

The structure of *Omeprazole* in the solid state: a ^{13}C and ^{15}N NMR/CPMAS study

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To our friend Professor Edmunds Lukevics on his 70th anniversary

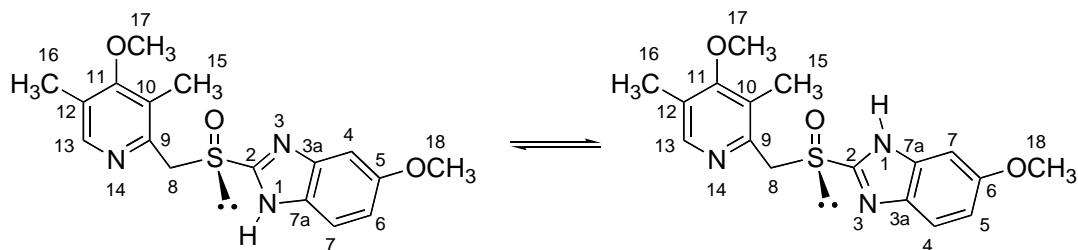
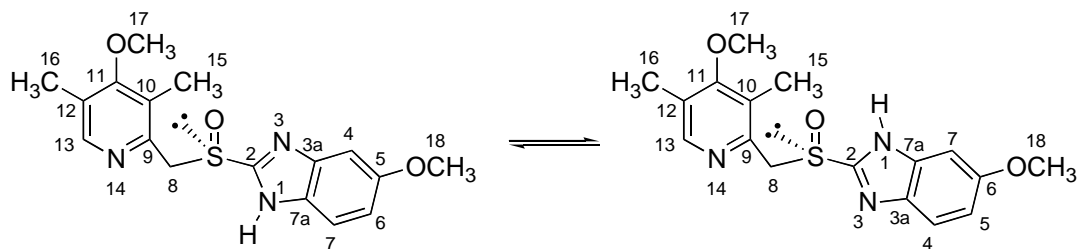
Abstract

The ^{13}C and ^{15}N CPMAS spectra of a solid sample of *Omeprazole* have been recorded and all the signals assigned. The sample consists uniquely of the 6-methoxy tautomer. For analytical purposes, the signals of the other tautomer, the 5-methoxy one, were estimated from the data in solution (*Magn. Reson. Chem.* **2004**, 42, 712).

Keywords: *Omeprazole*, NMR, ^{13}C , ^{15}N , CPMAS, tautomerism, benzimidazole

Introduction

Omeprazole, 5(6)-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl-1*H*-benzimidazole [**1**(**2**)], is an important ulcer drug,¹ that has been classified amongst the blockbuster drugs.² This compound presents two sources of structural differentiation. First, *Omeprazole* is chiral (**a** vs. **b**)³ since it has a stereogenic center on the sulfur atom but the commercial form has been sold, until recently, as a racemate. In 2001, *Esomeprazole* magnesium, the *S* enantiomer was approved.⁴ The second source of diversity is that these compounds present tautomerism (**1** vs. **2**). We have already devoted a paper to the tautomerism of *Omeprazole* in solution using ^1H and ^{13}C NMR spectroscopy.⁵ In this paper a complete assignment of the signals was carried out and the tautomeric equilibrium constant, $K_T = [\mathbf{2}]/[\mathbf{1}]$, was determined in THF at 195 K, to be 0.59 in favor of the 6-methoxy tautomer **2**.

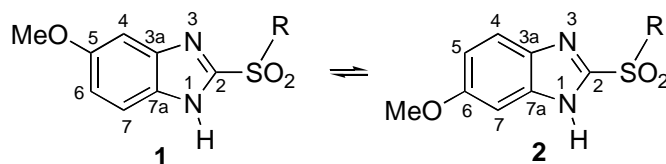
Tautomer 5-methoxy-(S)-(-)-Omeprazole **1a**Tautomer 6-methoxy-(S)-(-)-Omeprazole **2a**Tautomer 5-methoxy-(R)-(+)-Omeprazole **1b**Tautomer 6-methoxy-(R)-(+)-Omeprazole **2b**

Results and Discussion

We have devoted some publications to determine the relationships between tautomerism in solution and tautomerism in the solid state: the most frequent situation is that the tautomer predominant in solution is the only one present in the solid state.⁶ In the case of *Omeprazole* (37% of **1** - 63% of **2**) the prediction should be that in the solid state only **2** will be present.

We recorded the ¹³C and ¹⁵N CPMAS/NMR spectra of the sample without further purification. We have represented in Figure 1 the general ¹³C CPMAS NMR spectrum and in Figure 2, the corresponding NQS spectrum where only quaternary carbons are apparent. The first important observation is that **there is only one series of signals, that is, only one tautomer is present in the solid.**

The chemical shifts of Figure 1 are in good agreement with the data in solution for tautomer **2** and are rather different of those of tautomer **1** (see Table 1).⁵



The 4th and 5th columns of Table 1 correspond to the same spectra, those of Figure 1 in the case of ¹³C. Due to benzimidazole numbering, save C₂, the remaining six carbon and the two nitrogen atoms are different for each one of them. For instance, in tautomer **1** C₅ bears the methoxy group while in tautomer **2** it is *ortho* to the methoxy group and so on. Consequently, the

signal of C_7 appears at 113.1 and 94.0 ppm for tautomers **1** and **2** in solution (2nd and 3rd columns) and has to be compared with signals at 120.6 and 91.6 ppm of the CPMAS spectrum.

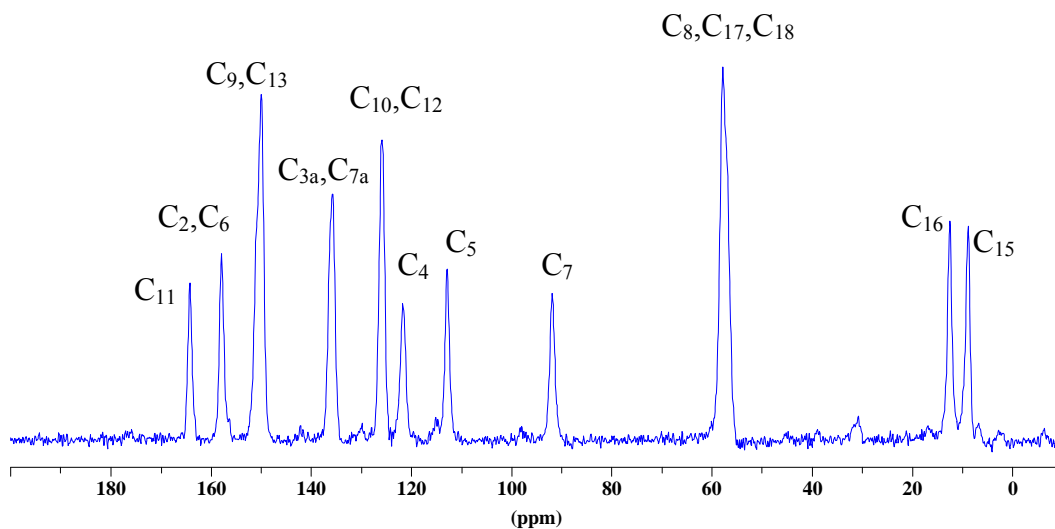


Figure 1. ^{13}C CPMAS NMR spectrum of *Omeprazole*

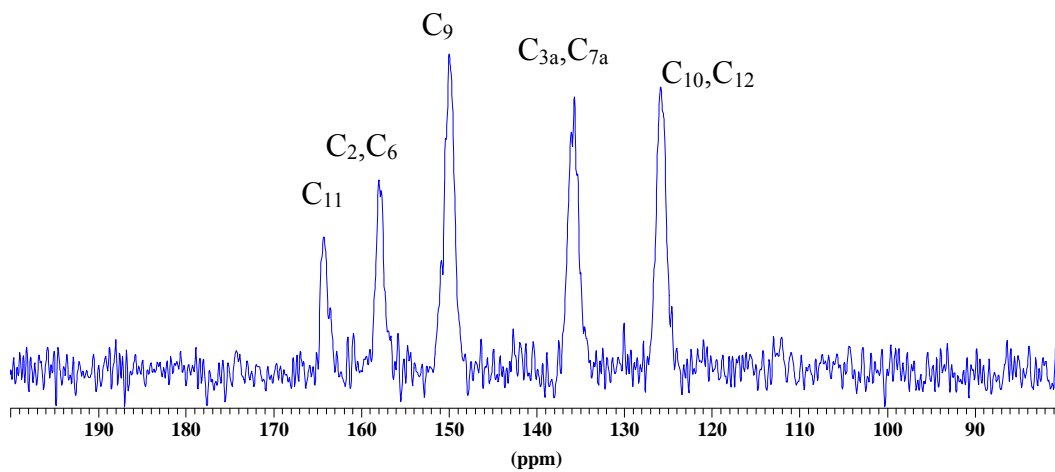


Figure 2. Expanded region of the NQS spectrum of *Omeprazole*

Table 1. ^{13}C and ^{15}N chemical shifts (δ , ppm) of tautomers **1** and **2** in THF- d_8 and ^{13}C and ^{15}N CPMAS chemical shifts (δ , ppm) of Figure 1

Signal	1	2	CPMAS ^a	CPMAS ^b
C ₂	155.4	153.5	156.6	156.6
C _{3a}	146.0	140.2	136.9	136.9
C ₄	101.1	121.6	91.6	120.6
C ₅	157.4	114.2	156.6	111.8
C ₆	115.3	158.2	111.8	156.6
C ₇	113.1	94.0	120.6	91.6
C _{7a}	129.9	136.5	136.9	136.9
C ₈	61.9	61.6	57.6	57.6
C ₉	151.5	151.4	150.4	150.4
C ₁₀	128.4	128.2	126.0	126.0
C ₁₁	164.6	164.6	163.9	163.9
C ₁₂	127.1	127.1	126.0	126.0
C ₁₃	150.2	150.2	150.4	150.4
C ₁₅	11.6	11.5	9.0	9.0
C ₁₆	13.5	13.5	12.2	12.2
C ₁₇	60.1	60.0	57.6	57.6
C ₁₈	55.4	55.5	57.6	57.6
----- ^c -----				
N ₁	-233.9	-233.0	-228.5	-228.5
N ₃	Not observed		-117.4	-117.4
N ₁₄	-74.0	-74.0	-74.0	-74.0

^a Numbered as tautomer **1**; ^b numbered as tautomer **2**; ^c for ^{15}N data see also Table 2.

A regression for each pair of values lead to two equations:

1st hypothesis: the solid has the structure **1** (5-methoxy)

$$\delta^{13}\text{C} (\text{CPMAS}) = -(2.1 \pm 2.7) + (1.01 \pm 0.02) \delta^{13}\text{C} (\text{solution}), n = 17, r^2 = 0.992 [1]$$

2nd hypothesis: the solid has the structure **2** (6-methoxy)

$$\delta^{13}\text{C} (\text{CPMAS}) = -(2.2 \pm 1.1) + (1.010 \pm 0.009) \delta^{13}\text{C} (\text{solution}), n = 17, r^2 = 0.999 [2]$$

The second hypothesis is better. Note that both tautomers only differ in the effects of the 5(6)-methoxy group that are only important for carbons C_{3a(7a)} and C₄₍₇₎. Considering only these

four signals, the difference is clearer:

$$\mathbf{1} \quad \delta^{13}\text{C (CPMAS)} = (2 \pm 43) + (0.98 \pm 0.34) \delta^{13}\text{C (solution)}, n = 4, r^2 = 0.800 \quad [3]$$

$$\mathbf{2} \quad \delta^{13}\text{C (CPMAS)} = -(3 \pm 7) + (1.015 \pm 0.054) \delta^{13}\text{C (solution)}, n = 4, r^2 = 0.994 \quad [4]$$

Concerning ^{15}N NMR results in solution, only N_{14} and N_1 were observed, the N_3 signals could not be detected even using different delays for evolution of long-range couplings.

In our previous paper we reported the absolute shieldings, σ ppm, calculated at the GIAO/DFT/6-311++G** level (Table 2).

Table 2. ^{15}N absolute shieldings (σ , ppm) and ^{15}N chemical shifts (δ , ppm) of tautomers **1** and **2**

Signal	1	2	Solution	CPMAS
NH N_1	100.4277	99.6338	-233.9/-233.0	-228.5
=N- N_3	-18.9396	-21.3590	Not observed	-117.4
Pyridine N_{14}	-90.6636	-90.6263	-74.0	-74.0

Here again, the correlation is better with tautomer **2** (eq. 6) than with tautomer **1** (eq. 5), but, as expected from the small effect of the 5(6)-methoxy group on the benzimidazole nitrogens, both are rather similar:

$$\mathbf{1} \quad \delta^{15}\text{N (CPMAS)} = -(142.5 \pm 6.8) - (0.82 \pm 0.09) \sigma^{15}\text{N}, n = 3, r^2 = 0.9891 \quad [5]$$

$$\mathbf{2} \quad \delta^{15}\text{N (CPMAS)} = -(143.4 \pm 6.0) - (0.82 \pm 0.08) \sigma^{15}\text{N}, n = 3, r^2 = 0.9915 \quad [6]$$

In conclusion, the sample of *Omeprazole* we have studied in this work is pure (or, at least, more than 95% pure) 6-methoxy tautomer **2**. When *Omeprazole* has been crystallized to obtain single crystals good enough for X-ray crystallography, the structure shows that they are 6-methoxy tautomers (unfortunately, in both cases the authors named them 5-methoxy-benzimidazoles!): they are reported in the Cambridge Structural Database⁷ with the refcodes VAYXOI and VAYXOI01(02).

It is possible that other samples of *Omeprazole* correspond to mixtures of **1** and **2**. The most useful signals to determine the tautomerism of *Omeprazole* in the solid state are C_4/C_7 and $\text{C}_{3a}/\text{C}_{7a}$. We have represented in Figure 3 the ^{13}C CPMAS spectra of **2** (Eq. [2] fitted) and **1** (Eq. [2] predicted from the solution data).

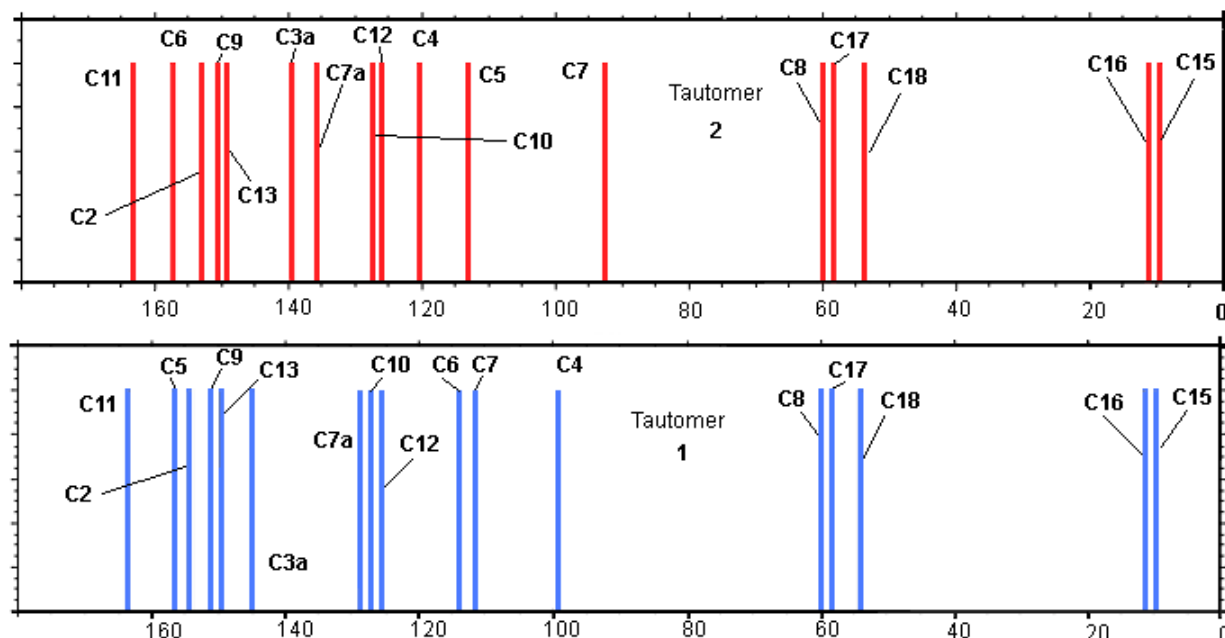


Figure 3. The ^{13}C CPMAS NMR spectra of *Omeprazole* tautomers **2** (fitted) and **1** (predicted).

A ^{13}C CPMAS NMR study of *Omeprazole* and its inclusion in β -cyclodextrin has been published in 2003.⁸ The spectrum, unassigned, is identical to that reported here, so it belongs to tautomer **2** although it is named as a 5-methoxy derivative **1**.

Experimental Section

Omeprazole was purchased from Sigma (O-104) which sells it under the name 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole, that is as tautomer **1**. The same tautomer was used by the *Chemical Abstract* to describe it under the Registry Number **73590-58-6**.

Solid-state NMR: ^{13}C (100.73 MHz) and ^{15}N (40.60 MHz) CPMAS NMR spectra were obtained on a Bruker WB 400 spectrometer at 300 K using a 4 mm DVT probehead. Samples were carefully packed in 4-mm diameter cylindrical zirconia rotors with Kel-F end-caps. Operating conditions involved $3.2 \mu\text{s}$ 90° ^1H pulses and decoupling field strength of 78.1 kHz by TPPM sequence. ^{13}C spectra were originally referenced to a glycine sample and then the chemical shifts were recalculated to the Me_4Si (for the carbonyl atom δ (glycine) = 176.1 ppm) and ^{15}N spectra to $^{15}\text{NH}_4\text{Cl}$ and then converted to nitromethane scale using the relationship: $\delta^{15}\text{N}$ (nitromethane) = $\delta^{15}\text{N}$ (ammonium chloride) – 338.1 ppm. To assign the C-atom signals in the solid state, we run non-quaternary suppression (NQS) experiments by conventional cross-polarization. The typical acquisition parameters for ^{13}C CPMAS were: spectral width, 40 kHz; recycle delay, 5 s; acquisition time, 30 ms; contact time, 2 ms; and spin rate, 12 kHz. And for

^{15}N CPMAS were: spectral width, 40 kHz; recycle delay, 5 s; acquisition time, 35 ms; contact time, 6 ms; and spin rate, 6 kHz.

Solution NMR: The ^{15}N NMR spectra were recorded on a Bruker DRX 400 (9.4 Tesla, 40.56 MHz) spectrometer with a 5-mm inverse-detection H-X probe equipped with a z-gradient coil. Chemical shifts (δ in ppm) are given from nitromethane (0.00) used as external reference. Proton detected heteronuclear shift correlation spectra, (^1H - ^{15}N) gs-HMQC and (^1H - ^{15}N) gs-HMBC, were acquired and processed using standard Bruker NMR software and in non-phase-sensitive mode.⁹

Acknowledgements

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