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Two methodologies in the molecular structure and the intermolecular interactions analysis of pharmaceuticals in the solid-state: X-ray diffraction and ^{13}C CPMAS NMR data mining

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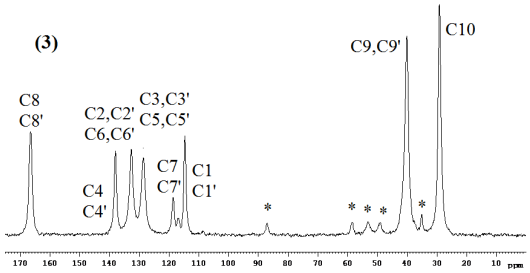
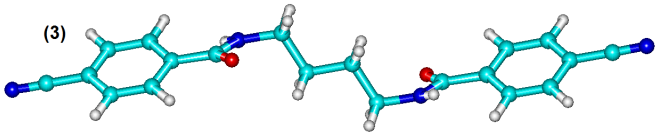
Graphical Abstract

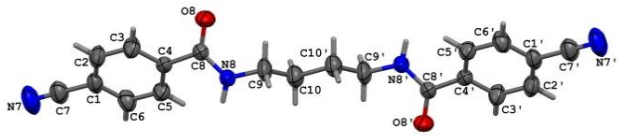
^{13}C CP/MAS NMR spectrum



theoretical structure derived from NMR resonances



X-ray structure



Abstract:

Increasing demands from the pharmaceutical industry for rapid molecular structure determination of pharmaceutical solids has prompted the development of X-ray diffraction and ^{13}C CP/MAS NMR data analyses. The solid-state form of the drug can have dramatic impact on the bioavailability, and the regulatory approval for many drugs is given only for the defined polymorph.

The intermolecular interactions are crucial in interpretation of interactions between the biomolecules and macromolecular targets and their analysis can provide essential information about how they occur.

The compounds presented in this report can be considered as the pentamidine analogs, which are of interest because they have potential use as the chemotherapeutics against Pneumocystis pneumonia, as potent NMDA receptor inhibitors or as anticancer and antimicrobial agents.

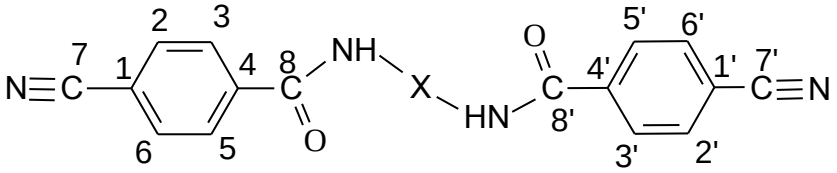
Keywords: bis-amidines; bis-nitriles; X-ray diffraction; ^{13}C CP/MAS NMR.

Introduction

Aromatic amidine groups are found in many bioactive compounds which exhibit antifungal, antiparasitic, and antitumor properties, but only pentamidne is clinically used in therapy of Pneumocystiss pneumonia, human African trypanosomiasis and antimony resistant Leishmaniasis. The relative structural simplicity of pentamidine has encouraged some laboratories to develop structural analogues with the hope to afford drug candidates with increased efficacy and reduced toxicity. The main synthetic route includes the preparation of appropriate bis-nitriles and their conversion to the bis-amidines. The bis-nitriles are not only the intermediates to the bis-amidines but are also the attractive substances because of their anticancer potency.

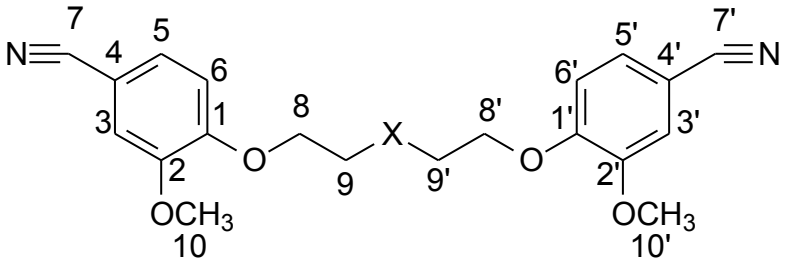
The objective of the studies was to discuss the structures and the intermolecular interactions of the bis-nitriles **1** - **7** and the bis-amidines **6a** - **7a** (see Fig. 1) in the solid-state, what is of special interest for the potential pharmaceuticals. The methods used are X-ray diffraction technique, and ^{13}C CP/MAS NMR spectroscopy combined with molecular modeling .

Introduction

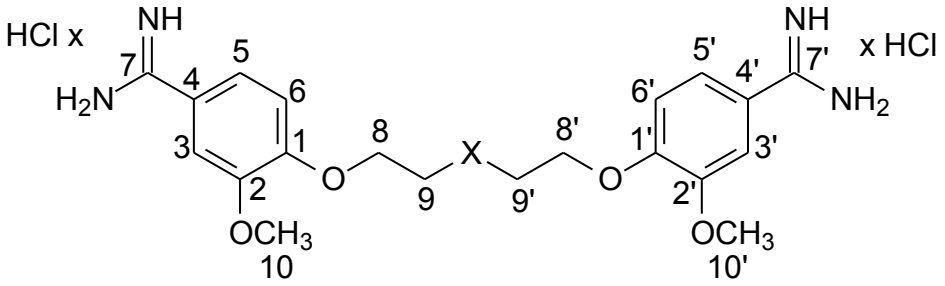


X = (CH_2CH_2) **1**, $(CH_2CH_2CH_2)$ **2**, $(CH_2CH_2CH_2CH_2)$ **3**,

$(CH_2CH_2CH_2CH_2CH_2)$ **4**, $(CH_2CH_2CH_2CH_2CH_2CH_2)$ **5**



X = N-CH_3 **6**, X = O **7**



X = N-CH_3 x HCl **6a**, X = O **7a**

Fig. 1. The chemical formulas of studied compounds with atom numbering.

Results and discussion 1

Firstly, the solid-state structures were discussed for N,N'-alkane-α,ω-diylbis(4-cyanobenzamides) (**1**) – (**5**) i.e. bis-nitriles joined by the aliphatic linker having different numbers of C atoms equal n = 2 to 6 and two amide groups .

The ^{13}C CP/MAS NMR spectra in the solid-state were recorded with a Bruker Avance DMX 400.

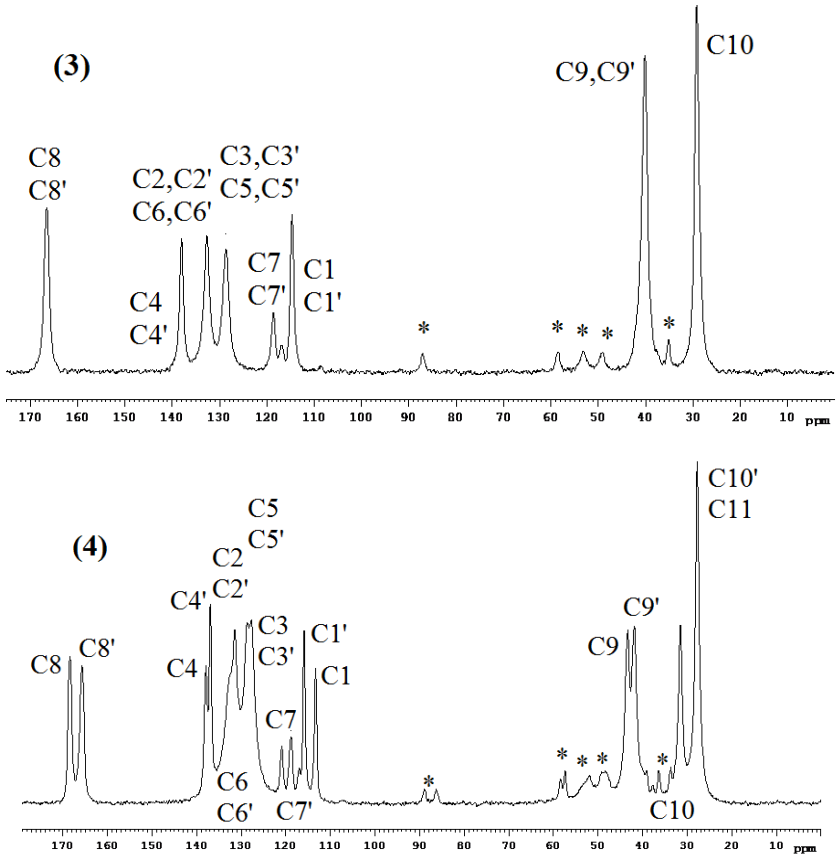
DFT method with B3LYP/6–311(d, p) hybrid functional was employed for structure optimization, and the GIAO approach for the NMR shielding constants computations using Gaussian 09 program. The location of the true minima was tested by vibrational analysis performed at DFT level with B3LYP/6–311(d, p) hybrid functional.

The X-ray diffraction data of compound **3** were also discussed using own crystallographic data (the solid state structure of **3** was partially discussed earlier in the paper J. Brisson, J. Gagne, F. Brisse. Can. J. Chem. 67 (1989) 840-849.

Results and discussion 1

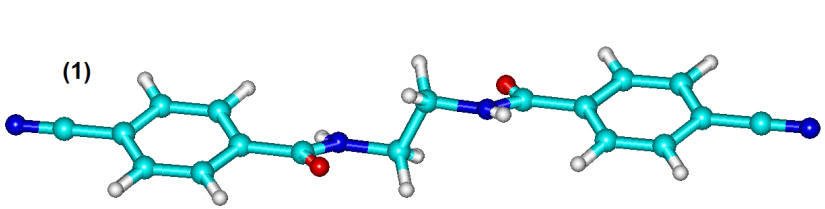
The chemical shifts of ^{13}C CP/MAS NMR in solid state δ [ppm] for **1**, **2**, **3**, **4**, **5** and the exemplary ^{13}C CP/MAS NMR spectra of **3** and **4**. Sidebands are marked with an asterisk.

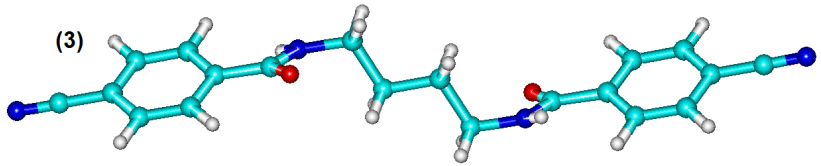
	Chemical shifts of in solid state δ [ppm]				
No	**1**	**2**	**3**	**4**	**5**
C1	113.2	114.0	114.6	113.3	115.2
C1'				115.9	
C2, C2'	134.0	131.5	132.7	131.4	132.5
C3, C3'	128.4	127.5	128.6	127.7	129.3
C4	137.8	136.8	138.0	137.9	138.5
C4'				136.9	
C5, C5'	128.4	129.7	128.6	128.7	129.3
C6, C6'	134.0	133.5	132.7	132.1	132.5
C7	118.0	120.0	118.0	120.7	118.4
C7'				118.6	
C8	166.8	165.2	166.5	168.4	167.1
C8'				165.7	
C9	39.1	37.3	40.1	43.3	41.6
C9'				41.9	
C10	-	28.6	29.2	31.5	30.4
C10'		-		27.8	
C11	-	-	-	27.8	29.2
C11'	-	-	-	-	

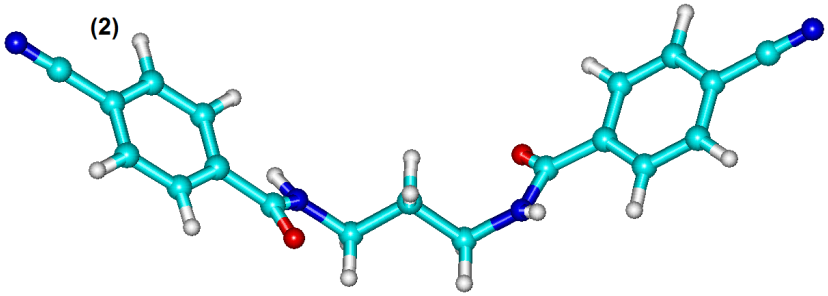


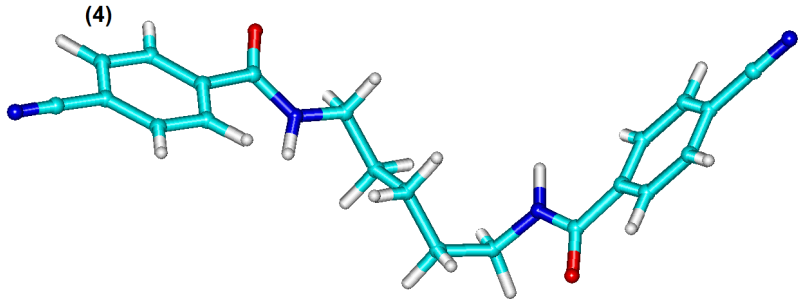
Results and discussion 1

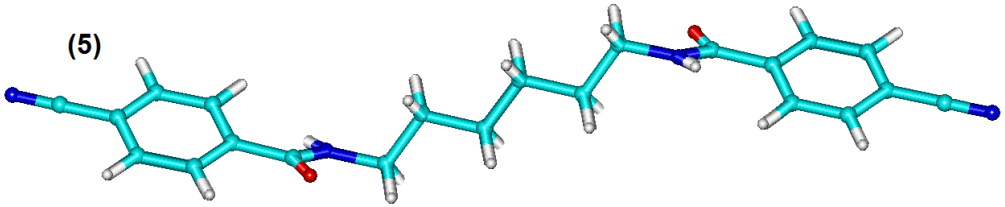
The theoretical conformations in the solid-state of **1**, **2**, **3**, **4** and **5**





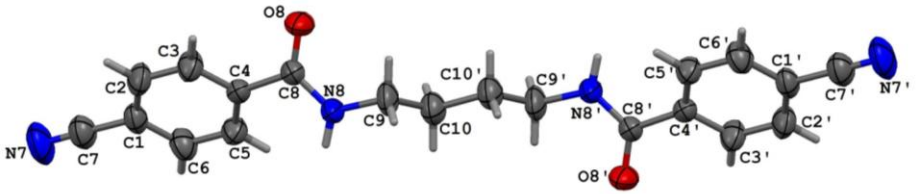




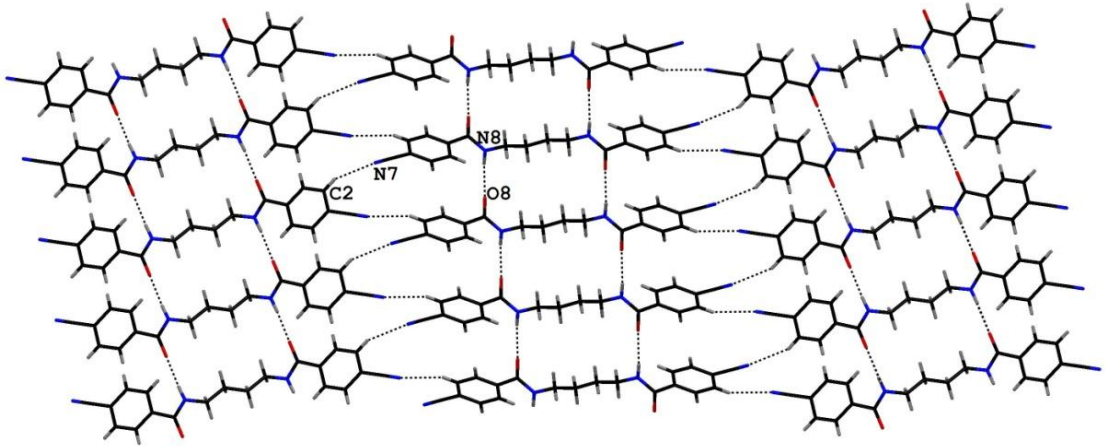


Results and discussion 1

The results of X-ray analysis harmonize well with the analysis of solid-state ^{13}C CP/MAS NMR spectra of **3**. Compound **3** crystallizes in the monoclinic space group P $2_1/n$.



The displacement ellipsoid representation of **3**, together with the atom numbering scheme



The interconnections within a layer for **3**

Results and discussion 1

The detailed analysis of the intermolecular interactions.

The molecules are linked by N8-H8A····O8 (x, y-1, z) hydrogen bond forming infinite tapes along the *b* axis, then the adjoining tapes are organized into layers parallel to the (103) plane *via* C2-H2A····N7 (-x+1.5,y+0.5,-z+1.5) contacts. Cohesion between layers results in C3-H3A····O8 (-x+1,-y+1,-z+2) interactions and three-dimensional supramolecular structure is created.

Hydrogen-bonding geometry [Å and deg.]

D-H····A	d(D-H)	d(H····A)	d(D····A)	<(DHA)
N8-H8A····O8^{i}	0.86	2.08	2.904(5)	159
C3-H3A····O8^{ii}	0.93	2.68	3.362(6)	131
C2-H2A ····N7^{iii}	0.93	2.61	3.474(6)	155

symmetry code: (i) x,y-1,z; (ii) -x+1,-y+1,-z+2; (iii) -x+1.5,y+0.5,-z+1.5

Conclusions 1

The proposed approach has of considerable value in understanding the solid-state structures of bis-nitriles.

Compounds **1**, **3** and **5** with an even number of CH_2 groups in the linker adopt the conformations with the benzene rings situated in two almost parallel planes, but the compounds **2** and **4** with an odd number of CH_2 groups in the linker adopt the 'butterfly' conformations.

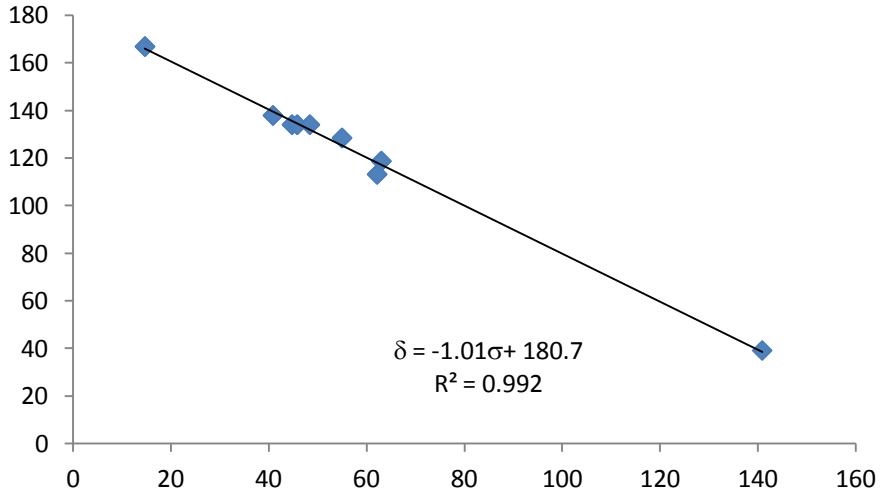
The packing mode of molecules is stabilized by quite strong intermolecular hydrogen bonds in which C=O carbonyl groups are engaged.

The nonplanarity of the amide groups with benzene rings is favored in all tested compounds.

The findings are in good agreement with X-ray analysis of compound **3**.

Results and discussion 2

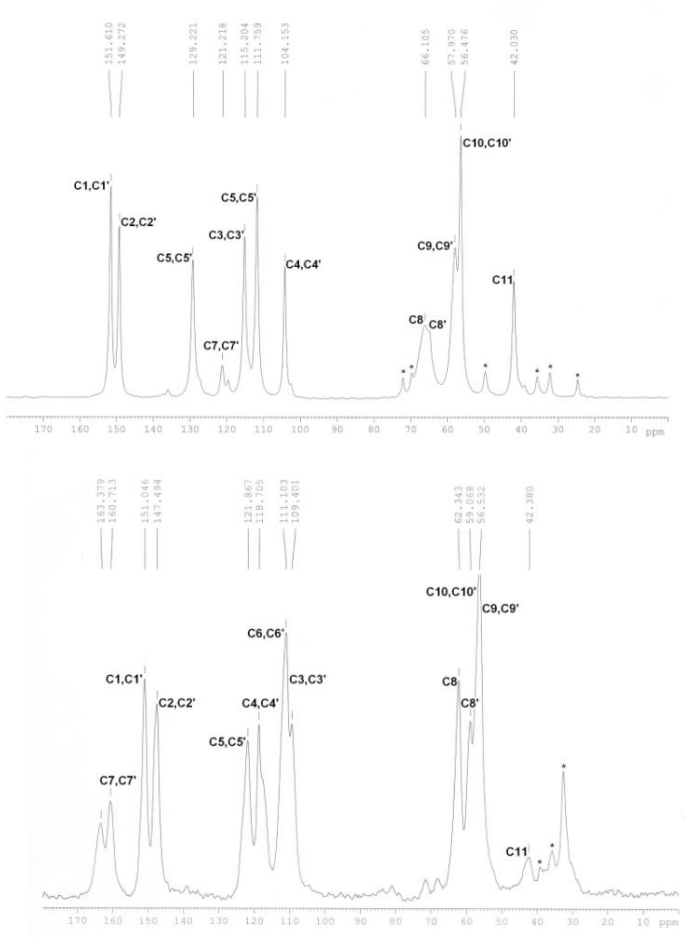
In this part of presentation we compared the solid-state structure of bis-nitriles with related bis-amidines. We analyzed ^{13}C CP/MAS NMR spectra of bis-nitriles **6** and **7** and bis-amidines **6a** and **7a** using the calculated shielding constants for the different conformations of all compounds. On the basis of the best correlation between the calculated values and the experimental chemical shifts we suggested the conformation related to the NMR spectra (see next slides with NMR spectra and the hypothetical conformations of compounds **6**, **6a** and **7**, **7a**.



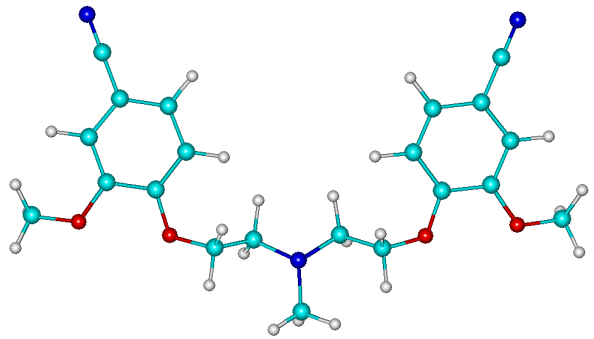
Selected graph of linear functions obtained during NMR analysis for the chemical shifts δ [ppm] and the shielding constants σ [ppm]: $\delta = f(\sigma)$.

Results and discussion 2

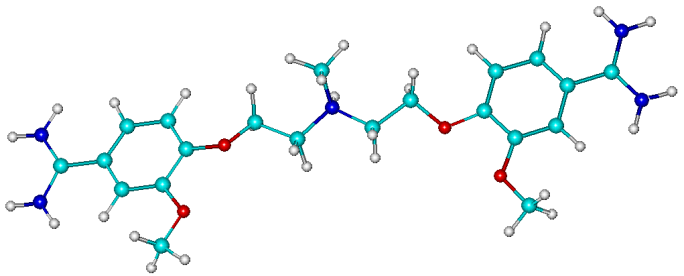
The ^{13}C CP/MAS NMR spectra of *bis*-nitrile **6** and *bis*-amidine **6a** in the solid-state together with hypothetical conformations in the solid. Sidebands are marked with an asterisk .



6

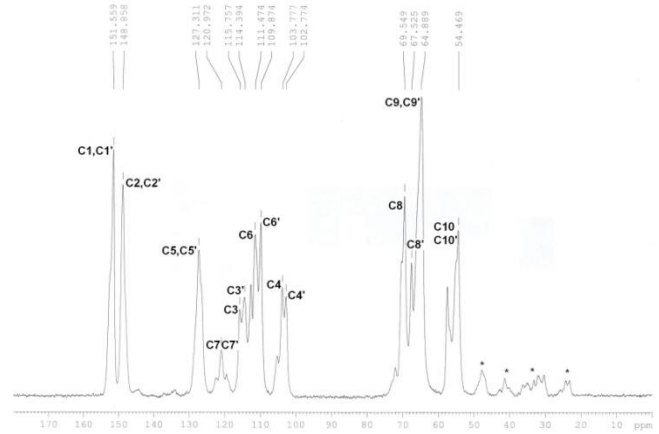


6a

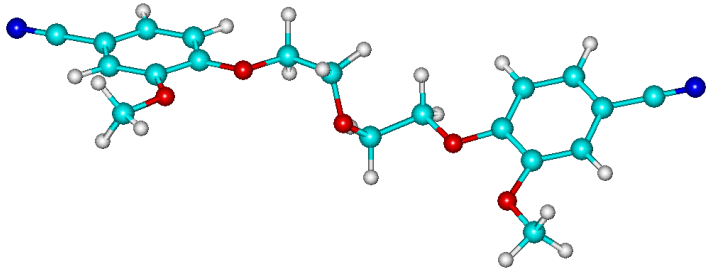


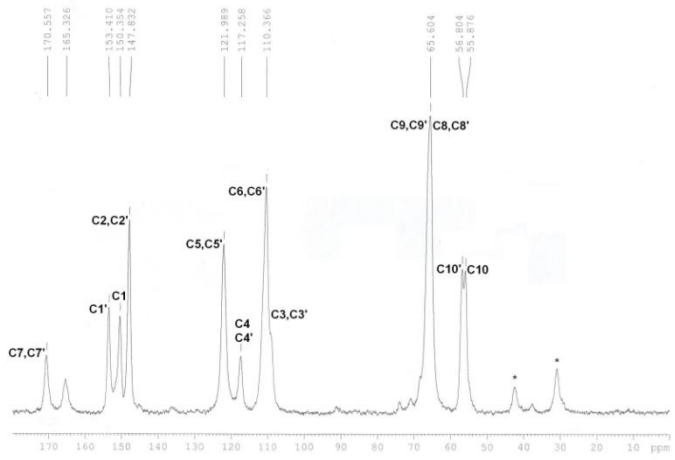
Results and discussion 2

The ^{13}C CP/MAS NMR spectra of *bis*-nitrile **7** and *bis*-amidine **7a** in the solid-state together with hypothetical conformations in the solid. Sidebands are marked with an asterisk.

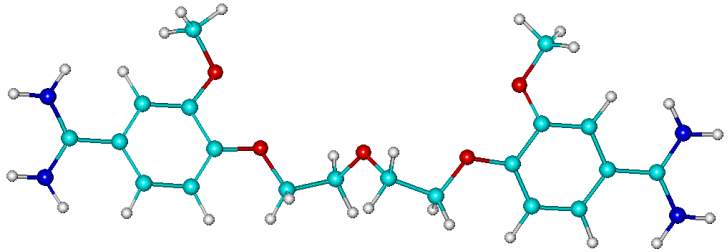


7





7a



Results and discussion 2

The favored solid-state conformations of bis-amidines **6a** and **7a** differed from those of bis-nitriles **6** and **7**. The suggested conformations of bis-amidines **6a** and **7a** were slightly folded with cationic amidine group out of the benzene ring plane.

The suggested conformations of bis-nitriles **6** and **7** were 'butterfly-like' with both benzene rings located in the different planes.

Conclusions 2

The computation of shielding constants for isolated molecules together with the solid-state spectrum are of considerable value in understadning the solid-state structures of pentamidine analogs.

The structural information and intermolecular interactions in bis-nitriles are not transferable to the structual analysis for bis-amidines.

Acknowledgments

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