Pyrazoles as molecular probes to study the properties of co-crystals by solid state NMR spectroscopy

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Abstract: Equimolar mixtures of 3,5-dimethylpyrazole (1) with four NH-imidazoles (2-5) have been studied by ¹³C and ¹⁵N CPMAS NMR and by DSC. In three cases, the solid mixture behaves as the sum of the individual components [imidazole (2), 2-methylimidazole (3) and 2,4(5)-dimethylimidazole (5)]. In one case [4,5-dimethylimidazole (4)], the mixture corresponds to a new species in which the dynamic behavior of ¹ no longer exists.

Keywords: Pyrazoles, imidazoles, tautomerism, solid-state NMR, DSC

1 Introduction

Pyrazoles and particularly 3,5-dimethylpyrazole (1), show a dynamic process in the solid state that consists in the transfer, generally concerted, of several protons between the nitrogen atoms [1-14]. This process (named SSPT, Solid State Proton Transfer) is illustrated in Fig. 1 for the case of 1.

This motion produces the magnetic exchange between "equivalent" signals of 1: C₃ and C₅, Me₃ and Me₅ and N₁ and N₂. Obviously this dynamic NMR aspect is both tem-
temperature and field dependent (all the following discussion is based on room temperature – about 300 K - spectra obtained at 4.7 T). The idea on which this study is based is that a mixture of 1 and another compound could afford two types of structures: a ”physical” structure where 1 and the additive do not interact (mixture of solid domains formed by large numbers of identical molecules) and a "chemical" structure where 1 and the additive interact forming new hydrogen bonds (HB). Only in the last case the dynamic behavior of 1 will be destroyed.

An examination of the literature for structures having an azole interacting with a second molecule shows that the situation is relatively infrequent: supramolecular assemblies in salts and co-crystals of imidazoles with dicarboxylic acids have been reported [15] as well as cooperative association of pyrazoles and phenols [16].

Another aspect that deserves attention is the two methods for preparing co-crystals: i) dissolving both components and evaporating the resulting solution (chemical) vs. ii) mechanical grinding (physical). Actually, mechanical grinding produces chemical reactions (mecanochemistry [17-22]): this method as well as the co-solution method was also applied in Ref. 6 where the tautomerism of (1) was used as a tool to detect and to study the interaction with silica and alumina. Finally, NH-imidazoles due to the 1,3-position of the N atoms cannot form cyclic structures and always crystallize in chains (catemers) [23-25].

2 Materials and methods

2.1 Sample preparation

The mixtures were prepared using two different methods: i) both components were mixed in a ceramic mortar and ground with a pestle for 10 min until a homogeneous mixture was obtained, ii) the compounds were dissolved in ethanol and the solvent was removed in vacuum. All compounds were commercially available except 4,5-dimethylimidazole (4) that was prepared according to Bredereck [26,27].
2.2 NMR spectroscopy

Solid state $^{13}\text{C}$ (50.32 MHz) and $^{15}\text{N}$ (20.28 MHz) CPMAS NMR spectra have been obtained with a Bruker AC-200 spectrometer at 298 K and a 7-mm Bruker DAB-7 probe-head, which achieves rotational frequencies of ca. 3.5-4.5 kHz. Samples were carefully packed in a ZrO$_2$ rotors with Kel-F end-caps and the standard CPMAS pulse sequence was used. To observe only the quaternary C-atoms, the NQS (Non-Quaternary Suppression) experiments were run by conventional cross-polarization (CP) at different contact times and with the dipolar dephased technique [28]. $^{13}\text{C}$ spectra were originally referenced to a glycine sample and then the chemical shifts were recalculated to the Me$_4$Si (for the carbonyl atom $\delta$ (glycine) = 176.1 ppm) and $^{15}\text{N}$ spectra to $^{15}\text{NH}_4\text{Cl}$ and then converted to nitromethane scale using the relationship: $\delta^{15}\text{N}(\text{nitromethane}) = \delta^{15}\text{N}(\text{ammonium chloride}) - 338.1$ ppm.

2.3 DSC experiments

The instrument used was a Seiko DSC 220C. The heating and cooling rates were normally $2 \degree \text{min}^{-1}$.

3 Results and discussion

We have used the following four imidazoles 2-5 together with pyrazole 1 (Scheme 1).

![Scheme 1](image)

**Scheme 1** 3,5-Dimethylpyrazole (1) and the selected imidazole derivatives (2-5) for equimolar mixtures.

3.1 Studies in solution and assignment problems of tautomeric imidazoles

Some literature results concerning $p$-tolylimidazoles 6-9 (Scheme 2) in CDCl$_3$ are worth reporting [29] because we will need them to assign the $^{13}\text{C}$ signals of imidazoles 2-5, our reviews of $^{13}\text{C}$ and $^{15}\text{N}$ NMR spectroscopy of azoles have also been used for assignment purposes [30-32]. Table 1 contains the $^{13}\text{C}$ and Table 2 the $^{15}\text{N}$ chemical shifts in CDCl$_3$ solution.

The assignment of the $^{13}\text{C}$ NMR signals of imidazoles 2-5 of Table 1 is straightforward by comparison with compounds 6-9 and references [30-32]. All the signals are
Scheme 2 $^{13}$C NMR model compounds (6-9).

| Compound | C₂ | C₃ | C₄ | C₅ | CH₃ |
|----------|----|----|----|----|-----|
| 1        | —  | 144.2 (broad) | 103.8 | 144.2 (broad) | 12.1 |
| 1⁠¹      | —  | 147.5        | 104.8 | 139.3        | 12.8 (Me₃), 10.5 (Me₅) |
| 2        | 135.1 | — | 121.6 | 121.6 | — |
| 3        | 144.6 | — | 121.1 | 121.1 | 13.6 |
| 4        | 132.2 | — | 126.5 | 126.5 | 10.5 |
| 5        | 143.8 | — | 131.6 | 116.9 | 13.7 (Me₂), 11.8 (Me₄) |

⁠¹ At low temperature [1]

Table 1 $^{13}$C NMR chemical shifts (ppm referenced to TMS) for azoles 1-5 in CDCl₃.

| Compound | N₁ | N₂ | N₃ |
|----------|----|----|----|
| 1        | —139.8 (broad) | —139.8 (broad) | — |
| 1⁠¹      | —172.3 | —94.3 | — |
| 2        | —170.7 | — | —170.7 |
| 3        | —174.2 | — | —174.2 |
| 4        | —168.9 | — | —168.9 |
| 5        | —177.7 | — | —164.9 |

⁠¹ At low temperature [2]

Table 2 $^{15}$N NMR chemical shifts (ppm referenced to nitromethane) for azoles 1-5 in CDCl₃.

average and narrow indicating rapid N₁-H/N₃-H tautomerism. Not in the case of pyrazole 1 that shows broad signals for C₃ and C₅ corresponding to an intermediate rate. Similarly, in Table 2 only the $^{15}$N NMR signal of 1 is broad and to be resolved in two signals, it would be necessary to record the spectrum at low temperature.
3.2 CPMAS NMR studies of pure compounds

| Compound | C_2     | C_3          | C_4       | C_5          | CH_3              |
|----------|---------|--------------|-----------|--------------|-------------------|
| 1        | —       | 143.3 (broad) | 104.7     | 143.3 (broad) | 11.7 (Me_3, Me_5) |
| 2        | 136.4   | —            | 126.8     | 115.6        | —                 |
| 3        | 144.8   | —            | 125.4     | 115.6        | 13.8              |
| 4        | 131.2   | —            | 131.2     | 122.0        | 10.9 (Me_4)       |
| 5        | 143.4   | —            | 125.9     | 122.3        | 12.2, 13.7 (Me_2) |
|          |         |              |           |              | 7.8, 10.0 (Me_4)  |

Table 3 $^{13}$C NMR chemical shifts (ppm) for azoles 1-5 in the solid state (CPMAS).

| Compound | N_1       | N_2       | N_3       | Average    | Solution     |
|----------|-----------|-----------|-----------|------------|--------------|
| 1        | -171.3    | -96.8     | —         | -134.0     | -139.8       |
| 2        | -210      | —         | -138      | -174       | -170.7       |
| 3        | -201.6    | —         | -132.3    | -167.0     | -174.2       |
| 4        | -198.2    | —         | -132.7    | -165.5     | -168.9       |
| 5        | -198.8    | —         | -124.9    | -161.9     | -177.7/-164.9 |

Table 4 $^{15}$N NMR chemical shifts (ppm) for azoles 1-5 in the solid state (CPMAS).

An examination of Tables 3 and 4 leads to the following observations: 3,5-dimethylpyrazole 1 presents SSPT, the broadening being lower in $^{15}$N CPMAS because the difference of the chemical shifts of tautomeric signals is larger than in $^{13}$C. The average values are close to those in solution but not identical because of the solvent effects in solution and the N–H···N bonds in the solid state that perturb the signals. Assuming that the splitting of some signals corresponds to the presence of more than one independent molecule in the unit cell, then the number of independent molecules should be: 2 (1 molecule, in agreement with X-ray data [23]), 3 (1 molecule), 4 (2 molecules) and 5 (2 molecules). Unfortunately the X-ray structures of 3-5 are not known. According to the data of Tables 3 and 4, imidazole 5 exists only as the 2,5-dimethyl tautomer (5b) in the solid state and as a mixture of both tautomers in solution (Scheme 3). The existence of annular tautomerism in imidazoles is a well-known fact [33].

3.3 CPMAS NMR studies of mixtures

We have recorded the spectra of equimolar mixtures of 1 with the four imidazoles 2-5. The results obtained have been identical with "solution/evaporation" and with "mechanical grinding", with the exception of compound 5 that yield, by "solution/evaporation" an oil, may be because in 5 the two tautomers are present in solution. Of the four mixtures, three correspond to a sum of the spectra of the individual components (1 + 2, 1 + 3, 1
Scheme 3 The two tautomers of 2,4(5)-dimethylimidazole (5).

+ 5) [as an example, the case 1 + 3 is represented in Fig. 2, note the isochrony of C3 and C5 in 3,5-dimethylpyrazole (1)].

Fig. 2 $^{13}$C CPMAS NMR spectra of a) 2-methylimidazole (3), b) 3,5-dimethylpyrazole (1), c) A 1:1 mixture of 1 + 3.

The only successful experiment was when 1 and 4 were mixed (Fig. 3). Not only C3 and C5 appear separated in Fig. 3c, but also C4 appears at 103.1 ppm. Although small, the upfield shift from 104.7 ppm to 103.1 ppm is typical of going from an NH-pyrazole with SSPT to another devoid of SSPT [1,27]. Therefore, 4 destroys the trimer of 1 forming new HBs in all probability a chain (catemer) 1···4···1···4···1···4···. We have not succeeded in obtaining co-crystals of 1 and 4 this preventing us to ascertain the polymeric structure. Another unanswered question is why 4 is the only imidazole, amongst the four tested, which has this property.

The data are reported in Tables 5 and 6. In $^{13}$C CPMAS, the differences are small
(less than 1 ppm) for the "physical mixtures". In the case of 1 + 4 ("chemical mixture") there are significant effects on the methyl groups of 4 (for instance, the signal at 6.3 ppm disappears). The $^{15}$N CPMAS results (Table 6) are more difficult to rationalize because several signals are not observed and because $^{15}$N is more sensitive than $^{13}$C to environment effects. Note the splitting of the imidazole signals in the 1 + 3 mixture indicating some perturbation of the imidazole catemer by the pyrazole.

3.4 DSC study of the pure compounds and the mixtures

When the melting points of the pure compounds (Table 7) and the mixtures (Table 8) are compared the expected decrease for the mixture is observed. It seems that 2-methylimidazole (3) presents polymorphism although only one of the polymorphs has been observed by $^{13}$C CPMAS NMR. 2,4(5)-Dimethylimidazole (5) does not solidify after melting probably because the liquid contains both tautomers 5a and 5b. The same happens to the 1 + 4 and 1 + 5 mixtures. Since 1 + 2 and 1 + 3 have the second melting point identical to the first one, this indicates that the physical mixture is not destroyed by fusion.
| Compound | C₂ | C₃ | C₄ | C₅ | Me |
|----------|----|----|----|----|----|
| 1        | —  | 143.3ᵃ | 104.7 | 143.3ᵃ | 11.7 (Me₃, Me₅) |
| 2        | 136.4 | —  | 126.8 | 115.6 | — |
| 1 + 2    | —  | 144.0ᵃ | 104.7 | 144.0ᵃ | 11.7 (Me₃, Me₅) |
|          | 135.9 | —  | 126.5 | 115.0 | — |
| 3        | 144.8 | —  | 125.4 | 115.6 | 13.8 (Me₂) |
| 1 + 3    | —  | 144.7ᵃ | 104.9 | 144.7ᵃ | 11.8 (Me₃, Me₅) |
|          | 144.6 | —  | 125.5 | 115.7 | 13.8 (Me₂) |
| 4        | 131.2 | —  | 131.2 | 122.0 | 10.9 (Me₄, 6.3, 7.8 (Me₄) |
| 1 + 4    | —  | 147.4 | 103.1 | 140.8 | 14.0 (Me₃), 7.9 (Me₅) |
|          | 131.9 | —  | 122.1 | 122.1 | 10.6 (Me₄ and Me₅) |
| 5        | 143.4 | —  | 125.9 | 122.3 | 13.7 and 12.2 (Me₂) |
| 1 + 5    | —  | 143.6ᵃ | 104.9 | 143.6ᵃ | 12.0 (Me₃, Me₅) |
|          | 143.4 | —  | 126.0 | 122.3 | 12.0 (Me₂), 7.8 (Me₄) |
| 1 + 5    | —  | 143.6ᵃ | 104.9 | 143.6ᵃ | 12.0 (Me₃, Me₅) |

ᵃ Broad signal. In the case of the mixtures the chemical shifts are referred to the underlined compound.

### Table 5

| ¹³C CPMAS NMR chemical shifts and Δδ = δ_mixture − δ_azole effects in ppm of the azole mixtures. |

## 4 Conclusions

Although no X-ray determination has been possible, by the combined use of CPMAS NMR and DSC, the probable structure of the equimolar mixtures of 3,5-dimethylpyrazole (1) and NH-imidazoles has been established. In the case of 4,5-dimethylimidazole (4), the data suggest that the trimer formed by 1 when pure is destroyed and a new structure, probably a chain, has been formed, even when mechanical grinding is used. This constitutes a new example of a mechanochemical reaction.
Table 6 $^{15}$N NMR CPMAS chemical shifts (ppm) and effects ($\Delta\delta = \delta_{\text{mixture}} - \delta_{\text{azole}}$) of azole mixtures.

| Mixture | Imidazole Derivatives |
|---------|-----------------------|
|         | $N_1$  | $N_2$  | $N_1$  | $N_3$  |
| 1 + 3   | -164.0 | -192.2 | -125.8 |
| Average effects | +7.3 | — | +4.6 | +3.9 |
| 1 + 4   | -165.5 | -97.9 | -203.9 | -124.1 |
| Effects | +5.8 | -1.1 | -5.7 | +0.8 |
| 1 + 5   | -200.6 | -134.5 |
| Effects | — | — | +1.8 | -9.6 |

$a$ not observed

Table 7 DSC experiments (pure compounds).

| Compounds | 1/°C Melting | 2/°C Solidification | 3/°C Melting | 4/°C Solidification |
|-----------|--------------|---------------------|--------------|---------------------|
| 1         | 106.7        | 100.6               | 106.9        | 98.9                |
| 2         | 88.4         | 40.0                | 88.9         | 40.8                |
| 3         | 96.2/146.1   | 140.4               | 144.2        | 139.8               |
| 4         | 119.3        | 88.6                | 117.9        | 88.2                |
| 5         | 83.6         | —                   | —            | —                   |

Table 8 DSC experiments (mixtures).

| Mixtures | 1/°C Melting | 2/°C Solidification | 3/°C Melting | 4/°C Solidification |
|----------|--------------|---------------------|--------------|---------------------|
| 1 + 2    | 49.3         | 24.9                | 49.2         | 20                  |
| 1 + 3    | 65.0         | 43.4                | 64.5         | 43.1                |
| 1 + 4    | 88.9         | —                   | —            | —                   |
| 1 + 5    | 43.1         | —                   | —            | —                   |

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