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Structural analysis of two foldamer-type oligoamides – the effect of hydrogen bonding on solvate formation, crystal structures and molecular conformation

Supplementary information

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1 Crystallography

1.1 Crystal data and data collection parameters

Table 1. Crystal data and data collection parameters of isostructural solvate structures of **3**.

	3-MeOH	3-toluene[a]
Formula	$C_{33}H_{25}N_5O_4 \cdot CH_4O$	$2C_{33}H_{25}N_5O_4 \cdot C_7H_8$
M/gmol^{-1}	587.62	1203.29
Crystal system	monoclinic	monoclinic
Space group	$P2_1/c$	P21/c
a/Å	12.7568	12.4748(5)
b/Å	16.6186	16.6624(5)
c/Å	16.5266	14.8765(6)
β/º	124.487(3)	92.7042
V/Å^3	2887.9(2)	3088.8
Z	4	2
ρ_{calc}/g cm^{-3}	1.352	1.294
Meas. reflns	7582	7311
Indep. Reflns	4714	4844
R_{int}	0.1038	0.0785
R_1 [I> 2σ(I)]	0.0732	0.0953
wR_2 [I> 2σ(I)]	0.1622	0.1938
GooF	1.068	1.076

[a] Low data completeness (88.1%)

1.2 MeOH-solvate of the pyridine variant 3

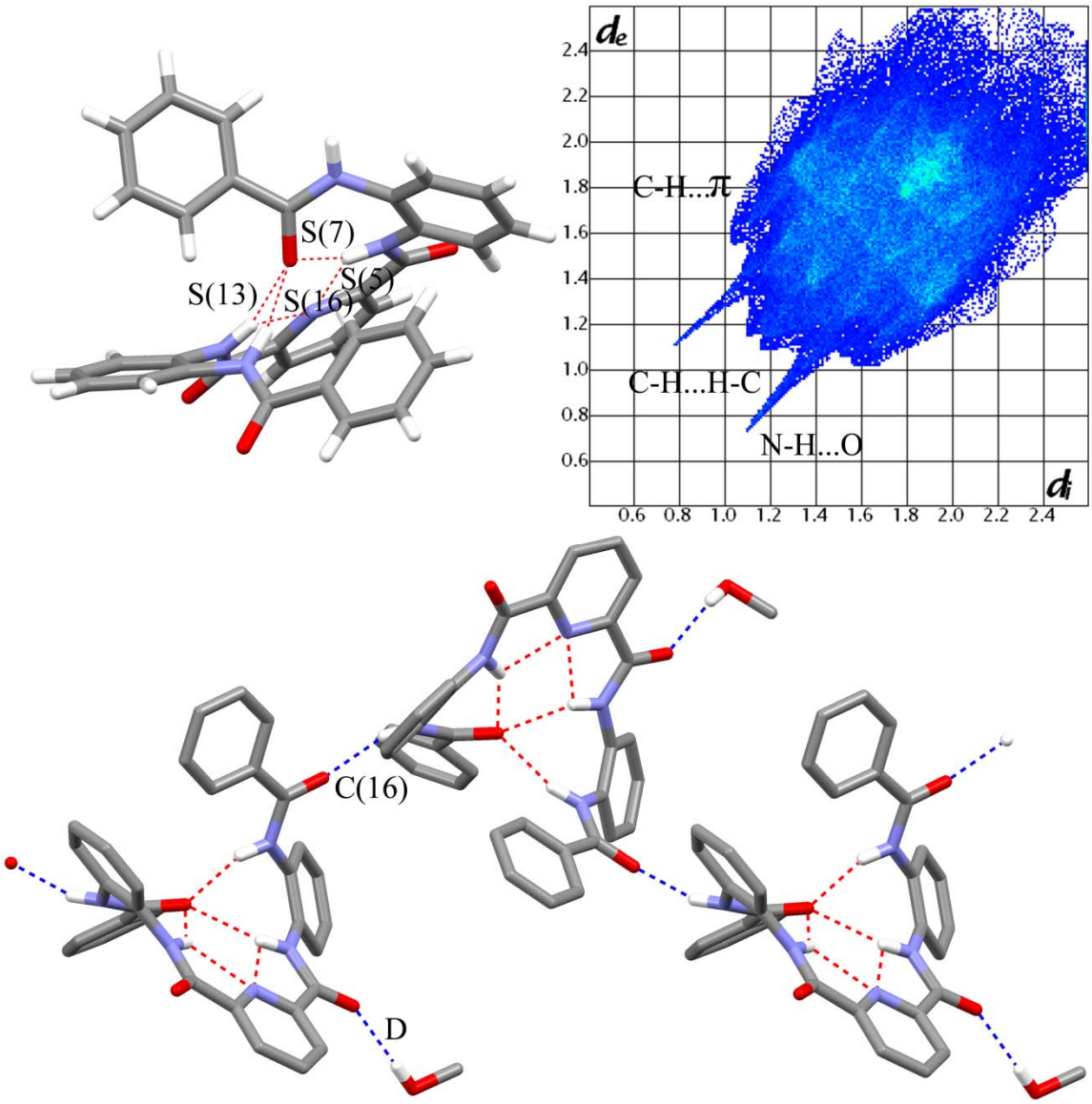

Fig. 1 Molecular conformation, fingerprint plot and the crystal packing of 3-MeOH solvate of the pyridine variant **3**. Non-hydrogen-bonded hydrogen atoms and solvent disorder were removed for clarity.

1.3 Toluene solvate of the pyridine variant 3

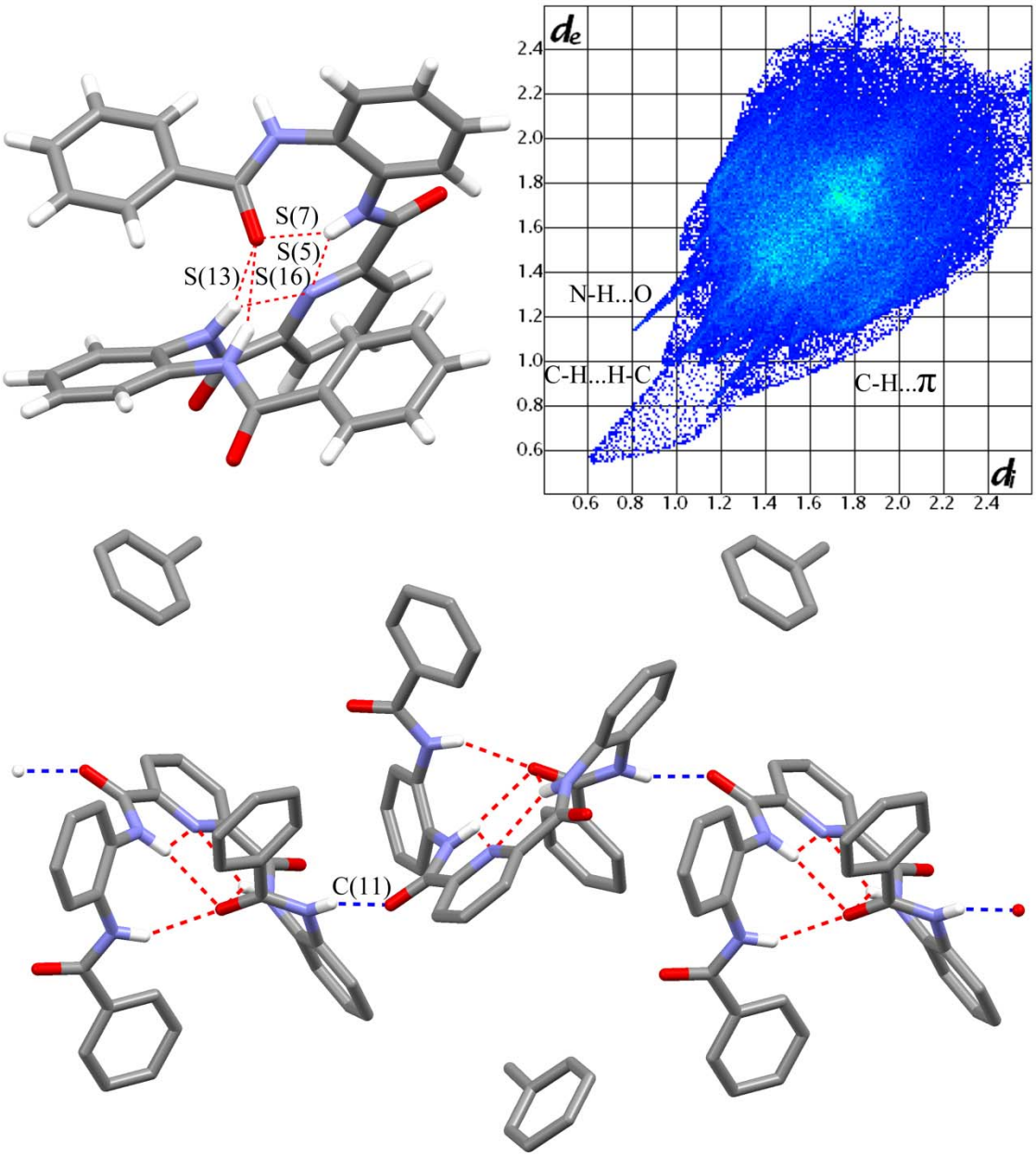

Fig. 2 Molecular conformation, fingerprint plot and the crystal packing of 3-toluene solvate of the pyridine variant **3**. Non-hydrogen-bonded hydrogen atoms and solvent disorder were removed for clarity.

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1.4 Notes on the crystallographic data

2-Form I was crystallized from DMF by slow evaporation as colorless plate crystals. Bond lengths between nitrogen and hydrogen were restrained to 0.91 Å using DFIX.

2-DMSO I was crystallized from EtOAc-DMSO by slow evaporation as colorless plate crystals. DMSO molecule is disordered over two positions (site occupancies 70:30 for the oxygen atom). Short intramolecular hydrogen-hydrogen distance of 1.90 Å between H2N and H16 is caused by the intramolecular hydrogen bond between H1N and O2.

2-DMSO II was crystallized from DMSO by slow evaporation as colorless block crystals.

3-Form I was crystallized from EtOAc by slow evaporation as colorless block crystals. One of the benzene rings is partially disordered at C30-C31-C32-C33 (restrained as 50:50). The structure contains voids of 33 $Å^3$.

3-EtOH was crystallized from EtOH by slow evaporation as colorless plate crystals. The bond length of the hydrogen and oxygen of the solvent hydroxyl group is restrained to 0.84 Å using DFIX.

3-MeOH was crystallized from MeOH by slow evaporation as colorless plate crystals. The methanol solvent is disordered over two positions (site occupancies 84:16). There is a short intermolecular distance between H31…H40E due to the disorder of the solvent molecule. The bond lengths between nitrogen and hydrogen are restrained to 0.91 Å using DFIX. Short intermolecular hydrogen-hydrogen distance (H31..H40E, 1.81 Å) is caused by disorder of the solvent molecule. Short intramolecular hydrogen-hydrogen distance of 1.99 Å between H1N and H1 is caused by the intramolecular hydrogen bond between H1N and O4 and an intermolecular hydrogen bond between O1 and H4N.

3-EtOAc was crystallized from hot EtOAc during recrystallization purification as colorless plate crystals. Severely disorder of solvent molecules (one molecule of EtOAc per two molecules of **3**) were removed using SQUEEZE routine of the PLATON program[15], which caused voids in the structure (188 $Å^3$). One of the benzene rings of compound **3** is disordered (C1-C2-C3-C4-C5-C6, restrained as 50:50) and restrained using EADP and SADI and forced to a planar ring conformation using AFIX 66. The differences between the calculated and the experimental absorption coefficient and molecular weight are caused by the ethyl acetate reported in the formula that was squeezed out of the molecule.

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3-toluene was crystallized from toluene by slow evaporation as colorless plate crystals. Compound **3** has a disordered benzene ring (C1-C2-C3-C4-C5-C6, restrained as 50:50). The short intramolecular distance between H1N and H5A is caused by the benzene ring disorder. Bond length between N1 and H1N is restrained to 0.91 with DFIX. The short intermolecular X-Y contact between C4B...C106, C4B...C105, C5B...C106 and C18…C103 is caused by the disorder of the benzene ring of compound 3 and the disorder of the toluene solvent. The disordered solvent molecule was refined isotropically. Large Hirshfeld difference between C7 and C6B is caused by the disorder of the benzene ring of compound 3 and the disorder of the toluene solvent. Low data completeness (88.1 %) is caused by poor crystal quality.

3-DMF was crystallized from DMF by slow evaporation as colorless plate crystals. The DMF solvent is disordered over two positions (88:12).

3-DMSO was crystallized from DMSO solution overnight as colorless block crystals. Compound **3** was dissolved in DMSO with heating.

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2 Hydrogen bonding parameters

Table 2. Hydrogen bonding parameters for the crystal structures of the benzene variant **2**.

2-Form I

	Intramolecular			Intermolecular	
Bond	**d(D…A)**	**<(DHA)**	**Bond**	**d(D…A)**	**<(DHA)**
N2-H2N…O1	2.740(3)	153(3)	N1-H1N…O2	2.897(3)	148(3)
N4-H4N…O3	2.714(3)	151(3)	N3-H3N…O4	2.890(3)	158(3)

2-DMSO I

	Intramolecular			Intermolecular	
Bond	**d(D…A)**	**<(DHA)**	**Bond**	**d(D…A)**	**<(DHA)**
N1-H1N...O2	2.714(4)	146(4)	N2-H2N...O1	2.916(5)	157(4)
N4-H4N...O3	2.717(4)	143(4)	N3-H3N...O4	2.915(5)	161(4)

2-DMSO II

	Intramolecular			Intermolecular	
Bond	**d(D…A)**	**<(DHA)**	**Bond**	**d(D…A)**	**<(DHA)**
N4-H4N...O3	2.662(3)	150(3)	N2-H2N...O1	2.929(3)	162(3)
N1-H1N...O2	2.529(?)	96(?)	N3-H3N...O4	2.943(3)	161(3)
			N1-H1N...O100	2.863(3)	159(3)

Table 3. Hydrogen bonding parameters for the pyridine variant **3**.

3-Form I

Intramolecular			Intermolecular		
Bond	**d(D…A)**	**<(DHA)**	**Bond**	**d(D…A)**	**<(DHA)**
N1-H1N...O4	2.928(4)	166(3)	N4-H4N...O3	2.892(3)	155(3)
N2-H2N...O4	3.179(3)	144(3)			
N2-H2N...N5	2.677(4)	117(2)			
N3-H3N...O4	2.699(3)	145(3)			
N3-H3N...N5	2.643(3)	111(3)			

3-MeOH

Intramolecular			Intermolecular		
Bond	**d(D…A)**	**<(DHA)**	**Bond**	**d(D…A)**	**<(DHA)**
N1-H1N...O4	2.904(4)	159(4)	N4-H4N...O1	2.853(4)	161(4)
N2-H2N...O4	3.074(4)	155(4)	O40A-H40A…O2	2.760(5)	155
N2-H2N...N5	2.666(5)	109(3)			
N3-H3N...O4	2.748(4)	143(4)			
N3-H3N...N5	2.660(5)	111(3)			

3-EtOH

Intramolecular			Intermolecular		
Bond	**d(D…A)**	**<(DHA)**	**Bond**	**d(D…A)**	**<(DHA)**
N1-H1N...O4	2.922(3)	163(3)	N4-H4N...O1	2.876(3)	167(3)
N2-H2N...O4	3.044(3)	155(3)	O100-H100…O2	2.786(3)	175(4)
N2-H2N...N5	2.671(?)	109(?)			
N3-H3N...O4	2.758(3)	146(2)			
N3-H3N...N5	2.652(?)	108(?)			

3-EtOAc

Intramolecular			Intermolecular		
Bond	**d(D…A)**	**<(DHA)**	**Bond**	**d(D…A)**	**<(DHA)**
N1-H1N...O4	2.928(4)	166(3)	N4-H4N...O3	2.892(3)	155(3)
N2-H2N...O4	3.179(3)	144(3)			
N2-H2N...N5	2.677(4)	117(2)			
N3-H3N...O4	2.699(3)	145(3)			
N3-H3N...N5	2.643(3)	111(3)			

3-toluene

Intramolecular			Intermolecular		
Bond	**d(D…A)**	**<(DHA)**	**Bond**	**d(D…A)**	**<(DHA)**
N1-H1N...O1	2.934(6)	150(6)	N4-H4N...O2	2.934(6)	164(6)
N2-H2N...O1	3.023(7)	150(6)			
N2-H2N...N5	2.626(7)	110(5)			
N3-H3N...O1	2.785(6)	136(6)			
N3-H3N...N5	2.639(7)	118(5)			

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3-DMF

	Intramolecular			Intermolecular	
Bond	**d(D…A)**	**<(DHA)**	**Bond**	**d(D…A)**	**<(DHA)**
N2-H2N…O1	2.700(3)	143(3)	N1-H1N…O2	2.960(3)	166(3)
N2-H2N…N5	2.647(3)	112(2)			
N3-H3N…O1	3.098(3)	147(3)			
N3-H3N…N5	2.654(3)	115(3)			
N4-H4N…O1	2.856(3)	153(3)			

3-DMSO

	Intramolecular			Intermolecular	
Bond	**d(D…A)**	**<(DHA)**	**Bond**	**d(D…A)**	**<(DHA)**
N2-H2N…O1	2.759(3)	149(3)	N1-H1N…O3	2.848(3)	163(3)
N2-H2N…N5	2.644(?)	108(?)	N4-H4N…O100	2.896(3)	171(3)
N3-H3N…O1	3.031(3)	143(3)			
N3-H3N…N5	2.657(3)	113(3)			

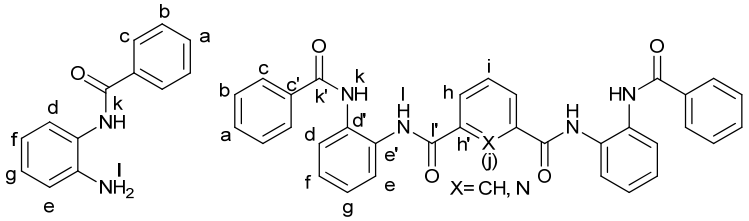
3 Solvent table for crystallizations of compound 2

Compound 2

2-Form I	Solvate form 1		Solvate form 2	Solvate form 3	
Solvent	**Solvent 1**	**Solvent 2**	**Solvent**	**Solvent 1**	**Solvent 2**
DCE	DMSO	EtOAc	DMSO	EtOAc	
DMF	DCM			DMF	Chloroform
EtOH	THF			DMF	EtOAc
MeCN				DMF	THF
MeOH				DMF	Toluene
				DMA	EtOH
				DMA	MeOH
				DMA	MeCN

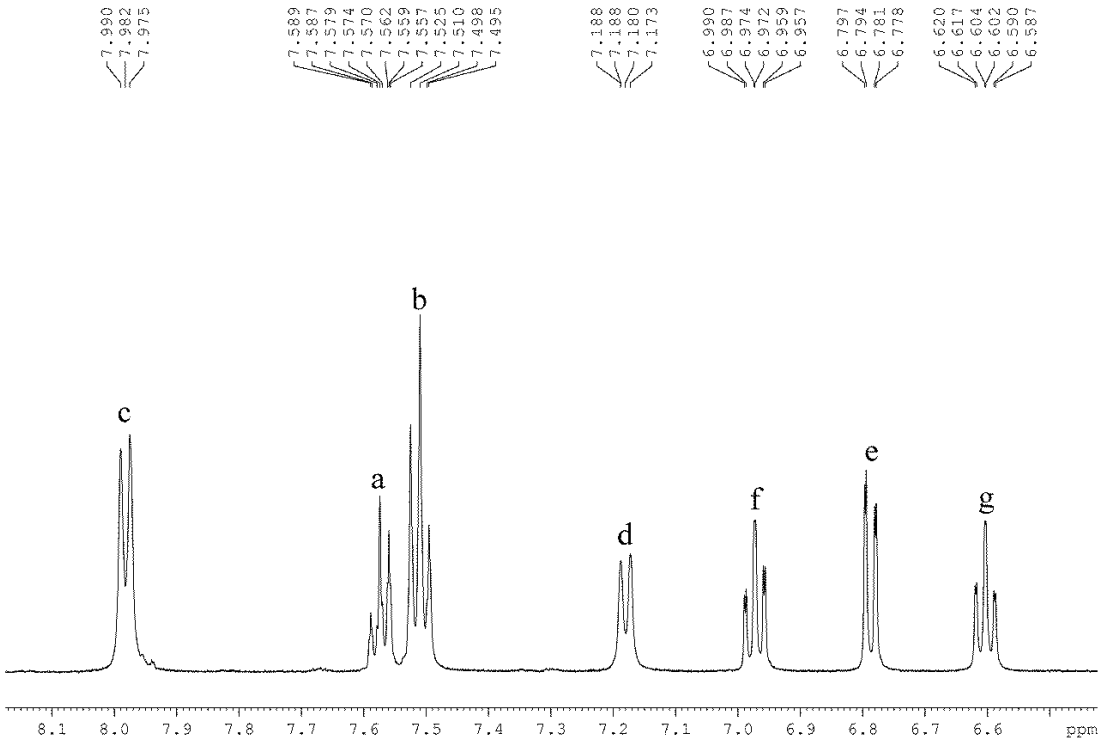
4 NMR spectra of compounds 1, 2 and 3

^{1}H, ^{13}C, COSY, HMBC and HMQC spectra were measured for compounds **2** and **3** from DMSO-d_6. ^{1}H, ^{13}C spectra for compound **1** were measured from DMSO-d_6. For clarity the spectra have been scaled to display only the aromatic and the N-H peaks, and in the ^{1}H and ^{13}C spectra only the aromatic peaks.

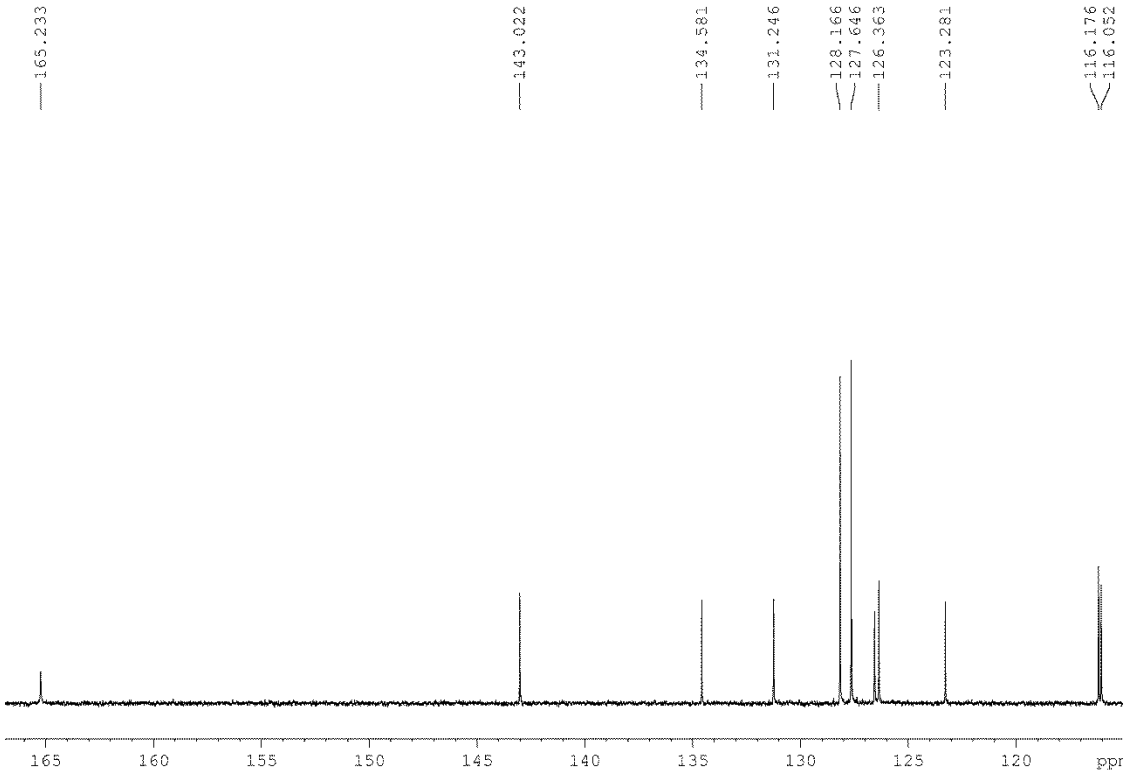


4.1 *N*-Benzoyl-2-amino aniline 1

^{1}H spectra

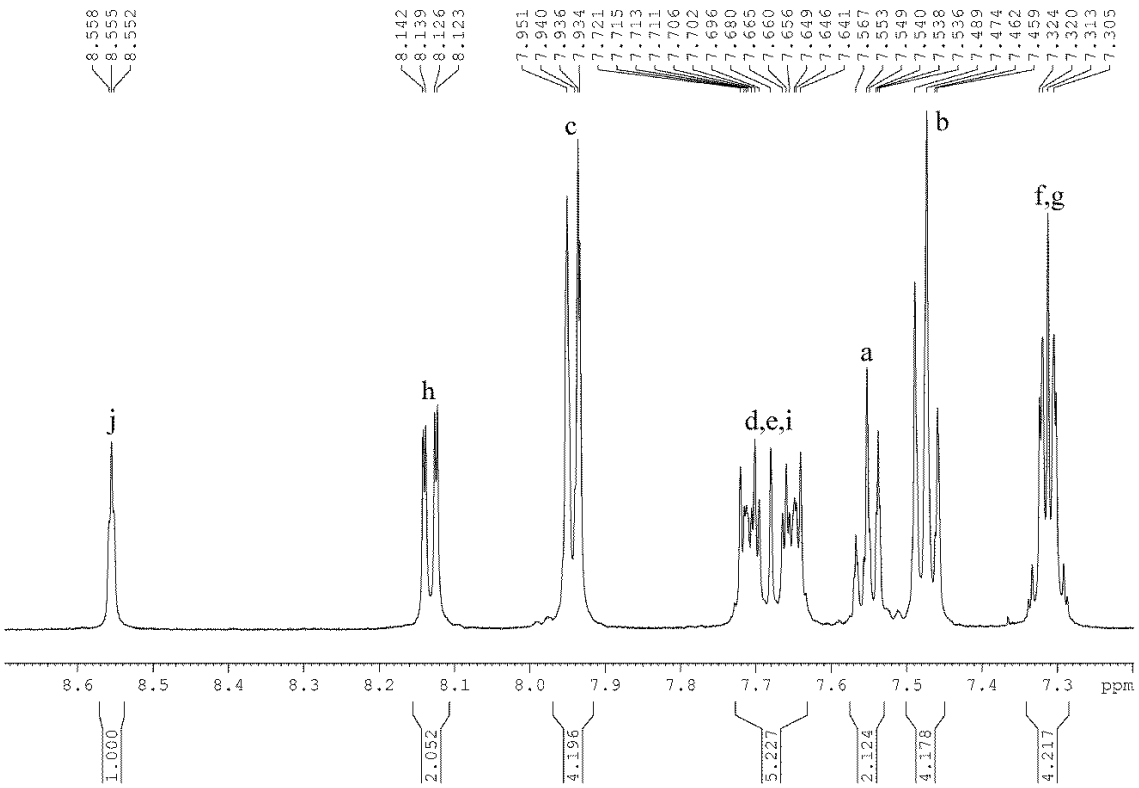


^{13}C spectra



4.2 Benzene variant 2

^{1}H spectra



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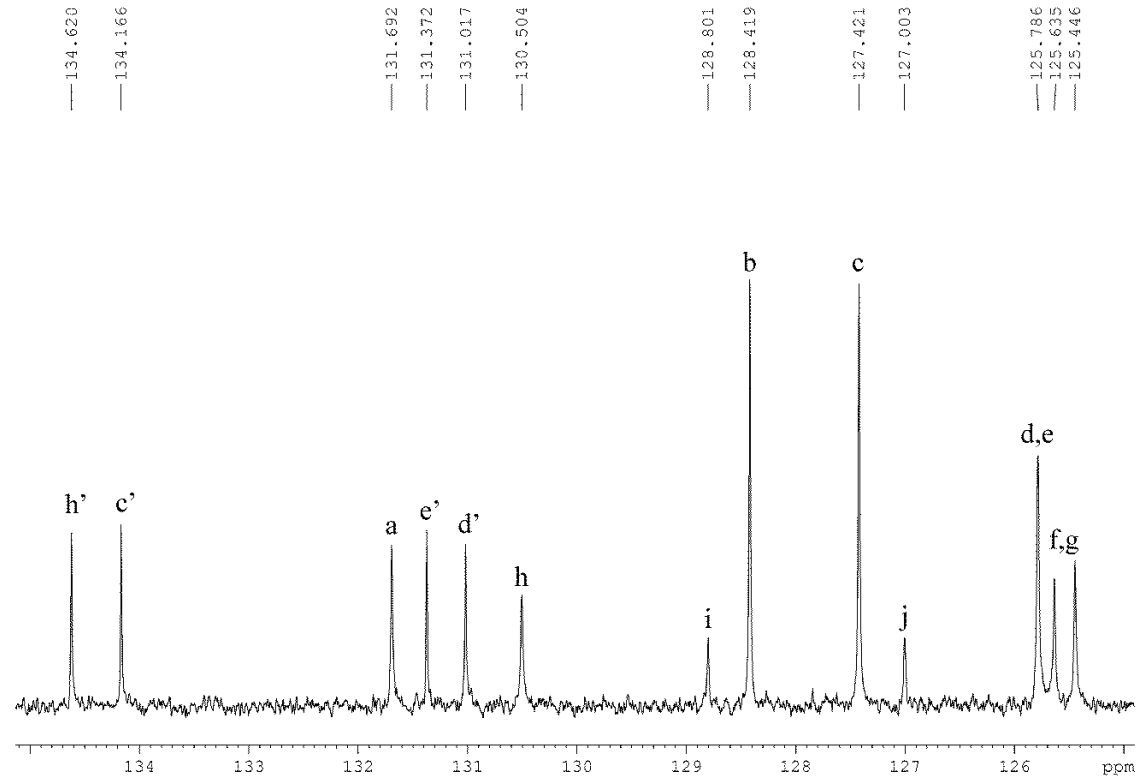
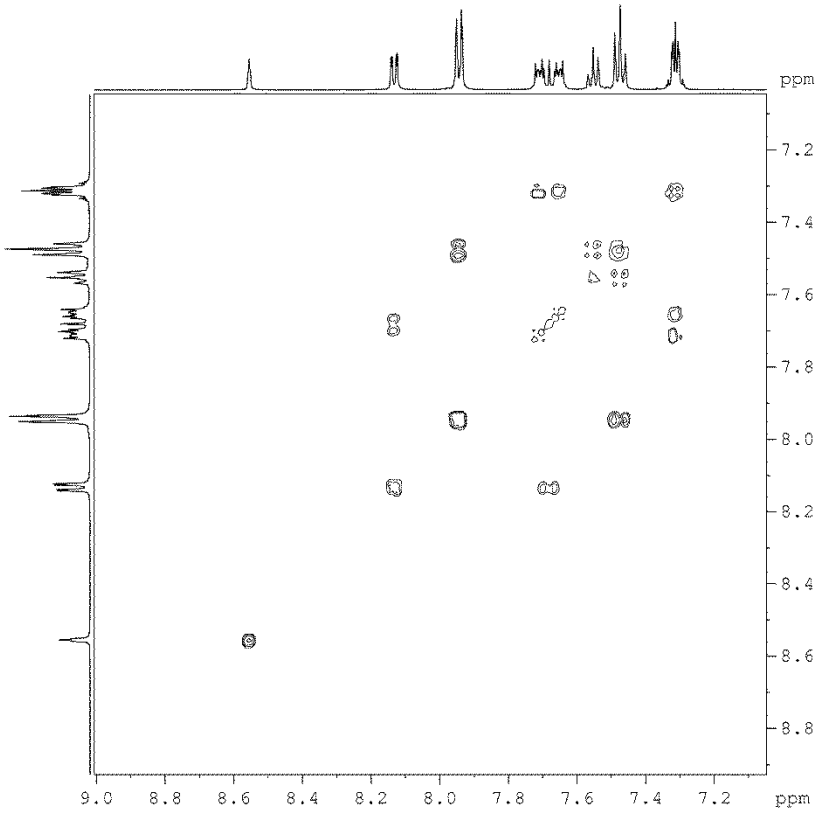


COSY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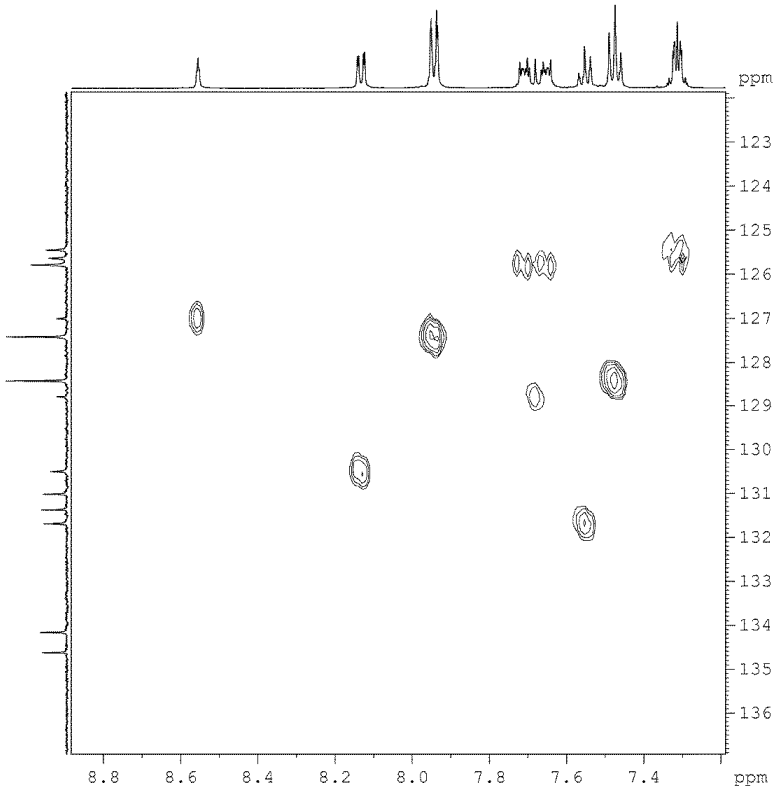
HMQC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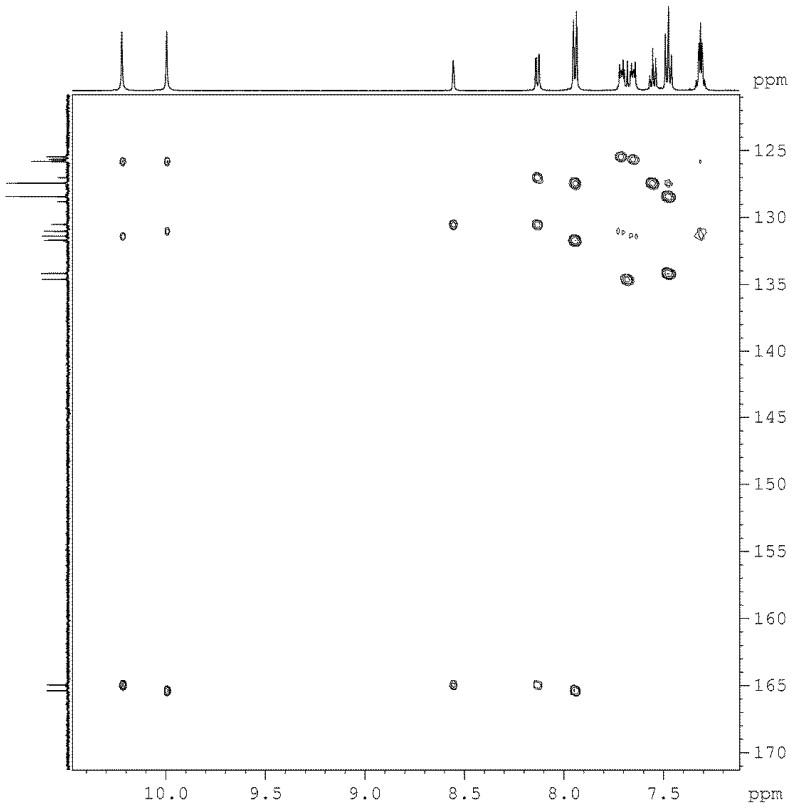
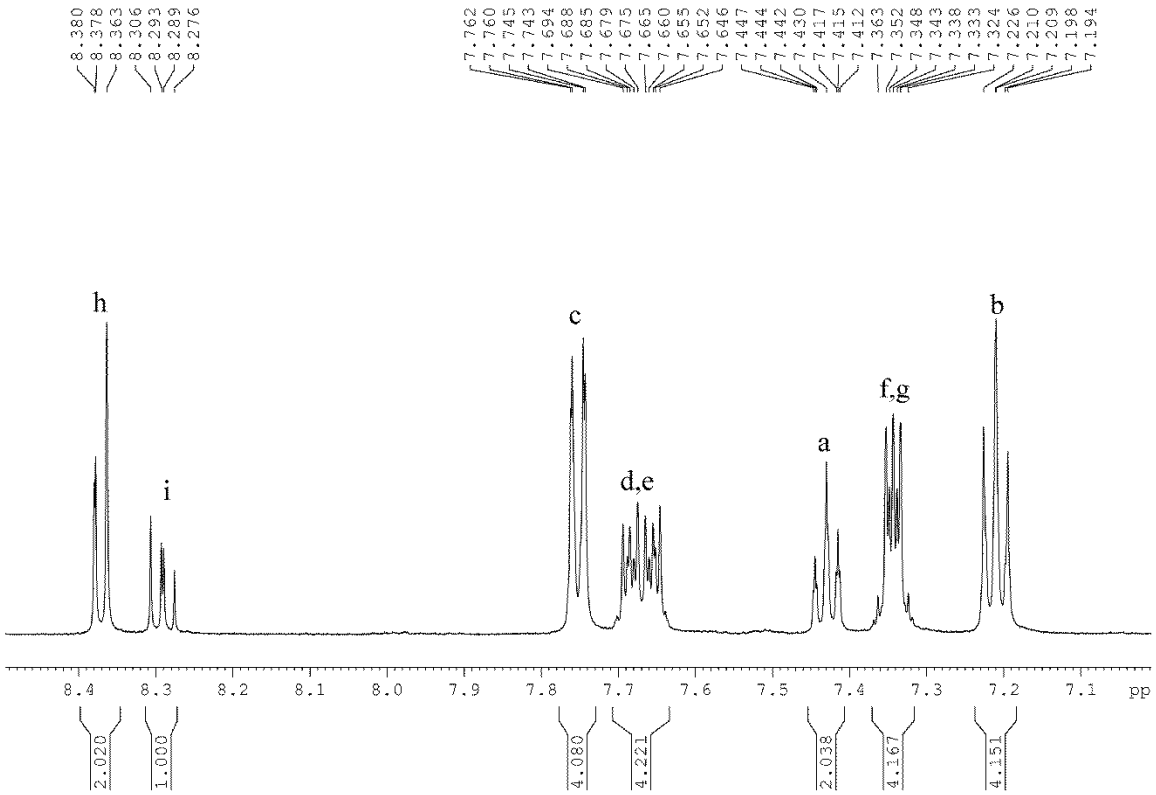
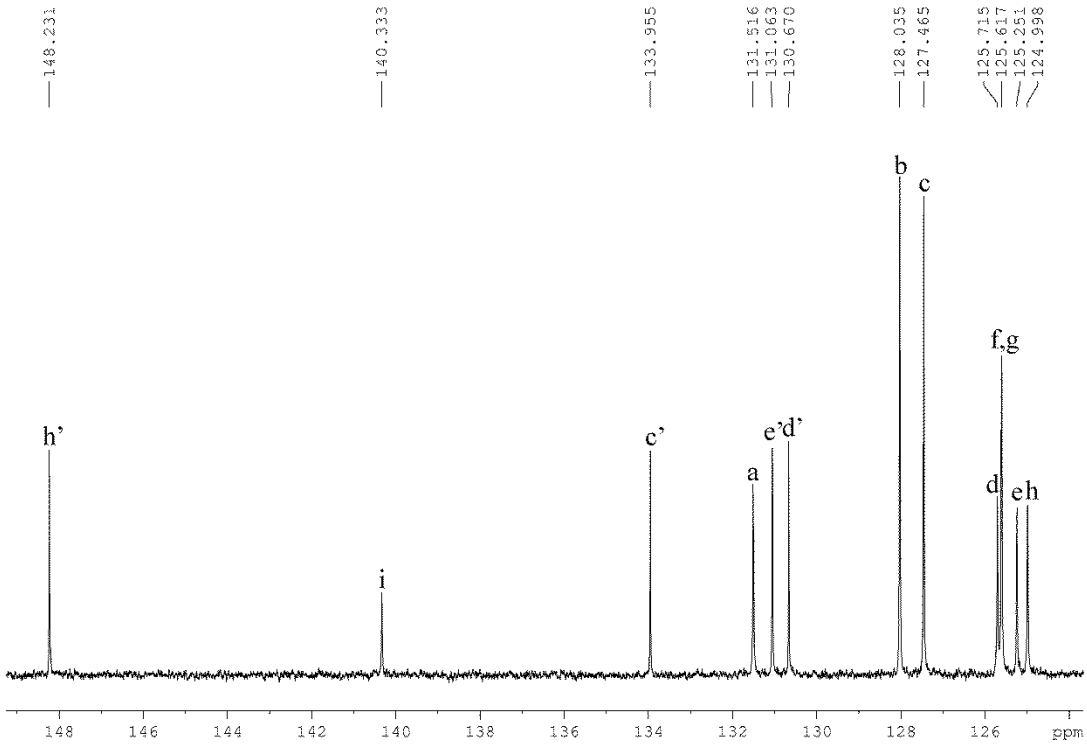


4.3 Pyridine variant 3

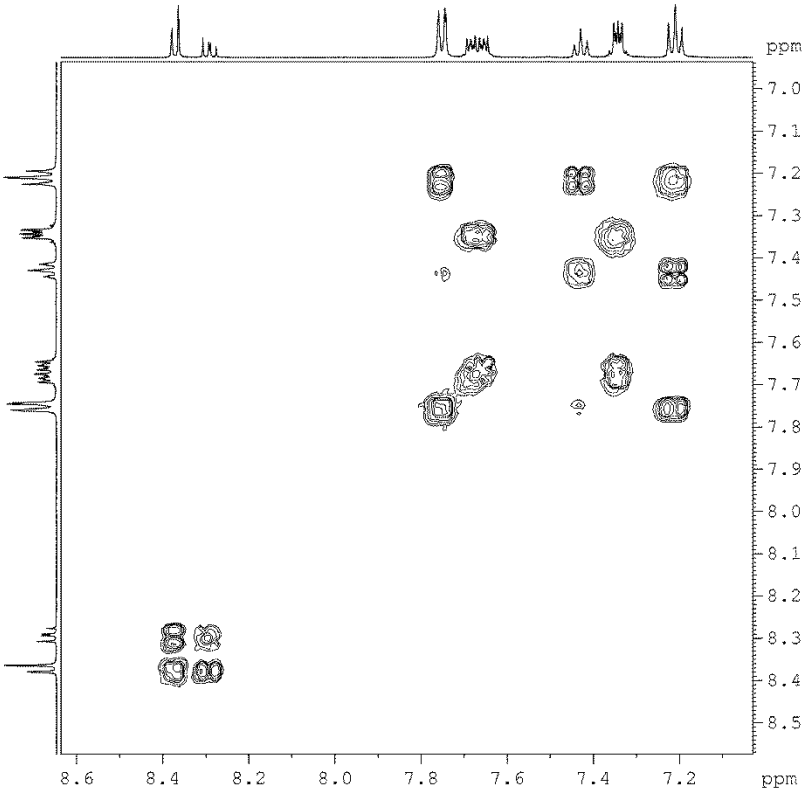
^{1}H spectra



^{13}C spectra



COSY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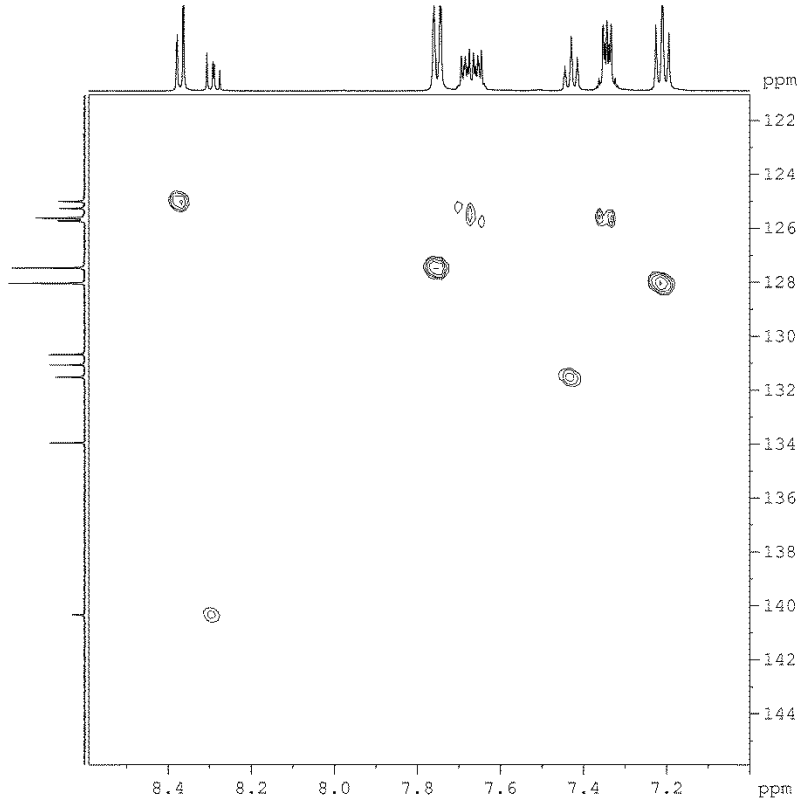
7.2
ppm

HMQC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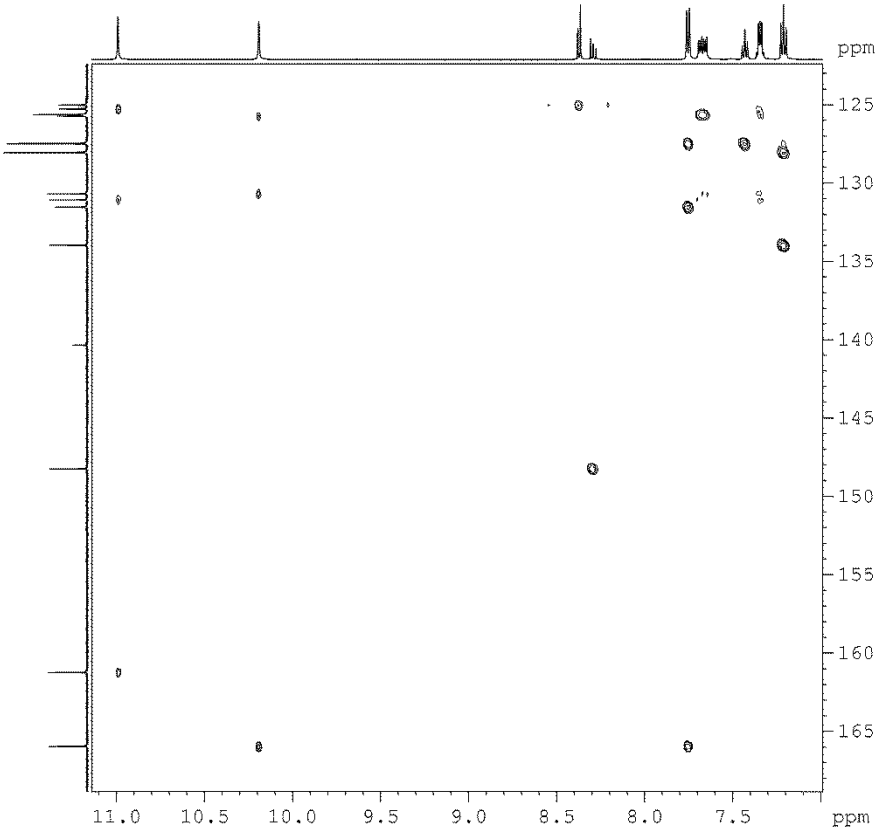
7.2
ppm

HMBC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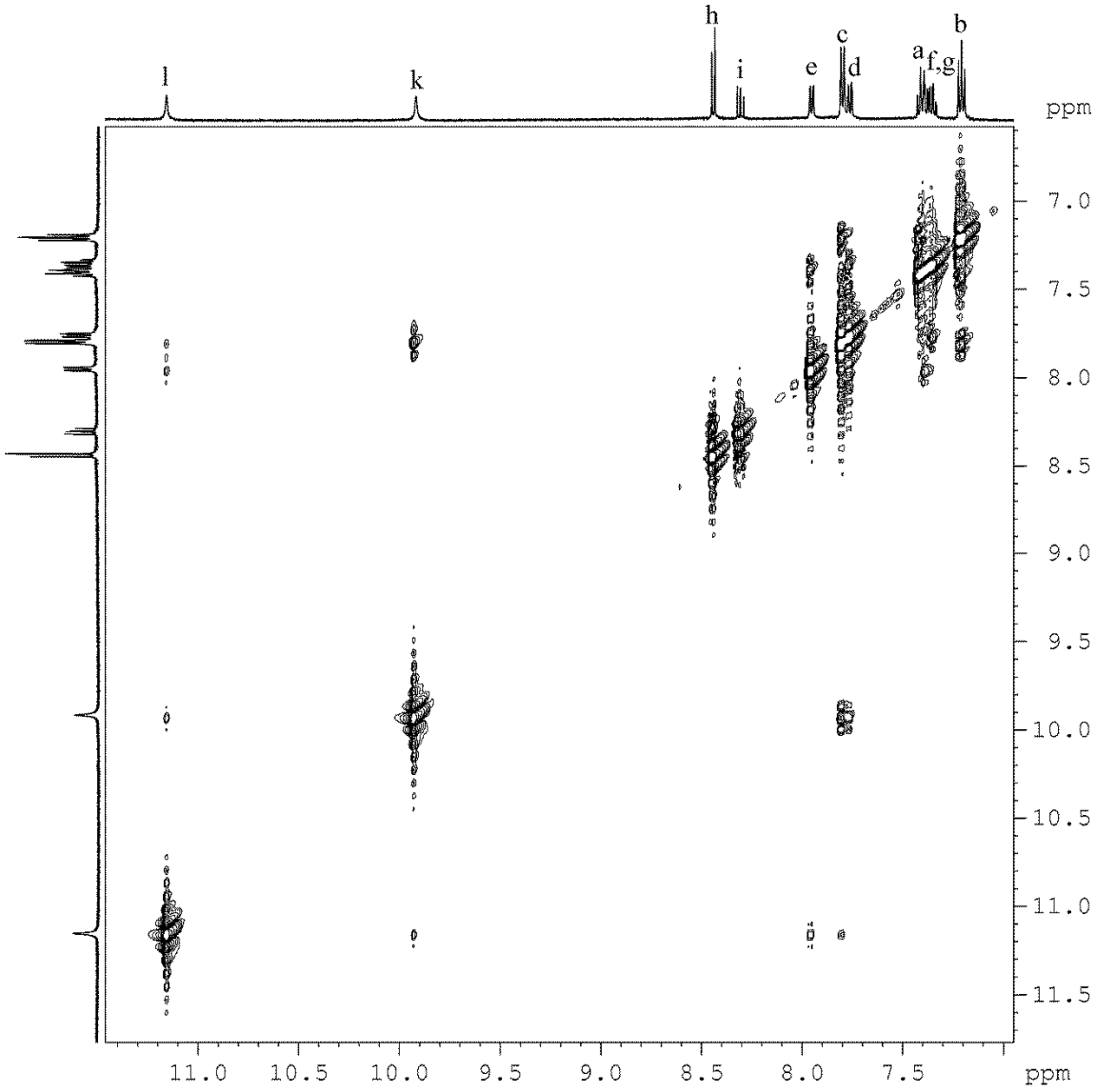
7.5
ppm

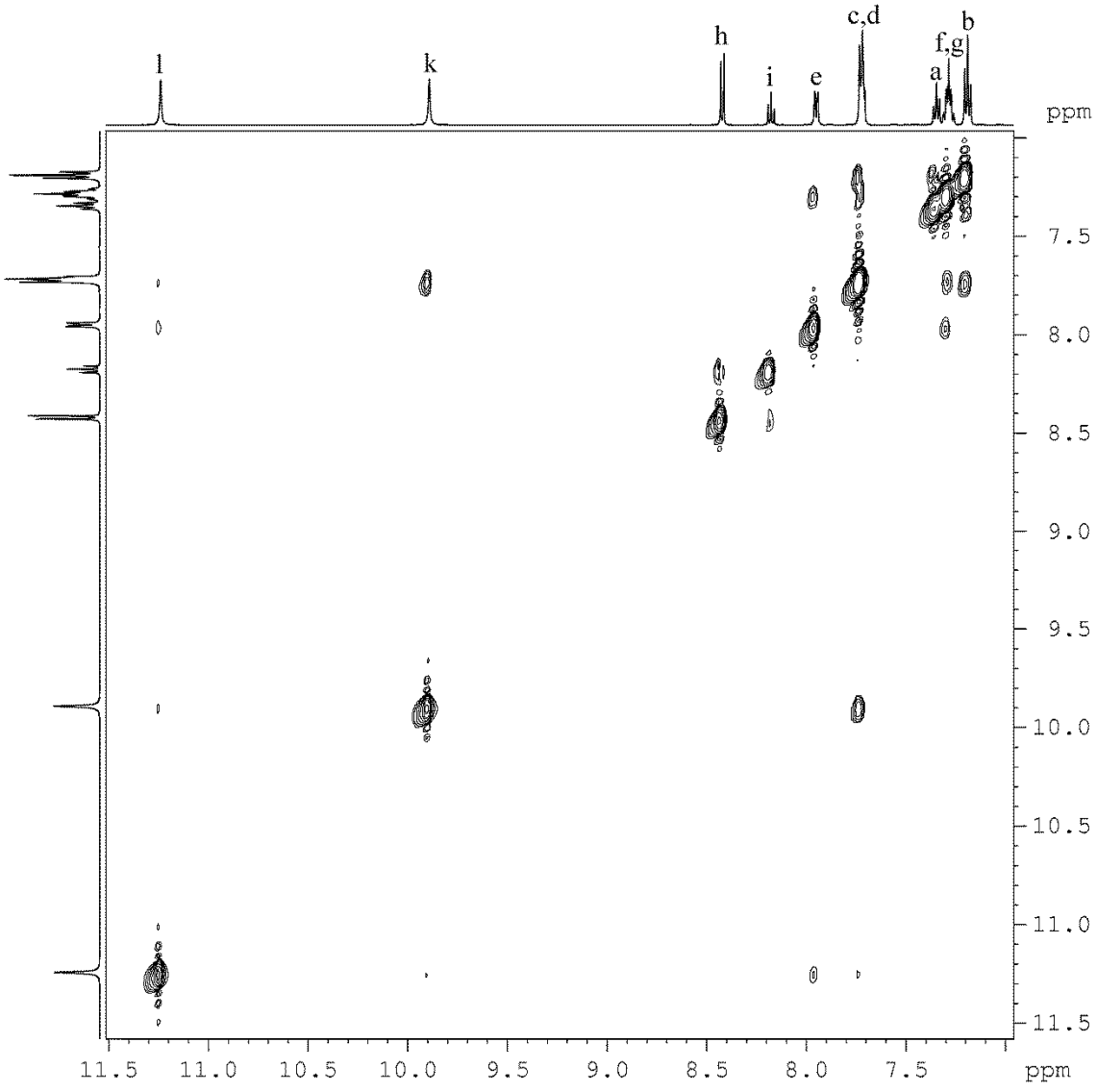
5 NOESY spectra of the pyridine variant 3

NOESY spectra were measured for compound **3** in acetone-d_6 and THF-d_8. For clarity the spectra have been scaled to display only the aromatic and the N-H peaks.

Acetone-d_6



THF-d_8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8.0
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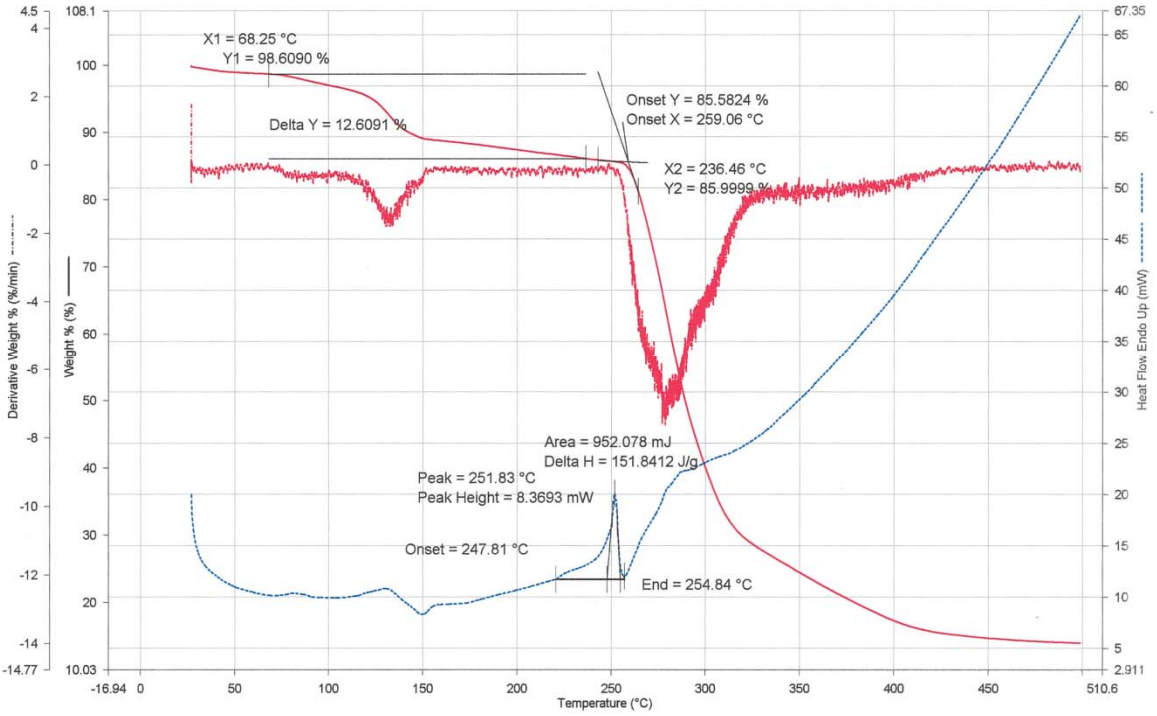
ppm

6 TGA-DTA measurements

TGA-DTA graph measured from the synthesis product of the benzene variant **2** that was dried in vacuum overnight. The 12.6 % drop in weight is caused by residual THF leaving from the product. Measurement was done under air atmosphere (45.0 ml/min) and the sample was heated from 27 ºC to 500 ºC at 5.00 ºC/min.



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TGA-DTA graph measured from MeCN slurry of the pyridine variant **3**. PXRD measured from the sample shows that the sample is form I. Measurement was done under air atmosphere (45.0 ml/min) and the sample was heated from 27 ºC to 350 ºC at 5.00 ºC/min.