#### Journal of Molecular Structure 1034 (2013) 29-37



Contents lists available at SciVerse ScienceDirect

### Journal of Molecular Structure



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

# DFT and experimental study of the structure and vibrational spectra of 2-(benzylthio)-*N*-{pyridinylmethylidene}anilines

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#### HIGHLIGHTS

▶ Synthesis and characterization of 2-(benzylthio)-N-{pyridinyl-4-methylidene}aniline.

- ► X-ray structure analysis of 2-(benzylthio)-*N*-{pyridinyl-3-methylidene}aniline.
- ▶ IR and Raman vibration assignments of 2-(benzylthio)-*N*-{pyridinylmethylidene}anilines.
- ▶ B3PW91/LanZ2DZ suitable level of theory for structure and vibration calculation of 2-(benzylthio)-*N*-{pyridinylmethylidene}anilines.

#### ARTICLE INFO

Article history: Received 19 June 2012 Received in revised form 15 August 2012 Accepted 15 August 2012 Available online 1 September 2012

Keywords: Synthesis Schiff base Vibrational analysis Crystal structure DFT FTIR

#### ABSTRACT

2-(Benzylthio)-*N* {pyridine-4-ylmethylidene}aniline was prepared by reaction of *S*-benzyl *ortho*-aminothiophenol with 4-pyridine carboxaldehyde and characterized by NMR, IR and Raman spectroscopy and mass spectrometry. The structure and the vibrational analysis of the series of 2-, 3-, and 4-pyridine derivatives was performed based on a comparative computational methodology study with the density functionals B3LYP and B3PW91 and the basis sets LanZ2DZ and 6-31++G(d,p). Comparison of computational results with single crystal X-ray diffraction results of 2-(benzylthio)-*N* {pyridine-3-ylmethylidene}aniline allowed the evaluation of structure predictions and confirmed B3PW91/6-31++G(d,p) as most accurate for structure determination of the four investigated levels of theories. B3LYP and B3PW91 with the LanL2DZ basis set consistently outperformed calculations for IR and Raman vibrational estimations when compared to level of theories using the 6-31++G(d,p) basis set. Application of scaling factors for IR and Raman frequency predictions showed excellent agreement with experimental values and supported the assignment of the major contributors of the vibration modes of the three pyridine pendant compounds. Overall, B3PW91/LanL2DZ level of theory showed best performance in accuracy and low computational cost for structural and vibrational analysis for the series of 2-(benzylthio)-*N*-{pyridinylmethylidene}anilines.

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#### 1. Introduction

Metalloproteins with predominantly nitrogen—metal bonds through histidine and sulfur—metal bonds through methionine and cysteine amino acids [1] side groups typically complex to Zn and Cu centers, such as the class of zinc-finger proteins [2,3], cytidine deaminase [4] and type I blue copper proteins [5–9]. Nitrogen and sulfur donor atoms show a rich diversity in coordination chemistry for their hard and soft binding ability, respectively [10]. The large diffuse orbitals of S allow single electron transfers forming localized, stable  $\pi$  radical ions which can have additional

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non-innocent ligand redox properties as found, e.g., in thiolate complexes [11–14]. Review articles on electron transfers in Cu containing proteins are available by Rorabacher [15], Farver and Pecht [16] and Warren et al. [17]. Recently, we have become interested in the non-blue/type II copper protein peptidylglycine  $\alpha$ -hydroxylating monooxygenase (PHM), which is one of the two non-coupled copper ion domains of the bifunctional peptidylglycine  $\alpha$ -amidating monooxygenase protein (PAM, EC 1.14.17.3). In contrast to type I copper complexes containing histidine and cysteine Cu coordination, type II complexes have histidine and methionine coordination. PHM is involved in the post-translational modification in the penultimate step of the biosynthetic pathway of amidated peptide hormones that has been found in mammals [18], insects [19] and cneridians [20]. Using kinetic isotope effects (KIEs),

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PHM displayed values in excess of the semi-classical limitation for C—H cleavage (11 Å) coupled with non-Arrhenius behavior [21,22]. The modified Marcus model for ground state hydrogen tunneling was studied using KIEs with an *N*-acylglycine library supporting a 'pre-organization' model of the substrate–enzyme complex allowing both hydrogen and deuterium particle transfer through a decrease in inter-nuclear sampling with tighter bound substrates [23]. PHM shows structural and mechanistic similarities to dopamine  $\beta$ -monooxygenase (D $\beta$ M, EC 1.14.17.1) and both contain non-coupled dicopper active sites that catalyze dioxygen-, copper-and ascorbate-dependent stereospecific hydroxylation reactions [23–25]. One Cu active site copper site contains two His and one Met amino acid side groups and is involved in O<sub>2</sub> activation and substrate oxidation, while the other Cu center has three His bonding environment and is involved with electron transfer reactions.

Palaniandavar presented a good literature overview on diversity of synthetic models of blue copper proteins involving thioether. imidazole, benzimidazole and pyridine functional groups [5]. We disseminated earlier the synthesis of a series of N,S-containing ligand systems with the ortho-aminothiophenol motif which is redox active and exhibits non-innocent ligand properties [26]. In addition, these N,S-ligands can be used to mimic His and Met residues and serve, complexed to a Cu center, as small transition metal models for the analysis of active sites such as PHM. The challenge of developing these small, biomimetic transition metal complex systems lies in finding suitable complexes that uphold the integrity of the active site in its structure and preserve its chemical activity while minimizing "protein clutter", i.e. the large peptide backbone that is not directly involved in the protein activity but necessary for formation of entatic states [27]. Therefore, having good computational models predicting the structures and properties of these *N*,*S*-ligands and their corresponding transition metal complexes will assist the analysis and evaluation of active sites which have been analyzed by structural X-ray based methods and vibrational (IR and Raman) methods and also will allow the efficient computational modeling for screening of Cu complexes for biomimetic enzyme studies.

Herein, we report the synthesis and characterization of 2-(benzylthio)-*N*-{pyridinyl-4-methylidene}aniline (**4**) and the evaluation of computational methodology of the series of *N*-methyl-imine pendant 2-(benzylthio)-*N*-{pyridinylmethylidene}anilines (**2**-**4**) for structural and vibrational analysis. The determination of the frequencies and the intensities of the IR and Raman vibrations is of interest as the three compounds can be used as planar *N*,*S*-biomimetic ligands in transition metal complex models of active sites of enzymes, in particular Cu protein complexes.

#### 2. Experimental section

#### 2.1. General

All solvents and chemicals (reagent grade; technical grade ( $\sim$ 90%) for *ortho*-aminothiophenol) were purchased from commercial sources (Sigma–Aldrich and Fisher Scientific) and were used without further purification. *S*-benzyl *ortho*-aminothiophenol (**1**) is commercially available and was identical to the produced compound using *S*-alkylation of *ortho*-aminothiophenol with benzyl chloride in methanolic solution [26]. 2-(Benzylthio)-*N*-{pyridin-2-ylmethylidene}aniline (**2**) and 2-(benzylthio)-*N*-{pyridin-3-ylmethylidene}aniline (**3**) were synthesized as previously reported [26].

NMR spectra were recorded on a 400 MHz Bruker Avance II spectrometer operating at 400.17 MHz for <sup>1</sup>H and 100.6 MHz for <sup>13</sup>C nuclei and referenced to Me<sub>4</sub>Si as  $\delta$  = 0 ppm. *J* values are given in Hz. GC analysis was performed on a Varian GC-450 equipped with a ICB-5 produced by J&K Scientific service number 6026 with

dimensions  $25 \text{ m} \times 0.25 \text{ mm} \times 0.25 \mu\text{m}$ . FTIR spectra were recorded on a Thermo Nicolet 6700 FTIR Spectrometer with 4 cm<sup>-1</sup> resolution as KBr pellet (approximately 10 mg compound in 300 mg anhydrous KBr) in the 4000–400 cm<sup>-1</sup> range. Experimental FTIR intensities were assigned for strong (s) and weak (w). FT-Raman spectra were recorded on a Thermo-Electron NXR 9650 FT-Raman Spectrometer with low powered laser intensity and a 4 cm<sup>-1</sup> resolution with solid sample in the range of 4000–400 cm<sup>-1</sup>. Experimental Raman activities were assigned for strong (s) and weak (w). MS data was obtained with an Agilent 6890 instrument equipped with mass spectrometer under El mode at 70 eV. Melting point was recorded on a ThermoScientific Mel-Temp 1101D instrument and was uncorrected. Elemental analysis was performed by M-H-W Laboratories, Phoenix, Arizona, USA.

## 2.2. Synthesis of 2-(benzylthio)-N-{pyridin-4-ylmethylidene}aniline (4)

In a 250 mL flask equipped with a Dean-Stark trap and condenser, S-benzyl ortho-aminothiophenol (1) (212 mg, 0.99 mmol) was dissolved in 80 mL toluene. 4-Pyridine carboxaldehyde (93 µL, 0.99 mmol) was added via syringe. The reaction mixture was heated at reflux for 7 days until water droplets were observed in the Dean-Stark trap. After cooling to ambient temperature, the solvent was removed under reduced pressure and the residue was dissolved in a minimal amount of hot toluene (approx. 10 mL). Then, 30 mL hexane was added to produce a yellow precipitate. Precipitation was further forced by cooling the solution to -20 °C for 12 h. The obtained yellow solid was filtered and dried in vacuo (140 mg, 46%). m.p. 175-177 °C. Anal. Calcd. for  $C_{19}H_{16}N_2S$ : C = 74.97%, H = 5.30%. Found: C = 74.59%, H = 5.39%. EI-MS: *m/z* (%): 304(29) [M<sup>+</sup>], 271(54), 213(70), 109(27), 91(100). For <sup>1</sup>H and <sup>13</sup>C signal assignments see Fig. 1; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 4.14, (s, 2H, CH<sub>2</sub>—Ph), 6.99 (m, 1H CH(15)), 7.19 (m, 2H, CH(6) and CH(13)), 7.28 (m, 2H, CH(4) and CH(14)), 7.34 (m, 2H, CH(5) and CH(7)), 7.77 (d, (J = 5.6 Hz), 2H CH(10)), 8.32 (s, 1H, CH imine), 8.74 (d, I = 5.6 Hz, 2H, CH(11)). <sup>13</sup>C{<sup>1</sup>H} NMR  $(100.6 \text{ MHz}, \text{ CDCl}_3)$ :  $\delta = 36.9 (CH_2-Ph), 117.6 (CH(15)), 122.3$ (CH(10)), 126.4 (CH(6)), 127.1 (CH(13)), 127.2 (CH(14)), 127.8 (CH(7)), 128. 5 (CH(4)), 128.9 (CH(5)), 132.5 (C(12)), 136.9 (C(2)), 142.8 (C(9)), 149.4 (C(3)), 150.5 (CH imine), 157.7 (CH(8)). IR (KBr) v (cm<sup>-1</sup>): 3057 (w), 3027 (w), 2922 (w), 2890 (w), 2860 (w), 1623 (s, C=N), 1596 (s), 1572 (w), 1553 (w), 1493 (s), 1463 (w), 1453 (s), 1435 (w), 1408 (s), 1321 (w), 1285 (w), 1268 (s), 1237 (w), 1182 (w), 1158 (w), 1067 (w), 1040 (w), 1026 (w), 1000 (w), 962 (w), 808 (s), 781 (s), 759 (s), 733 (s), 715 (s), 699 (s), 664 (w), 641 (w), 556 (w), 545 (w), 500 (s), 481 (s). Raman (solid) v (cm<sup>-1</sup>): 3059 (w), 1623 (s, C=N), 1597 (s), 1573 (s), 1556 (s), 1463 (w), 1287 (s), 1270 (w), 1245 (w), 1228 (w), 1203 (w), 1183 (s), 1160 (w), 1040 (w), 1002 (w), 988 (w).

#### 2.3. X-ray structure determination

Crystals of **3** were grown via slow diffusion of *n*-pentane into a dichloromethane solution of the compound. Data for compound **3** was collected using a Bruker APEX II CCD detector/D8 diffractometer [28] using Mo K $\alpha$  radiation, with the crystal cooled to -100 °C. The data was corrected for absorption through use of a multi-scan model. The structure was solved using the direct methods program *SHELXD* [29]. Refinements were completed using the program *SHELXD* [30]. Hydrogen atoms were assigned positions based on the idealized  $sp^2$  or  $sp^3$  hybridization geometries of their attached carbon or nitrogen atoms, and were given thermal parameters 20% greater than those of their parent atoms. ORTEP-III by Burnett and Johnson was used for crystal structure visualization.



Fig. 1. Assignment of the chemical shifts of <sup>1</sup>H and <sup>13</sup>C of compound 4.

The Listing of crystallographic experimental data is found in Tables 1 and 2 and Supplementary data.

#### 2.4. Computational methods

Density functional theory (DFT) calculations for geometry optimizations and vibrational frequencies determination were performed using the hybrid three-parameter exchange functional of Becke [31,32], (B3) in combination with the gradient-corrected correlation functionals of Lee, Yang and Parr [33], (LYP) and Perdew et al. [34] (PW91). The 6-31++G(d,p) [35] and LanL2DZ [36] basis sets were used in conjunction with both functionals, forming the B3LYP/LanL2DZ, B3PW91/LanL2DZ, B3LYP/6-31++G(d,p) and B3PW91/6-31++G(d,p) levels of theory, respectively, using the Gaussian G03 program [37]. The Cartesian coordinates of the

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Crystallographic experimental details for **3**.

	Data
Formula weight	304.40
Crystal dimensions (mm)	$0.36 \times 0.31 \times 0.11$
Crystal system	Monoclinic
Space group	<i>C</i> 2/ <i>c</i> (no. 15)
Unit cell parameters <sup>a</sup>	
a (Å)	11.7591 (9)
b (Å)	7.9649 (6)
<i>c</i> (Å)	33.186 (3)
° (deg)	97.0755 (9)
V (Å <sup>3</sup> )	3084.5 (4)
Ζ	8
$ ho_{ m calcd} ( m gcm^{-3})$	1.311
$\mu (\mathrm{mm}^{-1})$	0.207
Diffractometer	Bruker PLATFORM/APEX II CCD <sup>b</sup>
Radiation (λ [Å])	Graphite-monochromated Mo Kα
	(0.71073)
Temperature (°C)	-100
Scan type	$\omega$ scans (0.3°) (15 s exposures)
Data collection $2\theta$ limit (°)	52.86
Total data collected	11890 ( $-14 \leqslant h \leqslant 14$ , $-9 \leqslant k \leqslant 9$ ,
	$-41 \leqslant l \leqslant 41$
Independent reflections	$3157 (R_{int} = 0.0230)$
Number of observed reflections (NO)	2866 $[F_o^2 \ge 2\sigma(F_o^2)]$
Structure solution method	Direct methods (SHELXD <sup>c</sup> ) [23]
Refinement method	Full-matrix least-squares on F <sup>2</sup>
	(SHELXL-97) [24]
Absorption correction method	Gaussian integration (face-indexed)
Range of transmission factors	0.9775-0.9289
Data/restraints/parameters	3157/0/199
Goodness-of-fit $(S)^{c}$ [all data]	1.309

 $^a$  Obtained from least-squares refinement of 9368 reflections with 4.94° < 20 < 52.74°.

<sup>b</sup> Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

<sup>c</sup>  $S = [\sum w(F_o^2 - F_c^2)^2/(n-p)]^{1/2}$  (*n* = number of data; *p* = number of parameters varied;  $w = [\sigma^2(F_o^2) + (0.0382P)^2 + 8.4639P]^{-1}$  where  $P = [Max(F_o^2, 0) + 2F_c^2]/3$ ).

compound structures and calculated frequencies as well as intensities and activities for IR and Raman are available in the Supplementary data document. Frequencies are scaled by factors 0.961, 0.957, 0.964 and 0.960 for B3LYP/LanL2DZ, B3PW91/LanL2DZ, B3LYP/6-31++G(d,p) and B3PW91/6-31++G(d,p), respectively, as recommended by the National Institute of Standards and Technology [38]. The absence of imaginary frequencies was confirmed.

#### 3. Results and discussion

#### 3.1. Synthesis and characterization of 2-(benzylthio)-N-{pyridinyl-4methylidene}aniline (4)

2-(Benzylthio)-N-{pyridinylmethylidene}anilines 2-4 are readily obtained in a Schiff base condensation reaction by reaction of the aniline NH<sub>2</sub> group with the respective pyridine carboxaldehyde reagent (Scheme 1) and yields of more than 95% of the crude products were observed in reaction monitoring by thin layer chromatography and <sup>1</sup>H NMR analysis of the crude reaction mixture [24]. Compounds 2 and 3 were isolated and purified by recrystallization from hot MeOH. However, the same synthetic methodology was unsuccessful in preparing the 4-pyridine derivative (4), which was instead synthesized by the azeotropic removal of water in refluxing toluene for 7 days. Attempts to recrystallize **4** in alcoholic solutions (MeOH, EtOH and <sup>i</sup>PrOH) resulted in significant loss of product by cleavage of imine bond and formation of S-benzyl ortho-aminothiophenol (1) likely caused by imine bond activation in the para-substituted pyridine. Alternatively, flash chromatographic techniques on silica were unsuccessful as the acidic SiO<sub>2</sub> triggered cleavage of imine bond and product always contained small amounts (about 5% as determined in <sup>1</sup>H NMR analysis) of **1**. Recrystallization from hot toluene and forced precipitation by addition of non-polar hexanes was the most suitable method for the isolation and purification of 4, isolated as a yellow colored solid in 46% yield.

Based on the detailed NMR analysis of 2 and 3 [26], the characterization of compound 4 was also obtained from chemical shifts and coupling constants from a series of <sup>1</sup>H, <sup>13</sup>C{<sup>1</sup>H}, jmod, COSY, HSQC and HMBC NMR experiments (Fig. 1). The characteristic singlet <sup>1</sup>H signal of the imine function (H8) is observed at 8.32 ppm. The pyridine <sup>1</sup>H chemical shifts of protons H10 and H11 are found at 7.77 ppm and 8.74 ppm, respectively. The chemical shifts of the <sup>1</sup>H and <sup>13</sup>C signals are matching with the resonances observed in compounds 2 and 3 [26]. Mass spectrometric analysis produced the molecular ion signal at 304 m/z. The base signal is 91 m/zand is characteristic of tropylium cation derived by C-S bond cleavage of the benzyl group as well as the C=N bond cleavage resulting in the [C<sub>6</sub>H<sub>5</sub>N]<sup>+</sup> fragment. Corresponding to base signal is fragment 213 m/z which is obtained by the other major fragments of the cleaved products of C-S and C=N bonds. Fragment 271 m/z can be explained by loss of HS in a fragmentation rearrangement mechanism of the molecular ion.

#### Table 2

Comparison of selected geometrical parameters at four levels of theory with experimental values from the X-ray structure of compound **3** for the evaluation of structure predictions.

	Exp.		LanL2DZ		Z			6-31++G(d,p)			
	X-ray	Error <sup>a</sup> (%)	B3LYP	Error <sup>b</sup> (%)	B3PW91	Error <sup>b</sup> (%)	B3LYP	Error <sup>b</sup> (%)	B3PW91	Error <sup>b</sup> (%)	
Selected bond distance	es (Å)										
C1—S	1.817	0.34	1.855	2.09	1.845	1.54	1.798	-1.05	1.787	-1.65	
C10—S	1.767	0.33	1.936	9.56	1.920	8.66	1.865	5.55	1.850	4.70	
C2-N1	1.413	0.42	1.422	0.64	1.416	0.21	1.408	-0.35	1.403	-0.70	
C20-N1	1.272	0.47	1.296	1.89	1.294	1.73	1.279	0.55	1.278	0.47	
C21-N2	1.337	0.45	1.353	1.19	1.350	0.97	1.335	-0.15	1.332	-0.37	
C25-N2	1.343	0.45	1.361	1.34	1.358	1.12	1.343	0	1.340	-0.22	
Selected bond angles	(°)										
C1-S-C10	102.2	0.06	98.5	-3.62	98.3	-3.82	100.2	-1.96	99.9	-2.25	
S-C10-C11	107.1	0.06	110.3	2.99	110.0	2.74	110.2	2.87	109.9	2.62	
C2-N1-C20	120.1	0.05	122.0	1.58	121.7	1.29	119.7	-0.37	119.4	-0.58	
N1-C20-C22	120.9	0.05	122.1	0.98	122.0	0.97	122.9	1.48	122.4	1.23	
C21-N2-C25	116.2	0.05	117.9	1.51	117.8	1.42	117.6	1.19	117.5	1.09	
Selected torsion angle	s (°)										
C1-S-C10-C11	175.0	0.03	176.2	0.69	178.6	2.04	177.1	1.22	177.9	1.66	
C2-N1-C20-C22	-178.4	0.03	-178.3	-0.06	-179.4	0.53	-178.3	1.83	-178.5	0.06	
C6-C1-C11-C12	123.8	0.02	-174.7	-41.1	179.7	45.15	177.5	-47.4	-173.0	-39.7	

<sup>a</sup> Error in X-ray diffraction converted to % for comparison with computational data.

<sup>b</sup> Error calculated from (calculated value – experimental value)/(experimental value).



Scheme 1. Synthesis of 2-,3- and 4-substituted pyridinylmethylidene derivatives of S-benzylortho-aminothiophenol.

#### 3.2. Structure analysis

Suitable X-ray crystallographic crystals of the 3-pyridinyl derivative (3) were obtained by slow diffusion of *n*-pentane into a dichloromethane solution at room temperature and the ORTEP plot is shown in Fig. 2. Unfortunately, suitable crystals for X-ray analysis could not be obtained for compounds 2 and 4. The details of X-ray structure analysis data are given in Table 1 and selected geometrical parameters are listed in Table 2. The crystal structure of **3** has an expected planar geometry of the conjugated pyridineimine-thioaniline moiety which is measured by the dihedral angle C2-N1-C20-C22 of -178.4°. The C=N imine bond also possesses the thermodynamically favoured trans-configuration that was previously predicted [26]. The thioether group (C1-S-C10) has an angle of 102.2° and the phenyl group is placed most distant from the thioaniline ring with almost linear dihedral angle  $(-175.0^{\circ})$  of C1–S–C10–C11. The phenyl ring is tilted away, approximately perpendicular, from the conjugated pyridine-imine-thioaniline moiety, by 123.8° in the C6-C1-C11-C12 dihedral angle. The bond distances of S–C<sub>aromatic</sub> (C1–S) and S–C<sub>aliphatic</sub> (C10–S) are in the expected ranges with 1.817 Å and 1.767 Å, respectively. The imine C=N bond length (C20-N1) is 1.272 Å. There are no unexpected irregularities with bond distances and angles when they were compared with close related compounds reported by Ariza-Castolo and co-worker of pyridinyl aldimines [39].

For assignment of the IR and Raman vibrational modes of the three titular compounds (**2–4**), computational methods were employed. Hartree–Fock, Møller–Plesset, and local density models yield poor results for vibrational frequency and intensity calculations, and among the gradient-corrected and hybrid density functionals, none stands out as particularly better or worse than the

others [40]. The B3LYP functional is most popular density functional method and can provide reliable predictions on the structures and vibrational frequencies [41,42]. However, the less widely used B3PW91 functional can yield slightly better results than B3LYP [43,44], especially in cases where there are large electronegativity differences between bonded atoms, such as with imine and pyridine nitrogen functional groups. The basis sets LanZ2DZ and 6-31++G(d,p) were chosen as they are (i) flexible



**Fig. 2.** Perspective view of the 2-(benzylthio)-*N*-{pyridin-3-ylmethylidene}aniline (**3**) showing the atom labeling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 20% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.



Fig. 3. Comparative views ("top view" and "side view" parallel and perpendicular of *ortho*-aminothiophenol ring) of predicted compound structures (2–4) using B3PW91/ LanL2DZ.

enough to account for a heterogeneous charge distribution; (ii) small enough to not be prohibitively expensive when studying large molecules; and (iii) accommodate metal atoms for future work when studying transition metal complexes with 2-4 as ligands. The expanded LanL2DZ basis set, which uses effective core potentials for all atoms larger than Ne allowing for treatment of relativistic effects while reducing computational expense, was compared to the more commonly reported 6-31++G(d,p) basis set for organic molecules. One particular advantage of LanL2DZ is the modeling of metals beyond the 3d elements, while 6-31++G(d,p) is limited to elements up to Kr. LanL2DZ in conjunction with hybrid DFT functionals is well suited to predict heats of formation and ionization potentials [45] and bond dissociation energies [46]. 6-31++G(d,p) allows the modeling of compounds and modifies calculations for diffuse orbitals, observed with the thioether functional group, and polarization functions with strongly polar covalent bonds that occur with imine and pyridine nitrogens.

The availability of the X-ray crystal structure of **3** allowed the comparison of the structural results of computational methods with experimental data and the evaluation of accuracies. However, we note that the comparison is between a solid-state experimental structure, recorded at 173 K, and an ideal gas theoretical structure at 0 K. Bond distances and angles involving C-H and C=C bonds are uncharacteristic for structure evaluations but are available in the Supplementary data. The results of bond distance calculations for all four methods are in good agreement with the X-ray crystal structure, with B3PW91/6-31++G(d,p) having a slightly better accuracy among the four methods. On using B3LYP and B3PW91 with LanL2DZ, one consistent problem is that the bond lengths are consistently overestimated by up to 2% for C-N and C=N bonds and 4-6.5% for C-S bonds. In contrast, the bond distance calculations using the 6-31++G(d,p) basis set have no clear trend in comparison to experimental X-ray crystallographic data. The typical error range for the 6-31++G(d,p) basis set is acceptable and lies between ±3% from experimental values. The bond angle calculations using the LanL2DZ underestimate the C1-S-C10 bond angle at the order of -3% while the S-C10-C11 angle is overestimated by 2.6%. The angles of bonds involving nitrogen are slightly overestimated by up to +1.6%. Calculation results using the 6-31++G(d,p) basis set show no distinct preferential trend in bond angle determination. 6-31++G(d,p) is accurate to the same order of magnitude as LanL2DZ, but errors are slightly smaller. All three aromatic rings are planar and consistent within all computational methods. For dihedral angle analysis, we only looked at three structurally relevant values of the conjugated pyridine-imine-thioaniline moiety (C2-N1-C20-C22), the thioether functional group (C1–S–C10–C11) and the tilting of the phenyl group from the thioaniline ring (C6–C1–C11–C12). The calculated results of C2-N1-C20-C22 and C1-S-C10-C11 are accurate and only differ by up to 2% and are of same order of magnitude as predicted bond distances and bond angles. The phenyl group is rather tilted to 123.8° and deviates significantly from calculated values by 40-47%. Recalculations of all four methods with a starting phenyl tilt of 123.8° converged again to same torsion angles as listed in Table 2. Thus the unusual conformation is likely based on packing effects in the crystal lattice as calculations are conducted in gas phase without intermolecular interactions.

To visually compare the predicted structures of compounds **2–4**, a "top view" and "side view" structure of each compound is shown in Fig. 3 for the B3PW91/LanL2DZ model, which is in good agreement of structures calculated with three other models (not shown). In all cases, the imine group is in *trans* configuration which is more thermodynamically stable than the *cis* isomer. Most dominant is the tilting of the pyridine pendant ring against the aniline–imine moiety. In the 2-pyridine compound (**2**), the *ortho* position of the pyridine nitrogen is in alignment with the imine nitrogen, probably due to secondary electron interactions whereas in **3** and **4** with a more distant pyridine an increased tilt is observed. All other angles and distances are in good agreement in particular the bond angle of the thioether function which is observed in its typical 98–100° range.

Overall, all four DFT computational methods are suitable for predicting the structure of the compound **3** with experimental X-ray crystallographic results. There are minor preferences for 6-31G++(d,p) basis set over LanL2DZ but the advantage in slightly improved accuracy is lessened by increased computational expense and a future limiting issue of elements up to Kr, i.e. only 3d row elements when investigating transition metal coordination complexes. B3LYP and B3PW91 are both acceptable levels of theory, with the latter being slightly more accurate. We therefore Table 3

Comp.	Experimental	LanL2DZ				6-31++G(d,p)			
		<b>B3LYP</b> <sup>a</sup>	Scaled B3LYP <sup>b</sup>	B3PW91 <sup>a</sup>	Scaled B3PW91 <sup>b</sup>	B3LYP <sup>a</sup>	Scaled B3LYP <sup>b</sup>	B3PW91 <sup>a</sup>	Scaled B3PW91 <sup>b</sup>
	$IR (cm^{-1})$								
2	1621	1699 (4.81%)	1633 (0.74%)	1712 (5.61%)	1638 (1.05%)	1727 (6.54%)	1666 (2.76%)	1739 (7.28%)	1669 (2.96%)
3	1623	1683 (3.69%)	1618 (-0.31%)	1700 (4.74%)	1627 (0.25%)	1713 (5.55%)	1651 (1.73%)	1727 (6.41%)	1658 (2.16%)
4	1623	1683 (3.70%)	1617 (-0.37%)	1698 (4.62%)	1625 (0.12%)	1713 (5.55%)	1651 (1.73%)	1726 (6.35%)	1657 (2.10%)
	D ( -1)								
	Raman (cm ·)								1000 (0.000)
2	1620	1699 (4.87%)	1633 (0.80%)	1712 (5.68%)	1638 (1.11%)	1727 (6.60%)	1666 (2.77%)	1739 (7.35%)	1669 (3.02%)
3	1621	1683 (3.82%)	1618 (-0.19%)	1700 (4.87%)	1627 (0.37%)	1713 (5.67%)	1651 (1.85%)	1727 (6.54%)	1658 (2.28%)
4	1624	1683 (3.63%)	1617 (-0.43%)	1698 (4.62%)	1625 (0.06%)	1713 (5.54%)	1651 (1.66%)	1726 (6.34%)	1657 (2.03%)

Comparison of $v(C=$	=N) at four levels of theor	with experimental values of	the IR and Raman sn	ectra for <b>2 3</b> and <b>4</b>
companison or v(c-		y with experimental values of	the in and naman sp	

<sup>a</sup> Frequency (cm<sup>-1</sup>) and error calculated from (calculated value – experimental value)/(experimental value).

<sup>b</sup> Scale values: 0.961 for B3LYP/LanL2DZ; 0.957 for B3PW91/LanL2DZ; 0.964 for B3LYP/6-31++G(d,p); 0.960 for B3PW91/6-31++G(d,p). Frequency (cm<sup>-1</sup>) and error calculated from (calculated scaled value – experimental value)/(experimental value).

choose B3PW91/6-31++G(d,p) as the best suited method for structure determination, with a recommendation for B3PW91/LanL2DZ in cases where the 6-31++G(d,p) basis set is not possible.

#### 3.3. Vibrational analysis

The computational study was extended to vibrational spectroscopy for frequency as well as intensity (IR) and activity (Raman) analysis in order to support the assignment of experimental values of the vibration bands for **2–4**. The vibrational analysis was conducted by frequency calculations of each the geometry optimized structures (Tables S8–S19 in Supplementary data). No imaginary frequencies were found thus eliminating saddle points in the potential hyperenergy surface. As the vibrational modes of larger molecules, such as **2–4**, can be highly complex, we focused first on major bond interactions, i.e. the dominant and characteristic v(C=N) vibrational band which is active in both the IR and Raman modes (Table 3). The most characteristic band for each of the compounds is the C=N imine bond stretch found in the range of 1620–1624 cm<sup>-1</sup> which is in congruent with typical observed range of imine vibrations for related aryl–pyrdinyl imines in the

1590–1690 cm<sup>-1</sup> range [47]. The calculated vibrational IR and Raman spectra of all four different DFT methods showed a reliable agreement with experimental values although the frequencies were consistently overestimated by 3-8%. Such systematic frequency overestimation [38] is known for IR and Raman calculations using DFT methods, so to obtain a better picture of the accuracy of individual modes, the calculated frequencies were adjusted using the scaling factors recommended by the National Institute of Science and Technology: 0.961 for B3LYP/LanL2DZ: 0.957 for B3PW91/LanL2DZ: 0.964 for B3LYP/6-31++G(d.p): 0.960 for B3PW91/6-31++G(d.p). Katsvubu and co-workers [48] described ab initio (MP2) and DFT (B3LYP, M05, M05-2X) predictions for IR intensities and Raman activities and found that of these, B3LYP offers the most cost-effective choice for the prediction of molecular vibrational properties. Accurate IR intensities can be obtained with modest basis sets, whereas medium-sized sets were needed for accurate calculations of Raman activities [48]. Our results show that the errors of the calculated values for both IR and Raman frequencies were matching within the DFT methods for each of the compounds (2-4); in particular, the scaled frequency values are in the  $5-30 \text{ cm}^{-1}$ , or 0.25 to approximately 3%,

#### Table 4

Assignment of vibration modes, scaled<sup>a</sup> frequencies (cm<sup>-1</sup>), relative and absolute intensities (IR) or activities (Raman) for four levels of theory compared to experimental values for **2** in the range of 1700–400 cm<sup>-1</sup>.

	LanL2DZ		6-31++G(d,p)	
	B3LYP	B3PW91	B3LYP	B3PW91
Assignment of major contributors to IR vibration mode				
v(C==N)	1633 (100%, 121)	1638 (100%, 112)	1666 (100%,141)	1669 (100%, 129)
Sym. stretch of C—C in thioaniline ring	1572 (29%, 35)	1577 (30%, 34)	1573 (31%, 59)	1580 (32%, 41)
C—H rock in thioaniline and pyridine rings	1441 (40%, 48)	1443(41%, 46)	1438 (42%, 59)	1437 (46%, 59)
C—H rock in thioaniline and pyridine rings	1432 (27%, 33)	1435(30%, 34)	1433 (2%, 2)	1431 (6%, 5)
v(C <sub>aromatic</sub> -N <sub>imine</sub> ) and sym. stretch of C-C in thioaniline and pyrdine rings	1162 (17%, 21)	1167(20%, 22)	1169 (20%, 28)	1172 (17%, 22)
$v(C_{aromatic}-S)$ and sym. C–C stretch thioaniline	1059 (5%, 6)	1061 (7%, 8)	1058 (4%, 6)	1057 (5%, 6)
$v(C_{aromatic}-S)$ and C–H twist pyridine ring	1006 (7%, 8)	1013 (6%, 7)	1014 (4%, 5)	1014 (5%, 6)
C=N twist and C-H twist in thioaniline ring	844 (22%, 27)	845 (22%, 25)	845 (4%, 5)	849 (4%, 5)
$\delta(C_{aromatic}-S)$	797 (8%, 10)	799 (7%, 8)	796 (1%, 2)	795 (2%, 2)
C—H wag in pyridine ring	782 (37%, 45)	781 (38%, 43)	765 (24%, 34)	765 (16%, 20)
C—H wag in thioaniline ring	761 (73%, 88)	760 (76%, 85)	759 (7%, 10)	762 (12%, 18)
C—H twist out-of-plane in pyridine ring	744 (21%, 26)	741(31%, 35)	742 (38%, 54)	739 (41%, 53)
C—H wag in phenyl ring	701 (44%, 53)	697(51%, 57)	685 (31%, 44)	683 (41%, 53)
$v(C_{aromatic}-S)$ and C-C wag of thioaniline ring	668 (11%, 13)	668 (12%, 13)	662 (5%, 7)	672 (1%, 1)
$v(C_{aliphatic} - S)$	630 (17%, 21)	640 (13%, 14)	647 (4%, 5)	644 (5%, 6)
Assignment of major contributors to Raman vibration mode				
v(C=N)	1633 (100%, 1171)	1638 (100%, 1638)	1666 (100%, 1025)	1669 (100%, 1143)
Sym. stretch of C–C in thioaniline ring	1567 (14%, 166)	1577 (15%, 207)	1560 (14%, 70)	1580 (13%, 152)
Sym. stretch of C–C in pyridine ring	1556 (36%, 418)	1564 (38%, 532)	1570 (44%, 450)	1577 (42%, 477)
$v(C_{aromatic} \! - \! N_{imine})$ and sym. stretch of C–C in thioaniline and pyridine rings	1162 (16%, 183)	1167 (20%, 271)	1169 (33%, 340)	1172 (33%, 381)

<sup>a</sup> Scale values: 0.961 for B3LYP/LanL2DZ; 0.957 for B3PW91/LanL2DZ; 0.964 for B3LYP/6-31++G(d,p); 0.960 for B3PW91/6-31++G(d,p). Relative intensity compared to v(C=N). Calculated IR intensity (km/mol). Calculated Raman activity (A<sup>4</sup>/amu).

#### Table 5

Assignment of vibration modes, scaled<sup>a</sup> frequencies (cm<sup>-1</sup>), relative and absolute intensities (IR) or activities (Raman) for four levels of theory compared to experimental values for **3** in the range of 1700–400 cm<sup>-1</sup>.

	LanL2DZ		6-31++G(d,p)	
	B3LYP	B3PW91	B3LYP	B3PW91
Assignment of major contributors to IR vibration mode				
v(C=N)	1618 (100%, 141)	1627 (100%, 141)	1651 (100%, 167)	1658 (100%, 166)
Sym. stretch of C—C in thioaniline and pyridine rings	1563 (28%, 39)	1572 (29%, 41)	1569 (28%, 47)	1576 (29%, 48)
Sym. stretch of C—C in pyridine ring	1534 (24%, 34)	1544 (23%, 32)	1555 (23%, 38)	1562 (22%36)
C—H rock in pyridine ring	1443 (36%, 51)	1445 (38%, 54)	1456 (17%, 28)	1454 (19%, 31)
C—H wag in phenyl ring	1424 (6%, 8)	1424 (5%, 7)	1436 (20%, 34)	1435 (19%, 32)
C—C wag in thioaniline and pyridine rings	1161 (21%, 30)	1167 (28%, 39)	1170 (37%, 61)	1172 (33%, 55)
v(C <sub>aromatic</sub> —S) and sym. C—C stretch phenyl ring	1026 (8%, 11)	1030 (13%, 9)	1036 (10%, 6)	1035 (12%, 7)
$v(C_{aromatic}-S)$ and sym. C–C stretch thioaniline	1006 (9%, 12)	1010 (9%, 12)	1013 (3%, 5)	1014 (4%, 6)
C=N twist and C-H twist in thioaniline ring	834 (28%, 40)	835 (30%, 42)	843 (13%, 22)	840 (12%, 20)
$\delta (C_{aromatic} - S)$	769 (16%, 23)	768 (14%, 20)	759 (5%, 8)	762 (4%, 7)
C—H wag in thioaniline ring	764 (58%, 82)	763 (59%, 83)	745 (34%, 56)	741 (34%, 56)
C—H wag in pyridine ring	712 (29%, 41)	710 (31%, 44)	692 (18%, 30)	690 (18%, 30)
C—H wag in phenyl ring	698 (37%, 52)	696 (41%, 58)	683 (27%, 45)	682 (32%, 53)
$v(C_{aromatic}-S)$ and C-C wag of thioaniline ring	665 (6%, 9)	664 (6%, 8)	672 (5%, 9)	673 (4%, 6)
$v(C_{aliphatic} - S)$	631 (15%, 21)	638 (8%, 11)	644 (4%, 6)	640 (4%, 6)
Assignment of major contributors to Raman vibration mode				
v(C=N)	1618 (100%, 1259)	1627 (100%,1405)	1651 (100%, 998)	1658 (100%, 1067)
Sym. stretch of C—C in thioaniline ring	1571 (2%, 19)	1580 (1%, 12)	1581 (28%, 279)	1598 (28%, 296)
Sym. stretch of C—C in pyridine ring	1563 (72%, 902)	1572 (72%, 1009)	1569 (50%, 500)	1576 (47%, 497)
$\nu(C_{aromatic} - N_{imine})$ and sym. stretch of C–C in thioaniline and pyridine rings	1161 (20%, 250)	1167 (24%, 344)	1170 (35%, 348)	1172 (24%,258)

<sup>a</sup> Scale values: 0.961 for B3LYP/LanL2DZ; 0.957 for B3PW91/LanL2DZ; 0.964 for B3LYP/6-31++G(d,p); 0.960 for B3PW91/6-31++G(d,p). Relative intensity compared to v(C=N). Calculated IR intensity (km/mol). Calculated Raman activity (A<sup>4</sup>/amu).

respectively, when compared to experimental values. The LanL2DZ basis set consistently outperformed the 6-31++G(d,p) basis set with raw data and scaled data by a margin on the order of one third. Our results agree with Katsyubu's finding showing B3LYP as a good method for IR and Raman frequency predictions. B3LYP and B3PW91 levels of theory are almost identical with predictions of frequencies and on average B3LYP slightly out performs B3PW91, although this trend is too small to be significant.

With the good agreement of v(C=N) modes in IR and Raman, we then proceeded to analyze the vibration spectra in other regions. The C–H stretching bands for aliphatic and aromatic carbons in

typical range of  $3050-2850 \text{ cm}^{-1}$  are found in the respective regions of **2–4** and are too uncharacteristic, hence not listed in Tables 4–6. The scaled frequencies were normalized for relative intensities (IR) and activities (Raman) compared to the largest vibration band, i.e. v(C=N). The IR intensities were listed to a minimum threshold of 20% relative intensity; the Raman activities result threshold was 10% as there are fewer Raman signals compared to IR. This relatively conservative categorization allowed the comparison of strong to weak experimental values to the calculation results based on intensity. The calculated vibrational modes are visualized using the WebMO program interface and major contributors to the

#### Table 6

Assignment of vibration modes, scaled<sup>a</sup> frequencies (cm<sup>-1</sup>), relative and absolute intensities (IR) or activities (Raman) for four levels of theory compared to experimental values for **4** in the range of 1700–400 cm<sup>-1</sup>.

	LanL2DZ		6-31++G(d,p)	
	B3LYP	B3PW91	B3LYP	B3PW91
Assignment of major contributors to IR vibration mode				
v(C==N)	1617 (100%, 99)	1625 (100%, 101)	1651 (100%, 128)	1657 (100%, 122)
Sym. stretch of C—C in thioaniline and pyridine rings	1569 (36%, 36)	1578 (49%, 49)	1582 (30%, 38)	1589 (34%, 41)
Sym. stretch of C–C in pyridine ring	1534 (27%, 27)	1544 (27%, 27)	1547 (23%, 29)	1557 (24%, 29)
C—H rock in pyridine ring	1429 (40%, 40)	1433 (38%, 38)	_b	_b
C—H rock in thioaniline ring	_b	_b	1436 (29%, 37)	1436 (36%, 40)
C—C wag in thioaniline and pyridine rings	1161 (30%, 30)	1166 (27%, 27)	1169 (38%, 48)	1172 (33%, 40)
v(C <sub>aromatic</sub> —S) and sym. C—C stretch thioaniline	1026 (13%, 13)	1029 (14%, 14)	1036 (9%, 11)	1036 (10%, 12)
C=N twist and C-H twist in pyridine ring	826 (52%, 51)	823 (50%, 50)	803 (25%, 32)	832 (29%, 35)
C—H twist in phenyl ring	770 (23%, 23)	770 (20%, 20)	760 (7%, 9)	762 (6%, 7)
C—H wag in thioaniline ring	765 (82%, 81)	763 (81%, 80)	745 (43%, 55)	742 (45%, 52)
C—H wag in phenyl ring	698 (52%, 51)	696 (55%, 54)	684 (34%, 43)	683 (43%, 52)
$v(C_{aromatic}-S)$ and C-C wag of thioaniline ring	660 (11%, 11)	660 (10%, 10)	669 (8%, 10)	669 (6%, 7)
$v(C_{aliphatic}-S)$	635 (14%, 14)	643 (22%, 22)	_b	_b
C—C wag of thioaniline and phenyl rings	480 (21%, 21)	479 (24%, 24)	478 (12%, 15)	476 (15%, 18)
Assignment of major contributors to Raman vibration mode				
v(C=N)	1617 (100%, 1335)	1630 (100%, 1368)	1651 (100%, 1025)	1657 (100%, 1095)
Sym. stretch of C—C in thioaniline ring	1564 (20%, 270)	1579 (57%, 778)	1582 (27%, 275)	1589 (25%, 269)
Sym. stretch of C–C in pyridine ring	_b	_b	1570 (35%, 357)	1577 (35%, 381)
$v(C_{aromatic}-N_{imine})$ and sym. stretch of CC in thioaniline and pyridine rings	1161 (30%, 1161)	1166 (24%, 334)	1169 (41%, 419)	1172 (40%, 437)

<sup>a</sup> Scale values: 0.961 for B3LYP/LanL2DZ; 0.957 for B3PW91/LanL2DZ; 0.964 for B3LYP/6-31++G(d,p); 0.960 for B3PW91/6-31++G(d,p). Relative intensity compared to v(C=N). Calculated IR intensity (km/mol). Calculated Raman activity (A<sup>4</sup>/amu).

<sup>b</sup> Unable to assign.

molecule vibration were assigned. The focus was on significant vibrations, in particular involvement of S and N heteroatoms, as such vibrations will be shifted once 2-4 are complexed to transition metals. The  $v(S-C_{aliphatic})$  and  $v(S-C_{aromatic})$  are typically observed in the regions of  $790-630 \text{ cm}^{-1}$  and  $1100-1080 \text{ cm}^{-1}$ , respectively. Due to accuracy and complexity of vibration modes, we cannot assign with unambiguous confidence the exact mode of the experimental vibrations although we have high confidence in the assignments of the strong bands. The similarity of the three derivatives (2-4) is fitting with similarly assigned major vibrations of IR and Raman frequencies. The largest vibration bands in IR spectra of **2–4**, besides the dominant C=N stretch vibrations, are the C-H rocking and C-H wagging vibrations of the three aromatic subunits, i.e. for 2 of B3LYP/LanL2DZ 1441,1432, 844, 782, 761 and 744 cm<sup>-1</sup>, which can be assigned to the experimental values of 1473, 1433, 874, 777, 736 and 714  $\rm cm^{-1}$ , respectively. The assignments of vibrations across the four levels of theory are very consistent throughout all compounds and values within each set of basis set more similar. Nevertheless, the scaled values of B3LYP and B3PW91 with the 6-31++G(d,p) basis set tend to be more overestimated. The stretching or deformation vibrations [47] of the thioether function, found in the ranges of 1000-1070 cm<sup>-1</sup> and 630-660 cm<sup>-1</sup> assigned are of interest as those will be affected once a metal is bound though a sulfur lone pair; however, these vibrations are typically weak with about less than one fourth of the v(C=N).

The Raman vibrations of **2–4** are less abundant than the complementary IR vibrations and only four very active bands have been determined as most of the calculated values are far below the 5% threshold. B3LYP/LanL2DZ calculations resulted for compound **2** for major frequencies of 1633 (C=N), 1567, 1556 and 1142 cm<sup>-1</sup>, which excellently correspond to the four major experimental vibrations of **2** at 1620 (C=N), 1585, 1562 and 1194 cm<sup>-1</sup>. These are the C–C stretching modes of the aromatic rings that shown large changes in polarizability and observed in all three derivatives and hence small deviations. All other vibrations are far below the 5% threshold margin and were not assigned.

#### 4. Conclusion

The density functionals, B3LYP and B3PW91, with the basis sets LanZ2DZ and 6-31++G(d,p) were compared in a computational methodology study with experimentally available X-ray crystal structure, FTIR and FT-Raman data for a series of 2-(benzylthio)-*N*-{pyridinylmethylidene}anilines. 2-(benzylthio)-*N*-{pyridinyl-4methylidene}aniline (**4**) was synthesized by condensation reaction from S-benzyl ortho-aminothiophenol with 4-pyrdine carboxaldehyde and X-ray structure of 2-(benzylthio)-N-{pyridinyl-3-methylidene}aniline (3) was obtained. B3PW91/6-31++G(d,p) slightly outperformed the other three level of theories for prediction of molecular structure when compared to available X-ray structure of **3**. In general, all four levels of theories had the least accuracies for bond lengths and bond angles involving the sulfur atom. The LanL2DZ basis set is comparable to the 6-31++G(d,p) basis set to produce good estimates for structure analysis. However, for vibrational mode estimates LanL2DZ outperforms 6-31++G(d,p) within less than 3% error range when the appropriate scaling factors are used. Judging the effectiveness of the four investigated methods, B3PW91/LanL2DZ holds an edge for structural and vibrational accuracy as well for least computational cost. In addition, 2-(benzylthio)-*N*-{pyridinylmethylidene}anilines are potential *N*,*S*-ligand models for biomimetic protein studies involving His and Met coordination. The assignments of major contributors to the IR and Raman vibration bands of the three titular compounds assist in vibrational analysis of transition metal complexes with these

ligands and comparison of experimental vibrational data of the active sites of proteins. Furthermore, B3PW91/LanL2DZ is a suitable level of theory for theoretical compound model development of *S*-thioether, *N*-imine and *N*-pyridine based ligand designs for transition metal complexes such as type II Cu proteins and even transition metals beyond 3d elements.

#### Acknowledgments

We thank NSERC, Canada Foundation for Innovation, NSRIT, Enterprise Cape Breton Corporation and CBU for financial support of this research. B.M. McLellan is grateful to NSERC for an USRA award. Special thanks to Dr. C.D. Keefe for support of FTIR and FT-Raman spectrometry.

#### **Appendix A. Supplementary material**

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molstruc.2012.08. 026.

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