Proton Transfer in Solid Heterocycles: an X-Ray and CPMAS NMR Study

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1. Introduction.

The *intermolecular* transfer of heterocyclic protons in the solid state has been observed only in the case of pyrazoles and it is intimately related with annular tautomerism [1]. To discuss the tautomerism of pyrazoles in the solid state, two general parts are necessary: the first one dealing with the structures and properties of pyrazoles in the two other states of the matter (gas-phase and solution) and the second one discussing the two main methods we have used to gain a knowledge of the solid state, the X-ray crystallography and the CPMAS nmr spectroscopy.

The properties of pyrazoles in the gas-phase are necessary to determine their intrinsic behaviour, *i.e.* the properties of the isolated molecule. These properties are the only ones which can be compared with precise theoretical calculations due to the difficulty of introducing solvent effects at the same level of calculation. The properties in solution, mainly those related to nmr and to tautomerism, are important by a statistical reason: the results obtained in solution outweigh hundreds of times those determined in the gas-phase or in the solid-state. If some rules could be found relating the three states of the matter, then the results in solution could be used, at least, to estimate the other results.

2. Pyrazoles in the Gas Phase.

Two aspects are worth describing: that of geometries and that of energies.

a. The Geometry of Pyrazoles in the Gas Phase.

The description of the geometry of a pyrazole is a multidimensional problem (many bond lengths and bond angles). We have found it practical [2] to use the diagrams that Paul and Curtin [3] described for a very different purpose; they correspond to an easy two-dimensional plot of differences in angles *vs* differences in bonds (multiplied by 100 to have comparable units) (Figure 1):

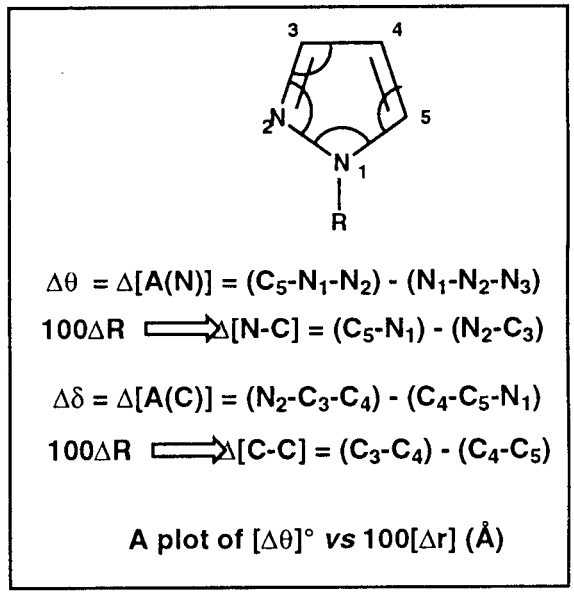
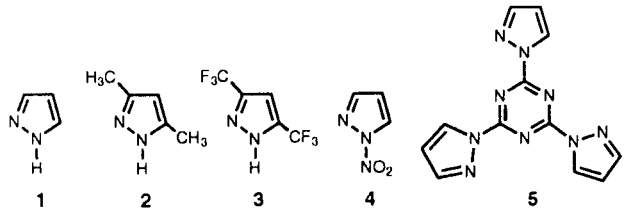


Figure 1

The sources of information about the geometries in the gas phase came from microwave spectroscopy (MW) and from electron diffraction (ED). Both methods have been used only once in pyrazoles: the MW structure of pyrazole itself **1** was reported long ago by the well known Danish team [4] and those of 3,5-dimethylpyrazole **2** and 3,5-bis(trifluoromethyl)pyrazole **3** were recently determined by ED [5]. Two other structures are in progress, those of 1-nitropyrazole **4** (by MW) [6] and of 2,4,6-tris(pyrazol-1-yl)-1,3,5-triazine **5** (by ED) [7]. It is worth noting that the MW geometry of pyrazole itself is not well reproduced at the 6-31G** level of accuracy (the 6-31G* geometry is near the same).



1 2 3 4 5

b. The Energies of Pyrazoles in the Gas Phase.

The relative stabilities of different pyrazole tautomers and isomers are obtained by a combination of gas-phase proton affinities (PAs) and classical thermochemical experiments (heats of sublimation, heats of vaporization and heats of combustion). In a study of 32 *N*-H and *N*-methylpyrazoles [8] the experimental PAs were discussed in two ways: i) by comparing them to 6-31G//6-31G calculations; ii) through a Taft-Topsom analysis of C-substituent effects.

The calculated 6-31G//6-31G protonation energies are excellent estimators of PAs, $-\Delta Ep = (218.51 \pm 0.25) + (1.479 \pm 0.021)PA$ [8]. An analysis of substituent effects is summarized in Figure 2.

Polarizability (P)	σ_α
Field (F)	σ_F
Resonance (R)	σ^+_R

ΔG (kcal mol^{-1}), X = Me, Et, But, Ph, NO_2, NH_2, CO_2Et

3-**X**: $\Delta G = -9.4\ \sigma_\alpha - 28.1\ \sigma_F - 17.4\ \sigma_R$

5-**X**: $\Delta G = -7.7\ \sigma_\alpha - 27.4\ \sigma_F - 22.1\ \sigma_R$

Tautomeric Equilibria:

$\Delta\Delta G = -1.7\ \sigma_\alpha - 0.7\ \sigma_F + 4.7\ \sigma_R$

Figure 2. Taft-Topsom Analysis of Substituent Effects (SEs)

It appears that the substituent effects are important (and similar to those found for 2-substituted pyridines) but their differences, which are proportional to ln K_T (K_T being the tautomeric equilibrium constant between 3-X and 5-X pyrazoles), are much smaller. The main conclusion is that, *intrinsically*, both tautomers are quite similar in energy. In solution, solvent effects (mainly if the tautomers have very different dipole moments) could shift the equilibrium towards one side or the other. But, this will be only a perturbation of the main conclusion.

A final comment concerning the tautomerism of azoles in the gas phase: we have recently demonstrated that to reproduce the tautomeric equilibrium constant a very high level of the theory must be used, no less than MP2//6-31G** [9,10].

3. Pyrazoles in Solution.

a. NMR as a Privileged Tool for the Study of Pyrazoles.

Historically, ^1H nmr spectroscopy was the first tool used to study azoles [11,12], this has gradually been replaced by ^{13}C nmr spectroscopy [13,14]. There was a time when it was expected that ^{15}N nmr spectroscopy would become the standard method for the study of the structure of these compounds [15-17]. This has not been the case and probably never will. Two are the main reasons why ^{15}N nmr will not replace ^{13}C nmr spectroscopy for the study of azoles: i) experimentally it is much more difficult (on the other hand it is much easier to label azoles with ^{15}N than with ^{13}C); ii) concerning their applications to tautomerism and although the atoms which are involved in this phenomenon are the nitrogen atoms, tautomeric equilibrium constants depend on the *C*-substituents and *C*-substituent effects are more clear, more additive and much easier to interpret on *ipso* carbons than on nitrogen atoms which are two or three bonds away from the substituent.

For instance, in the case of pyrazoles, the statistical survey of 1168 pyrazoles [14] lead to the following SCSs [substituent chemical shifts, by definition, SCS(H) = 0.0] (Table 1 reported the values for only four substituents).

Table 1

Substituent	At position	On C at position	SCS (ppm)	At position	On C at position	SCS (ppm)
CH_3	3	3	8.0	4	3	-1.5
CH_3	5	3	-1.4	3	4	-0.6
CH_3	4	4	8.5	5	4	-0.7
CH_3	3	5	0.8	4	5	-1.4
CH_3	5	5	7.8			
C_6H_5	3	3	11.2	4	3	-2.2
C_6H_5	5	3	-0.2	3	4	-2.2
C_6H_5	4	4	15.1	5	4	0.5
C_6H_5	3	5	2.8	4	5	-2.0
C_6H_5	5	5	12.8			
NH_2	3	3	16.1	4	3	-10.1
NH_2	5	3	-1.7	3	4	-12.3
NH_2	4	4	25.3	5	4	-16.5
NH_2	3	5	0.1	4	5	-12.6
NH_2	5	5	15.9			
NO_2	3	3	15.3	4	3	-2.6
NO_2	5	3	-2.0	3	4	-3.0
NO_2	4	4	28.0	5	4	0.6
NO_2	3	5	3.2	4	5	-2.8
NO_2	5	5	14.5			

b. The Tautomerism of Pyrazoles in Solution.

It is relatively simple to use these SCS for establishing the tautomeric structure of a pyrazole, for instance, in the

solid state (*vide infra*). On the other side, a similar approach is not possible with ^{15}N chemical shifts due to paucity of data. In this case, we used a different approach: that of freezing the equilibrium at low temperature [18] (Figure 3).

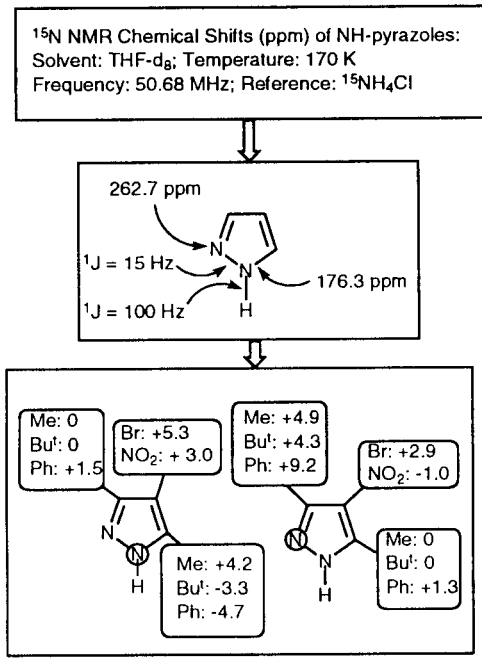


Figure 3

As it can be seen in Figure 3, the SCS on positions 3 and 5 (which serves for determining the position of the tautomeric equilibrium) are not so different. Moreover, ^{15}N chemical shifts (particularly that of N_2) are extremely sensitive to solvent effects and to hydrogen bonds. All in all, a useful but delicate to handle method.

c. The Mills-Nixon Effect.

When Mills and Nixon described this effect in 1930 [19], they stated (Figure 4):

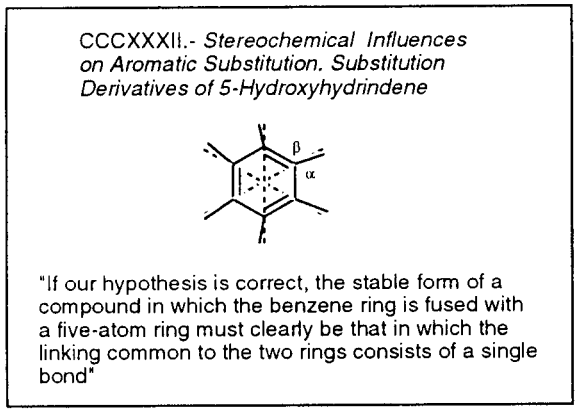


Figure 4

Assuming [20] that there is relationship between bond order and tautomerism (see Figure 5) then ring strain would favor the pyrazole 2*H*-tautomers.

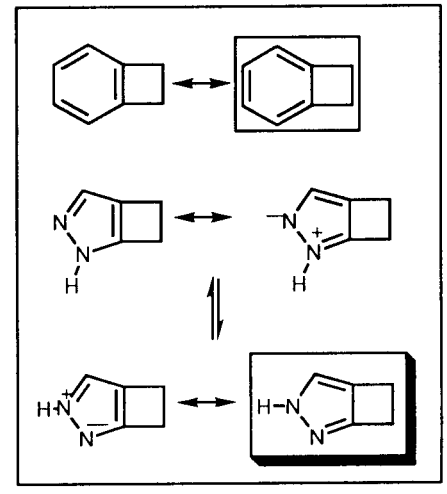


Figure 5

The effect has been studied in solution by ^{13}C and ^{15}N nmr spectroscopy and the results obtained have been explained by *ab initio* calculations: four-membered ring **6** (represented in Figure 4) >99% of 2*H*-tautomer, five-membered ring, **7**, 98% of 2*H*-tautomer, six-membered ring (**8**, tetrahydroindazole), 60% of 2*H*-tautomer, seven-membered ring, **9**, 38% of 2*H*-tautomer.

4. The Study of Pyrazoles in the Solid State.

a. NMR *vs* Crystallography.

Insight into the molecular solid state was for long the priviliged field of crystallography (including X-ray and neutron diffraction). Pauling [21] was one of the first to recognize the importance of metrical molecular structures determined by X-ray crystallography for chemistry and biology. Although crystal disorder and the importance of low-temperature studies was recognized a long time ago [22], the image that crystallography usually provided was that of ordered assemblies of molecules subject to thermal motions of very limited amplitude.

That was the situation until ten years ago. Then, crystallographers realized the possibility of using crystallography to study the dynamics of crystals [23], particularly, rotational barriers. The method needs the determination of accurate crystal structures at several temperatures, including very low ones and the mathematical treatment of the "anisotropic displacement factors" (ADP's, related to the well-known thermal ellipsoids) is rather elaborate. Nevertheless several activation barriers have been measured.

Solid-state high resolution dynamic nmr has proved to be the method of choice for studying dynamic phenomena in solids. It can solve one of the most difficult problems for diffraction methods: to distinguish between static and dynamic disorder. Amongst the classical applications of SSHR-DNMR, we have mentioned here those involving intramolecular proton transfer through a hydrogen bond: porphyrins [24,25], and azophenins [26].The interest of NH-pyrazoles is that they constitute the only example known so far of *intermolecular proton transfer in crystals* [27,28].

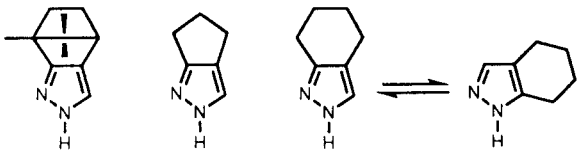
b. Geometries.

We have carried out a statistical survey of pyrazoles reported in the Cambridge Structural Database [2]. Three are the main conclusions of this study:

1. Average pyrazole geometries can be classified according to the substituent on the nitrogen. These average geometries can be reasonably reproduced by 6-31G** calculations.

2. The effect of *N*-substituents on the geometry of pyrazole are the same as those described for *C*-substituents on benzene rings with the main exception of the amino group.

3. In the case of *N*-H pyrazoles, the geometry of the ring can be used as evidence of prototropic disorder. The Mills-Nixon effect determines the tautomer structures of pyrazoles with ring strain such as campho[2,3-*c*]pyrazole **10** [29].



10 **7** **8a** **8b**

c. Solid State NMR.

As an instrument to determine the structure of pyrazoles in the solid state we have made abundant use of ^{13}C CPMAS NMR spectroscopy [30]. In this way we ascertained that 3(5)-methyl-4-substituted pyrazoles (4-*H* **11** is a liquid at room temperature) exist in the solid state as 4-X-5-methyl tautomers. As the Mills-Nixon effect predicts, compound **7** exists as tautomer 2-*H* in the solid state while compound **8** exists as a 50/50 mixture of tautomers **8a** and **8b** (a not so common situation) [20].

d. Proton Transfer.

A large effort has been made to find and study proton transfer in solid pyrazoles. After the accidental discovery that 3,5-dimethylpyrazole **2** (a cyclic trimer) presents this phenomenon [31], other pyrazoles [27,28,32] were found (all of them crystallizing in cyclic structures) which shows dynamical behavior in CPMAS nmr.

In these complexes, degenerate multiple hydrogen transfer processes could be detected by solid state ^{15}N CPMAS nmr spectroscopy of the ^{15}N labelled solids [33]. For solid **2**, it was possible to obtain the HHH/HHD/HDD/DDD isotope effects. At high temperatures, almost equal HHH/HHD, HHD/HDD and HDD/DDD isotope effects are observed. However, low temperature "magnetization transfer" experiments indicated a non-Arrhenius behavior of the HHH reaction. Further studies are underway in order to obtain information on the dependence of the kinetic isotope effects on the number of protons transferred.

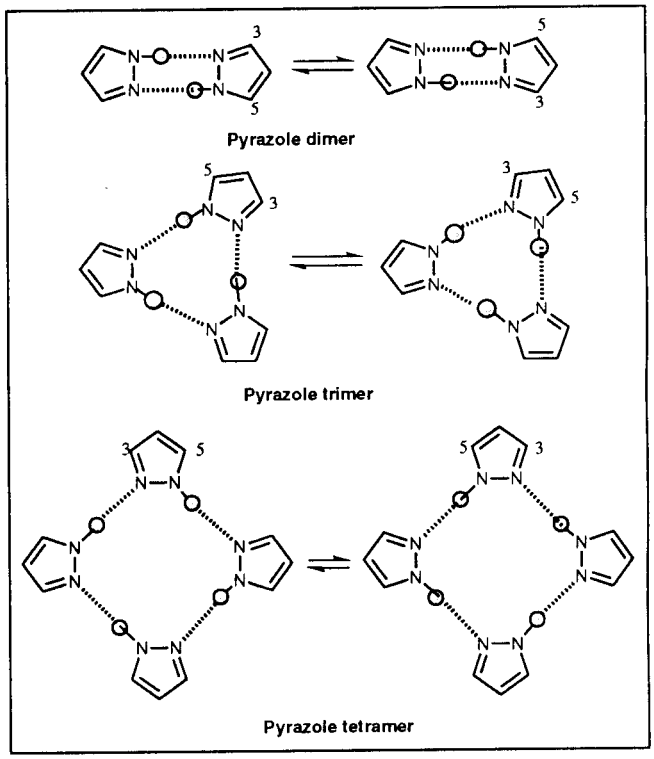


Figure 6

Dimers and trimers are more common than tetramers and although the number of structures is not large enough it does not seem probable that this order would be reversed in the future.

Amongst the pyrazoles which crystallize in long chains of molecules (catamers) is pyrazole itself **1** [33-35] which crystallizes in a sort of eight-shaped chain. Another, very interesting structure is that of 3,5-dimethyl-4-nitropyrazole **12** [36]: the chain has a helical form with a number three thread but, most important, there is only *one* helix, thus the crystal is chiral showing non-linear optical properties.

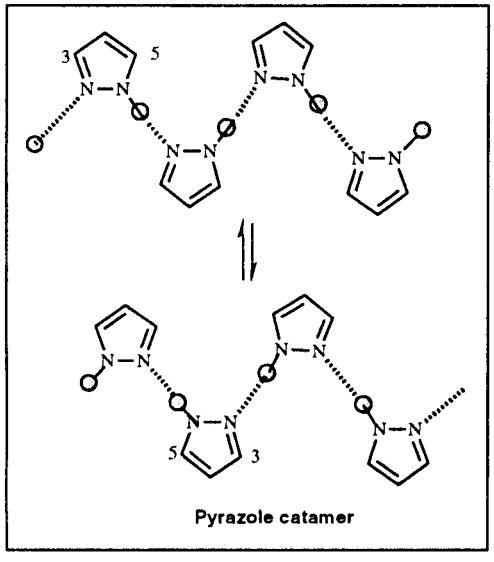
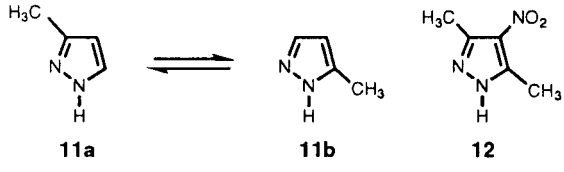


Figure 7



It is possible to summarize all the information we have gathered so far on the structure and dynamic properties of NH-pyrazoles in two figures (Figures 8 and 9):

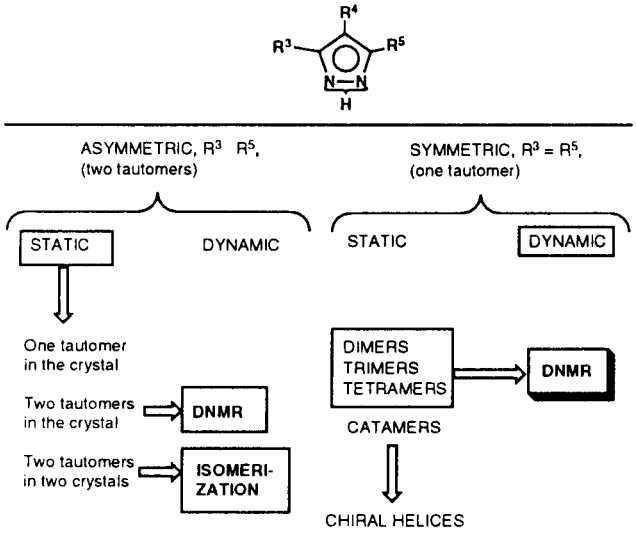
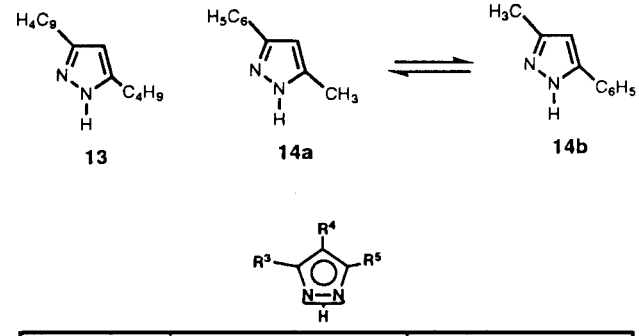


Figure 8

Other pyrazoles have not been studied as carefully as 3,5-dimethylpyrazole (DMP, **2**) but compounds such as solid di-*tert*-butylpyrazole **13**, and 3(5)-phenyl-5(3)-methylpyrazole (PMP, **14**) provide useful information about phase transitions, static *vs.* dynamic disorder and polymorphism.



	$R^3 = R^5$	R^3 R^5
CYCLIC DIMERS	$R^3 = R^5 = Ph$, $R^4 = Br$ $R^3 = R^5 = Bu^t$, $R^4 = H$ $R^3 = R^5 = Bu^t$, $R^4 = NO_2$	$R^3 = Me$, $R^4 = NO_2$, $R^5 = H$
CYCLIC TRIMERS	$R^3 = R^5 = H$, $R^4 = NO_2$ $R^3 = R^5 = Me$, $R^4 = H$	$R^3 = H$, $R^4 = NO_2$, $R^5 = Me$ $R^3 = Ph$, $R^4 = Br$, $R^5 = H$ Campho[c]pyrazole
CYCLIC TETRAMERS	$R^3 = R^5 = Ph$, $R^4 = H$	$R^3 = Ph(Me)$, $R^4 = H$, $R^5 = Me(Ph)$ (both tautomers)
CATAMERS	$R^3 = R^5 = R^4 = H$ $R^3 = R^5 = Me$, $R^4 = NO_2$ (chiral helix)	$R^3 = N_3$, $R^4 = Ph$, $R^5 = H$

R = CH_2OH, CO_2H, pz, CH_2pz: complex H-bond network

Figure 9

e. Host-Guest Chemistry.

Toda's hosts [35-37] proved well suited for including azoles. Proton transfer in these host-guest compounds can be detected by X-ray crystallography using Paul-Curtin's diagrams and studied by SSHR-DNMR.

5. Conclusions.

Although a review on pyrazoles, covering till 1984 [41] is available, the pace of research in pyrazole chemistry is so quick that in ten years an enormous amount of new results has been accumulated. In particular, solid state studies have progressed spectacularly.

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