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

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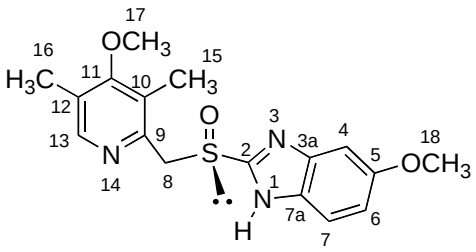
**To our friend Professor Edmunds Lukevics on his 70th anniversary**

**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).

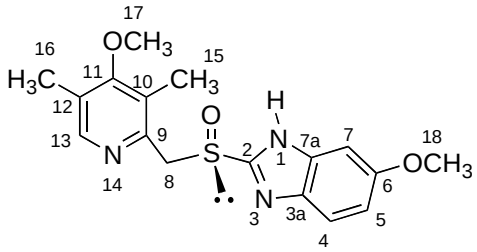
**Keywords:** Omeprazole, NMR, $^{13}C$, $^{15}N$, CPMAS, tautomerism, benzimidazole

## Introduction

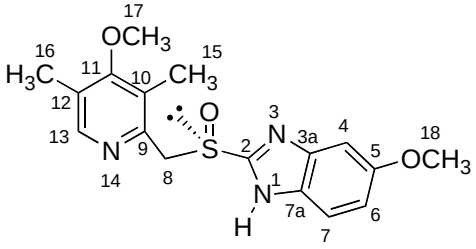
*Omeprazole*, 5(6)-methoxy-2-**{**(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1*H*-benz - imidazole [**1**(**2**)], is an important ulcer drug,[1] that has been classified amongst the blockbuster drugs.[2] This compound presents two sources of structural differentiation. First, *Omeprazole* 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 $^{1}H$ and $^{13}C$ NMR spectroscopy.[5] In this paper a complete assignment of the signals was carried out and the tautomeric equilibrium constant, $K_T$ = [**2**]/[**1**], was determined in THF at 195 K, to be 0.59 in favor of the 6-methoxy tautomer **2**.



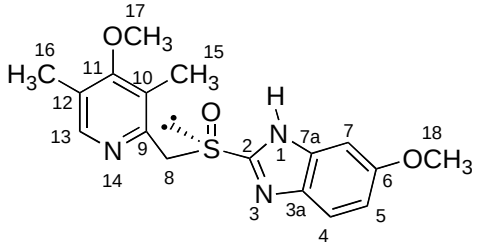
Tautomer 5-methoxy-(*S*)-(–)-Omeprazole **1a**



Tautomer 6-methoxy-(*S*)-(–)-Omeprazole **2a**



Tautomer 5-methoxy-(*R*)-(+)-Omeprazole **1b**



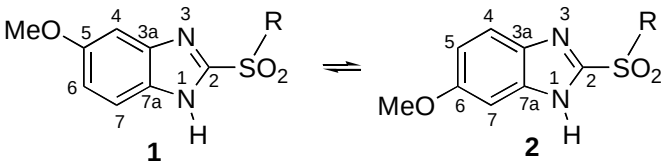
Tautomer 6-methoxy-(*R*)-(+)-Omeprazole **2b**

## 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 $^{13}C$ and $^{15}N$ CPMAS/NMR spectra of the sample without further purification. We have represented in Figure 1 the general $^{13}C$ 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]



**1** **2**

The 4th and 5th columns of Table 1 correspond to the same spectra, those of Figure 1 in the case of $^{13}C$. Due to benzimidazole numbering, save $C_2$, the remaining six carbon and the two nitrogen atoms are different for each one of them. For instance, in tautomer **1** $C_5$ 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.

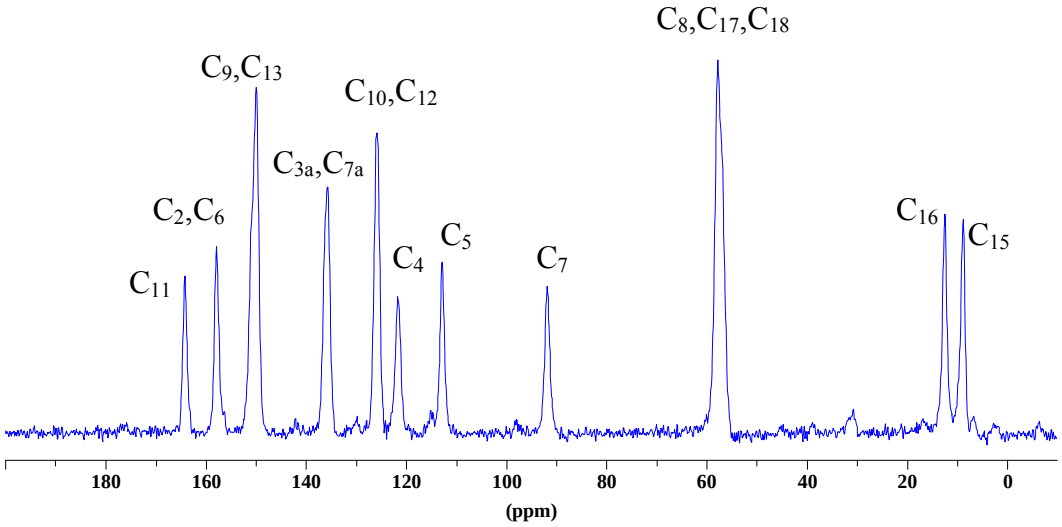



**Figure 1.** $^{13}$C CPMAS NMR spectrum of *Omeprazole*

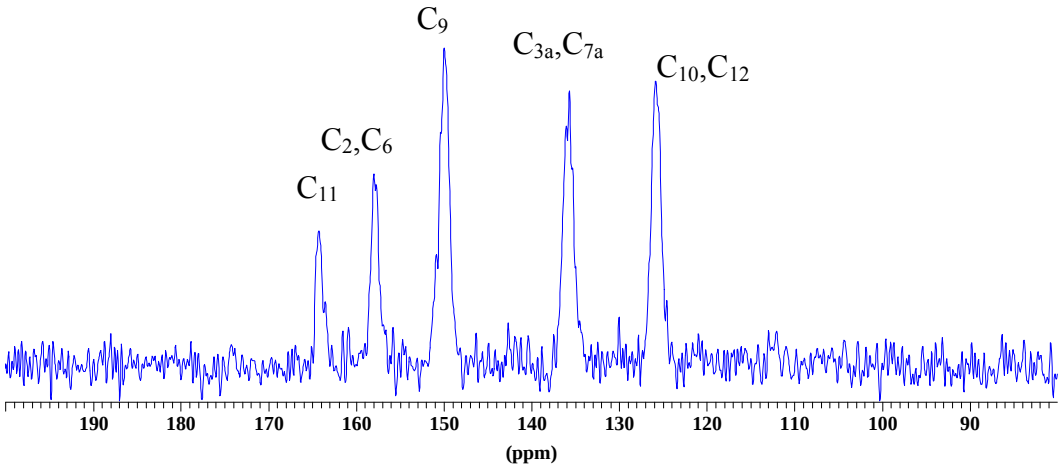



**Figure 2**. Expanded region of the NQS spectrum of *Omeprazole*

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

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

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

$\delta^{13}C$ (CPMAS) = –(2.2±1.1) + (1.010±0.009) $\delta^{13}C$ (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 $C_{4(7)}$. Considering only these

four signals, the difference is clearer:

**1** $\delta^{13}$C (CPMAS) = (2±43) + (0.98±0.34) $\delta^{13}$C (solution), n = 4, $r^2$ = 0.800 [3]
**2** $\delta^{13}$C (CPMAS) = –(3±7) + (1.015±0.054) $\delta^{13}$C (solution), n = 4, $r^2$ = 0.994 [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, $\sigma$ ppm, calculated at the GIAO/DFT/6-311++G** level (Table 2).

**Table 2.** $^{15}$N absolute shieldings ($\sigma$, ppm) and $^{15}$N chemical shifts ($\delta$, 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:

**1** $\delta^{15}$N (CPMAS) = –(142.5±6.8) – (0.82±0.09) $\sigma^{15}$N, n = 3, $r^2$ = 0.9891 [5]
**2** $\delta^{15}$N (CPMAS) = –(143.4±6.0) – (0.82±0.08) $\sigma^{15}$N, n = 3, $r^2$ = 0.9915 [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 Database[7] 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 $C_{3a}$/$C_{7a}$. 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).

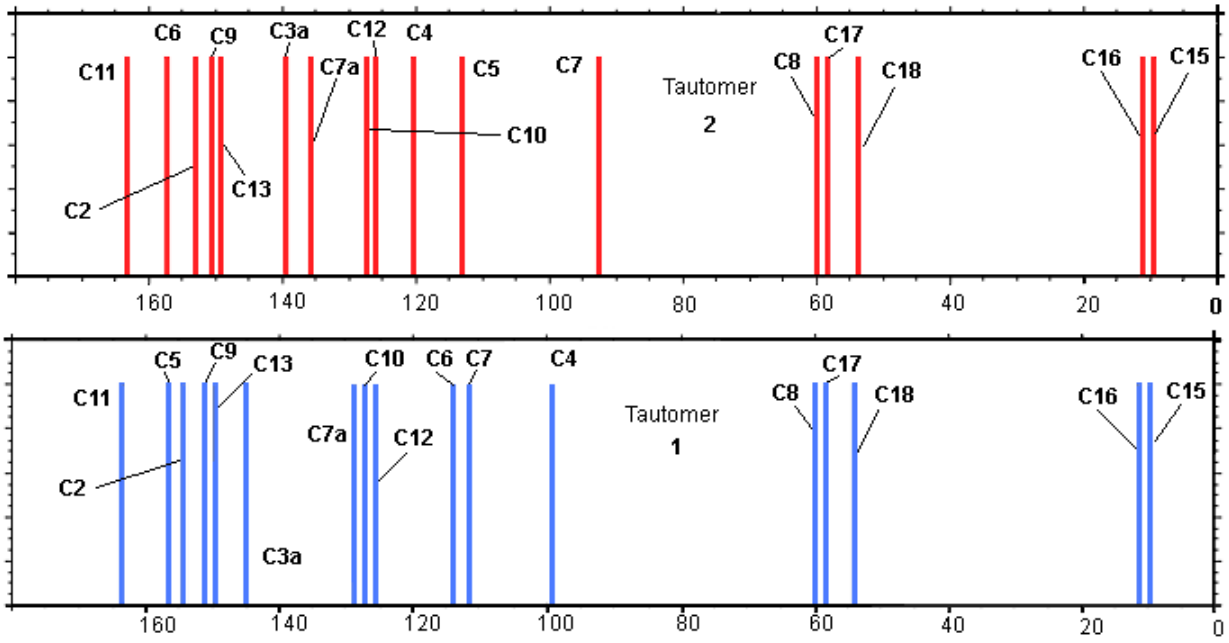



**Figure 3**. The $^{13}$C CPMAS NMR spectra of *Omeprazole* tautomers **2** (fitted) and **1** (predicted).

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 μs 90° $^{1}$H 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 $\delta$ (glycine) = 176.1 ppm) and $^{15}$N spectra to $^{15}NH_4Cl$ and then converted to nitromethane scale using the relationship: $\delta^{15}$N (nitromethane) = $\delta^{15}$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 ($\delta$ in ppm) are given from nitromethane (0.00) used as external reference. Proton detected heteronuclear shift correlation spectra, ($^{1}$H-$^{15}$N) gs-HMQC and ($^{1}$H-$^{15}$N) gs-HMBC, were acquired and processed using standard Bruker NMR software and in non-phase-sensitive mode.[9]

## Acknowledgements

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