. V. Denisko, *Adv. Heterocycl. Chem.*, 2000, **76**, 1.
33 J. Elguero, A. Fruchier and V. Pellegrin, *J. Chem. Soc., Chem. Commun.*, 1981, 1207.
34 A. Baldy, J. Elguero, R. Faure, M. Pierrot and E.-J. Vincent, *J. Am. Chem. Soc.*, 1985, **107**, 5290.
35 F. H. Allen, J. E. Davies, J. J. Galloy, O. Johnson, O. Kennard, C. F. Macrae, E. M. Mitchell, G. F. Mitchell, J. M. Smith and D. G. Watson, *J. Chem. Inf. Comput. Sci.*, 1991, **31**, 187.
36 F. Aguilar-Parrilla, G. Scherer, H.-H. Limbach, C. Foces-Foces, F. H. Cano and J. Elguero, *J. Am. Chem. Soc.*, 1992, **114**, 9657.
37 C. Fernández-Castaño, C. Foces-Foces, N. Jagerovic and J. Elguero, *J. Mol. Struct.*, 1995, **355**, 265; C. Foces-Foces, L. Infantes, R. M. Claramunt, C. López, N. Jagerovic and J. Elguero, *J. Mol. Struct.*, 1997, **415**, 81.
38 J. A. S. Smith, B. Wehrle, F. Aguilar-Parrilla, H.-H. Limbach, C. Foces-Foces, F. H. Cano, J. Elguero, A. Baldy, M. Pierrot, M. M. T. Khurshid and J. B. Larcombe-McDouall, *J. Am. Chem. Soc.*, 1989, **111**, 7304.
39 M. Pietrzak, J. Wehling, H.-H. Limbach, N. S. Golubev, C. López, R. M. Claramunt and J. Elguero, *J. Am. Chem. Soc.*, 2001, **123**, 4338.
40 A. L. Llamas-Saiz, C. Foces-Foces, F. H. Cano, P. Jiménez, J. Laynez, W. Meutermans, J. Elguero, H.-H. Limbach and F. Aguilar-Parrilla, *Acta Crystallogr., Sect. B*, 1994, **50**, 746.
41 J. Elguero, N. Jagerovic, C. Foces-Foces, F. H. Cano, M. V. Roux, F. Aguilar-Parrilla and H.-H. Limbach, *J. Heterocycl. Chem.*, 1995, **32**, 451.
42 F. Aguilar-Parrilla, H.-H. Limbach, C. Foces-Foces, F. H. Cano, N. Jagerovic and J. Elguero, *J. Org. Chem.*, 1995, **60**, 1965.
43 C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, VCH, Weinheim, 2nd edn., 1990.
44 J. Catalán, V. López, P. Pérez and R. Martín-Villamil, *Liebigs Ann. Chem.*, 1995, 241; J. Catalán, V. López and P. Pérez, *Liebigs Ann. Chem.*, 1995, 793; J. Catalán, *J. Org. Chem.*, 1995, **60**, 8315; J. A. Paéz, N. Campillo and J. Elguero, *Gazz. Chim. Ital.*, 1996, **126**, 307.
45 J. Catalán, C. Díaz, V. López, P. Pérez, J. L. G. de Paz and J. G. Rodríguez, *Liebigs Ann. Chem.*, 1996, 1785; J. Catalán and C. Díaz, *Liebibs Ann. Chem/Rec. Trav. Chim. Pays-Bas*, 1997, 1941; J. Catalán and C. Díaz, *Eur. J. Org. Chem.*, 1999, 885; J. Catalán, C. Díaz and F. García Blanco, *J. Org. Chem.*, 2001, **66**, 5846.
46 C. W. Bird, *Tetrahedron*, 1997, **53**, 3319.
47 C. Foces-Foces, I. Alkorta and J. Elguero, *Acta Crystallogr. Sect. C*, 2000, **56**, 1018.
48 J. B. Stothers, *Carbon-13 NMR Spectroscopy*, Academic Press, New York, 1972.
49 E. Breitmaier and W. Voelter, *^{13}C NMR Spectroscopy*, Verlag Chemie, Weinheim, 2nd edn., ż1978.
50 W. Holzer and W. von Philipsborn, *Magn. Reson. Chem.*, 1989, **27**, 511.
51 M. Begtrup, G. Boyer, P. Cabildo, C. Cativiela, R. M. Claramunt, J. Elguero, J. I. García, C. Toiron and P. Vedsø, *Magn. Reson. Chem.*, 1993, **31**, 107.
52 R. M. Claramunt, D. Sanz, C. López, J. A. Jiménez, M. L. Jimeno, J. Elguero and A. Fruchier, *Magn. Reson. Chem.*, 1997, **35**, 35.