Structure and Dynamics of Crystalline Carbimazole by NMR Crystallography and Relaxometry

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Introduction

Molecular dynamics and structural characteristics of a solid drug strongly affect its pharmaceutical properties and release profiles. Solid State NMR (SSNMR) has been proved to be a very important technique in the study of pharmaceuticals, allowing many different experiments to be performed in order to obtain important information on dynamic and structural properties on a broad space and time range [1].

Sample: Carbimazole

Carbimazole is one of the most used drugs currently for the treatment of hyperthyroidism and Grave's disease. Two X-ray crystal structures are reported in the Cambridge Structural Database (JOVDIH and JOVDIH01) [2][3].

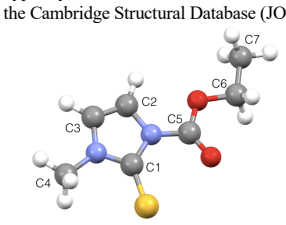


Figure 1. Carbimazole with labels of the carbon nuclei

^{13}C CP MAS Spectra

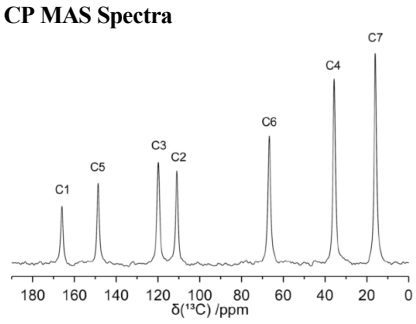


Figure 2. ^{13}C CP-MAS spectrum of carbimazole (ν_{MAS} = 22 kHz). The assignment of the peaks is reported on the spectrum.

The absence of multiplicity of resonance of the signals confirms the presence of a single independent molecule in the unit cell (Z'=1).

^{1}H MAS and CRAMPS Spectra

The ^{1}H MAS spectrum recorded at ν_{MAS} = 22 kHz (Figure 3a) shows a scarce resolution. In order to improve the spectral resolution, MAS had to be combined with suitable pulse sequences, such as Phase Modulated Lee-Goldburg (PMLG) and Decoupling Using Mind Boggling Optimization (DUMBO), aimed at better removing the ^{1}H homonuclear dipolar coupling.

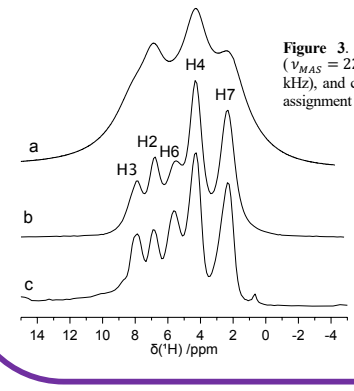


Figure 3. ^{1}H spectra of carbimazole: a) MAS (ν_{MAS} = 22 kHz), b) PMLG-MAS (ν_{MAS} = 15 kHz), and c) DUMBO-MAS (ν_{MAS} = 12 kHz). The assignment of the peaks is reported on the spectra.

NMR Crystallography

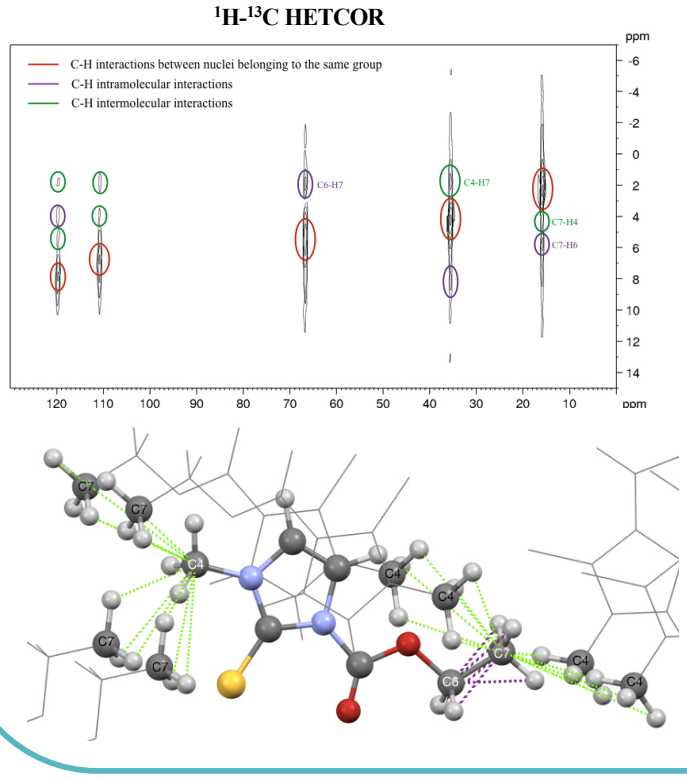
DFT-GIPAW

Assignment	Experimental Isotropic Chemical Shift δ (ppm)	δ at the DFT level; X-ray structure (ppm)	δ at the DFT level: only H optimized (ppm)	δ at the DFT level: all atoms optimized (ppm)
H7	2.31	2.28	2.36	2.46
H4	4.28	4.20	4.30	4.16
H6	5.59	5.77	5.45	5.44
H2	6.85	7.17	6.84	6.80
H3	7.85	7.58	7.92	8.02
RMSD	-	**0.19**	**0.07**	**0.13**
C7	16.0	10.9	13.6	14.1
C4	35.6	36.5	35.7	34.9
C6	66.8	68.6	68.8	69.2
C2	111.0	116.5	111.6	110.7
C3	119.8	123.7	121.9	122.1
C5	148.7	147.8	149.1	151.1
C1	166.0	159.8	163.0	161.7
RMSD	-	**4.0**	**1.8**	**2.4**

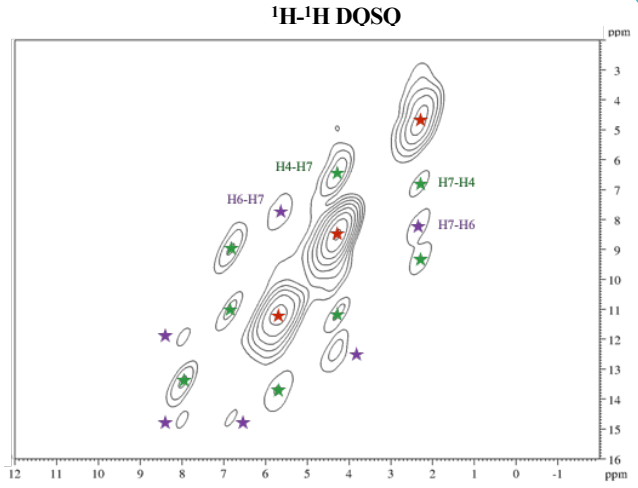
- The lowest RMSD value is achieved when only H atoms are optimized [4].
- Orthorhombic unit cell; a = 7.698 Å; b = 6.650 Å; c = 17.388 Å

2D NMR Experiments

^{1}H-^{13}C HETCOR



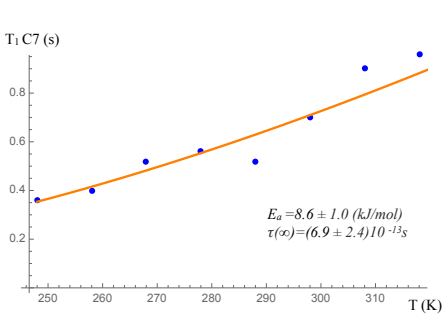
^{1}H-^{1}H DQSQ

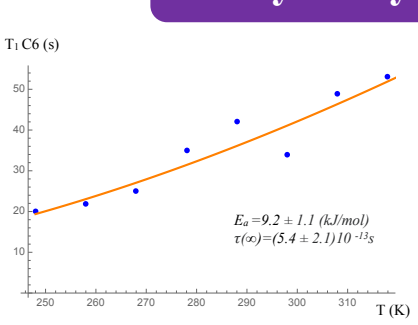


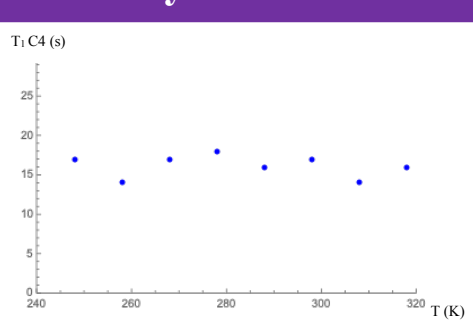
The signals intensities are in excellent (although semi-quantitative) agreement with the strengths of the dipolar couplings predicted from the inter-nuclear distances of the optimized structures.

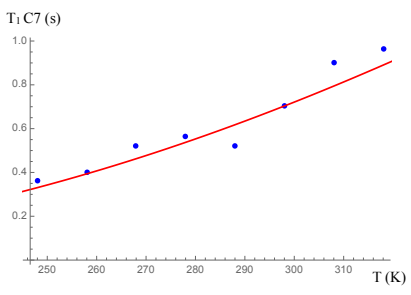
Strong intermolecular dipolar interactions are observed between the methyl groups 4 and 7 [4].

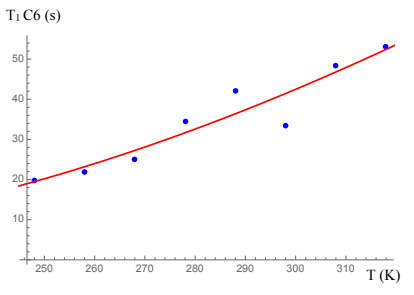
Study of Dynamics by NMR Relaxometry

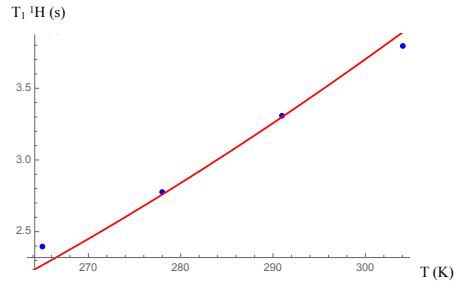






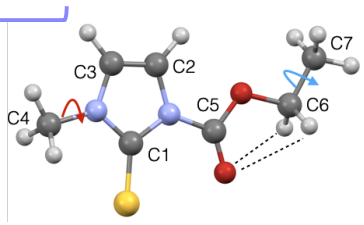






Simultaneous fitting of T_1(C7), T_1(C6) and T_1(^{1}H) taking only the rotation of the methyl group 7 into account

$E_a = 9.3 \pm 0.8$ (kJ/mol) ; $\tau(\infty) = (5.2 \pm 2.1)\ 10^{-13}$ s; $C_H = (1.7 \pm 0.7)\ 10^9$ s^{-2}



^{13}C T_1 at room temperature

Nuclei	T_1 (s)
C7	0.750 ± 0.010
C4	16.9 ± 0.5
C6	45 ± 5
C2	$\gg 100$
C3	$\gg 100$
C1	$\gg 100$
C5	$\gg 100$

Fitting Model: Bloembergen-Purcell- Pound (BPP)

$$R_1(^{13}C) = (T_1)^{-1} = \frac{2N}{15}K'\left[\frac{\tau_C}{1+(\omega_H-\omega_C)^2\tau_C^2} + \frac{3\tau_C}{1+\omega_C^2\tau_C^2} + \frac{6\tau_C}{1+(\omega_H+\omega_C)^2}\right]$$

$$K' = \left(\frac{\mu_0}{4\pi}\right)^2 \frac{\gamma_I^2\gamma_S^2}{r_{IS}^6}\hbar^2 I(I+1)$$

$$R_1(^1H) = T_1^{-1}(^1H) = \frac{3}{2}C_H[J^{(1)}(\omega_0) + J^{(2)}(2\omega_0)]$$

The only motions that occur in the molecule are the rotational motions of the two methyl groups;
The rotation of the C4 methyl group is probably too fast to give an efficient relaxation of the C4 magnetization, while the rotation of the C7 methyl group is able to effectively relax its own magnetization, the one of C6 and the magnetization of the proton nuclei;
The rotation of the ethyl group around the C6-O bond is stucked, probably due to the interactions taking place between methylene hydrogens and carbonyl oxygen.

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References:

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[4] A. Scarperi; G. Barcaro; A. Pajzderska; F. Martini; E. Carignani; M. Geppi. *Molecules* **2021**, 26, 4577.

NMR Methods. Solid State NMR spectra were recorded on a Bruker Avance Neo spectrometer working at the Larmor frequencies of 500.13 and 125.77 MHz for ^{1}H and ^{13}C nuclei, respectively, equipped with a triple-resonance CP-MAS probehead accommodating rotors with an external diameter of 2.5 mm. The 90 degree pulse duration was 2.08 and 5 μs for ^{1}H and ^{13}C nuclei, respectively. The ^{1}H-^{13}C CP-MAS spectrum was recorded at a MAS frequency of 22 kHz, using a contact time of 2 ms and accumulating 1000 scans. The ^{1}H MAS spectrum was recorded at a MAS frequency of 22 kHz accumulating 4 scans. The ^{1}H PMLG-MAS spectrum was recorded at a MAS frequency of 15 kHz accumulating 32 scans. The ^{1}H DUMBO-MAS spectrum was recorded at a MAS frequency of 12 kHz accumulating 32 scans. The ^{1}H-^{13}C HETCOR spectrum was recorded at a MAS frequency of 15 kHz, using a contact time of 0.5 ms, accumulating 128 rows and 64 scans. The ^{1}H DQ-SQ spectrum was recorded at a MAS frequency of 12 kHz, using the eDUMBO-1$_{22}$ scheme for decoupling during acquisition, accumulating 256 rows and 16 scans. ^{1}H and ^{13}C spin-lattice relaxation times were measured using Inversion Recovery and Torchia pulse sequences, respectively, spinning the sample at the magic angle with a frequency of 22 kHz; the variable delay ranged from 1 ms to 10 s for the measurement of the ^{1}H nuclei and from 1 ms to 80 s for the measurement of the ^{13}C nuclei. In all relevant experiments, a SPINAL-64 decoupling scheme was applied on ^{1}H nuclei while acquiring the ^{13}C signal.