Solid State Nuclear Magnetic Resonance 39 (2011) 41–46

Contents lists available at ScienceDirect

Solid State Nuclear Magnetic Resonance

journal homepage: www.elsevier.com/locate/ssnmr

Kinetics of $^{1}H \rightarrow {}^{13}C$ NMR cross-polarization in polymorphs and solvates of the antipsychotic drug olanzapine

Waclaw Kolodziejski [a,*], Joanna Herold [a], Marzena Kuras [a], Irena Wawrzycka-Gorczyca [b], Anna E. Koziol [b]

[a] Medical University of Warsaw, Faculty of Pharmacy, Department of Inorganic and Analytical Chemistry, ul. Banacha 1, 02-097 Warszawa, Poland
[b] Maria Curie-Sklodowska University, Faculty of Chemistry, Department of Crystallography, 20-031 Lublin, Poland

ARTICLE INFO

Article history:
Received 10 November 2010
Received in revised form
10 December 2010
Available online 4 January 2011

Keywords:
Solid-state NMR
^{13}C NMR
Cross-polarization
Kinetics
Olanzapine
Principal component analysis

ABSTRACT

The $^{1}H \rightarrow {}^{13}C$ NMR cross-polarization (CP) was studied under magic-angle spinning at 7.5 kHz in various crystal forms of the antipsychotic drug olanzapine: two polymorphs (metastable I and stable II) and eight solvates containing organic solvent and water molecules. The CP kinetics followed the non-classical I–I*-S model, in which CP begins in a spin cluster of proximate abundant spins I* and rare spins S, then is controlled by spin diffusion of the abundant spins I from bulk to the I* spins of the spin cluster and finally is governed by spin-lattice relaxation of the abundant spins in the rotating frame. The corresponding CP kinetics parameters were determined and analyzed. It was demonstrated that the, λ and T_{df} values (the CP time constant, the cluster composition parameter and the ^{1}H spin-diffusion constant, respectively) were very useful to discriminate the functional groups, especially in the 3D parameter space. In order to conveniently analyze the large amount (175) of the collected CP parameters, the number of the observed variables was reduced using the principal component (PC) analysis. The 2D plot of PC2 vs. PC1 showed adequate separation of the CH_3, CH_2, CH and C cases (C stands for carbons without adjacent hydrogens). It was demonstrated that those cases were located along the PC1 axis in the order of increasing $^{1}H–{}^{13}C$ dipolar couplings: $C < CH_3 < CH < CH_2$. Our study showed the I–I*-S model at work and established ranges of its parameters for various functional groups.

1. Introduction

Olanzapine, 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno [2,3-*b*] [1,5] benzodiazepine (Fig. 1), is a second-generation antipsychotic approved for the treatment of schizophrenia, bipolar mania and associated agitation [1,2]. This important drug crystallizes in more than 25 solid forms, including three anhydrous polymorphs (I–III) and various hydrates and solvates [3] The polymorphism of olanzapine crystals was studied using X-ray crystallography, differential scanning calorimetry, IR and Raman vibrational spectroscopies, and high-resolution solid-state NMR [3–10]. The number of newly discovered solvates of olanzapine is rapidly growing, while those chemical and crystallographic efforts are accompanied by intensive patenting activity.

It follows that olanzapine provides us with large number of solid-state structures composed of the molecules of the same main compound (host) and solvent molecules as guests. In the polymorphic crystals, the olanzapine molecules show differences in the spatial arrangement and molecular dynamics, both dependent on molecular interactions, and in some cases, they demonstrate variations in molecular conformation. Those differences affect ^{13}C chemical shifts in the solid state NMR [3] and possibly the process of $^{1}H \rightarrow {}^{13}C$ cross-polarization (CP). The latter subject is to be studied in this work.

CP was invented to enhance weak NMR signals from diluted spins I, e.g. ^{13}C or ^{15}N, by polarization transfer from abundant spins S, usually protons [11,12]. The process relies on heteronuclear dipolar couplings between the nuclei involved. The CP kinetics is the dependence of the peak intensity on the contact time. It is recommended to use it in peak assignment, quantitative analysis and structural matters [13]. With olanzapine, one meets unique opportunity to examine parameters of the CP kinetics of different functional groups ($-CH_3$, $>CH_2$, $\equiv CH$ and quaternary carbons) from the same substance in various molecular arrangements stabilized by an environment in the crystal lattice. This will be accomplished in our work for CP following the non-classical I–I*-S model [13], which has been occasionally used for various organic solids [13–17].

Vast majority of former studies of the CP kinetics were based on the classical two-stage (rise-decay) I-S model of Pines et al. [11]. However, it has been argued [13] that with accurate, frequent sampling of the beginning of the CP kinetic curve one

* Corresponding author. Fax: +48 81 533 3348.
E-mail address: waclaw.kolodziejski@wum.edu.pl (W. Kolodziejski).

0926-2040/$ - see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.ssnmr.2010.12.003

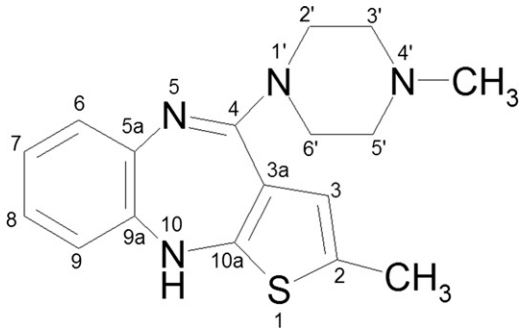

Fig. 1. Chemical structure of olanzapine.

Table 1
Characteristics of the studied crystalline forms of olanzapine.

Designation	Components	Stoichiometry	Space group
Form I	Pure Olz	–	[a]
Form II	Pure Olz	–	$P2_1/c$
Olz/AcMe	Olz/H_2O/AcMe	1:1:0.5	$C2/c$
Olz/AcOMe	Olz/H_2O/AcOMe	1:1:0.5	$C2/c$
Olz/EtOH	Olz/H_2O/EtOH	2:2:1	$P2_1/c$
Olz/*n*-PrOH	Olz/H_2O/*n*-PrOH	1:1:0.5	$C2/c$
Olz/*i*-PrOH	Olz/H_2O/*i*-PrOH	1:1:0.5	$C2/c$
Olz/*n*-BuOH	Olz/H_2O/*n*-BuOH	1:1:0.5	$C2/c$
Olz/*sec*-BuOH	Olz/H_2O/*sec*-BuOH	1:1:1	$P2_1/c$
Olz/CypenOH	Olz/H_2O/CypenOH	1:1:0.5	$C2/c$

[a] Not determined yet.

finds often three-stage functional behavior (fast rise–slower rise–decay), typical of the non-classical I–I*-S model [13]. If the sampling procedure is inadequate, those models can be easily confused. As a matter of fact, each CP model has different theoretical background and thereby is described by different set of parameters. Our study shows the less popular, non-classical I–I*-S model at work, presents its fine performance for the $^1H \rightarrow {}^{13}C$ CP and establishes ranges of its parameters for various functional groups.

2. Experimental

Olanzapine was synthesized according to the procedure described in Ref. [18]. Olanzapine polymorphs I (metastable) and II (stable) were crystallized using previously reported methods [3]. Olanzapine solvates were synthesized from respective solutions and characterized using single-crystal X-ray crystallography (Table 1) [4,5,9]. Phase purity of polycrystalline solvate samples was assessed using powder X-ray diffraction. The NMR measurements were done on powder samples.

Solid-state NMR cross-polarization (CP) experiments from protons to carbon-13 were done at 298 K on a Bruker Avance 400 WB spectrometer in the magnetic field of 9.4 T using the proprietary Bruker magic-angle spinning (MAS) probe and ZrO_2 rotors spun by dry air. The resonance frequencies for ^1H and ^{13}C were 400.1 and 100.6 MHz, respectively. The high-resolution $^1H \rightarrow {}^{13}C$ CP/MAS NMR spectra were measured on polycrystalline samples in a 4 mm probe under MAS at 7.5 kHz. CP based on the Zeeman order was set and adjusted on adamantane, which was also used as a secondary chemical shift reference. The conventional single-contact $^1H \rightarrow {}^{13}C$ CP pulse sequence with reversal of spin temperature in the rotating frame was applied with high-power proton decoupling during signal acquisition. The variable-contact time CP experiments were performed with optimized recycle delays of 6 s using 2.5 μs $\pi/2$ pulses, 360 scans and 32 arrayed contact time values in the range from 25 μs to 20 ms. Signal intensities were measured at peak tops. The solid-state NMR spectra were processed with the Bruker proprietary software XWINNMR and the NUTS NMR Data Processing Program (Version 5.097, Acorn NMR, 1995). The CP kinetic functions were fitted to experimental points with the KaleidaGraph program (version 3.5 for PC, Synergy Software, 2000), which employs the nonlinear least-squares algorithm with the Levenberg–Marquardt gradient descent method of minimization of the error function. Three-dimensional (3D) graphs showing CP kinetics parameters were done using the Graphis 2.9.44 program (Kylebank Software Ltd. 2010).

3. Statistical analysis

The principal component analysis [19] (PCA) was done using the Statistica 9.0 computer program (Stat Soft. Inc., 2009). PCA allows one to reduce the number of interrelated observed variables down to their uncorrelated latent principal components, while retaining as much as possible of the variation present in the original data set. The first principal component (PC1) describes as much of the variability in the data as possible, and each next component (PC2, PC3 …) accounts for as much of the remaining variability as possible. PCA can be understood as a mathematical procedure which rotates the coordinate system in such a manner that maximum variability is projected onto the new PC axes. In that resultant PC space, the scores are the coordinates of the cases (various types of carbons in this work) and the cases from the same classes have close scores and thereby form groups. The usual procedure is to plot the most important components against each other, normally PC2 vs. PC1, in order to identify the groups and discuss their interpretation.

Each PC is a linear combination of observed variables (and *vice versa*), which enter into the corresponding equation with adequate weight coefficients, called loadings. Analogous to Pearson's *r*, the squared loading of an observed variable on each PC is the fraction of variance explained by that PC for that observed variable. The sum of the squared loadings of a given observed variable on all PC's equals 1. The sum of the squared loadings of all observed variables on one particular PC gives its eigenvalue. The eigenvalue for a given component expresses the variance in all the observed variables which is accounted for by that PC. The eigenvalue divided the number of the observed variables and multiplied by 100 gives the percent of variance in all the observed variables accounted for by the pertinent component. The number of components generated by the computer program is always equal to the number of the observed variables. The researcher has to select only those, which can satisfactory explain the variation present in the original data set. There are various criteria to make the decision. We applied an arbitrary, variance justified criterion, that the components to keep should account for 90% of the variance (PC1 and PC2 in this work).

4. Theory

According to the non-classical I–I*-S model [13], CP begins in an isolated group of proximate, strongly coupled spins I* and S. Such group of spins can be a spin pair I*–S or a spin cluster I_n^*–S, consisting of *n* abundant spins and one rare spin. Within this model, the abundant spins do not have common spin temperature. The initial exchange of polarization between spins I* and S proceeds in an oscillatory manner, damped by subsequent spin-diffusion from distant bulk spins I. The oscillation frequency is dependent on the I*–S dipolar interaction. For rotating powder