

## B3LYP theoretical calculations and structure of 4-[(2-[(1E)-1-methyl-3-oxobutylidene]amino)ethyl]imino]pentan-2-one

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### Abstract

In this work we present the synthesis 4-[(2-[(1E)-1-methyl-3-oxobutylidene]amino)ethyl]imino]pentan-2-one. We also propose evidence for the presence of various tautomers for this molecule, and theoretical density functional theory (DFT)-B3LYP/6-31G\* calculations to characterize the potential energy surface of these species. NMR, IR, MS techniques and X-ray are also used to analyze the molecule **3** and its tautomeric preferential form.

**Keywords:** Ethambutol analogue, tautomerism, X-ray structure, B3LYP calculations

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### Introduction

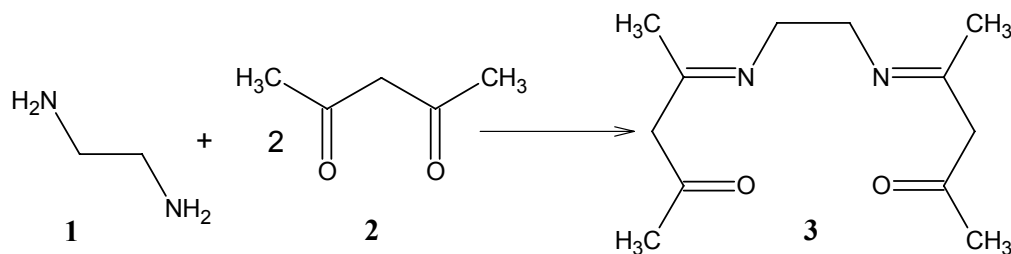
Metallo-organic complexes containing conjugated nitrogen ligands represent an important class of nonlinear optical chromophores.<sup>1</sup> Efficient systems involving organometallic and coordination compounds with pyridine,<sup>2</sup> diimine,<sup>3</sup> *salen*-type<sup>4</sup> or Schiff-base ligands have been described.<sup>5</sup> We have also demonstrated the direct impact of dipolar in drug design of functionalised bis-armed quinoxaline<sup>6</sup> and imidaz[1,2-*a*]pyridine (or pyrimidine) ligands.<sup>7,8</sup>

In connection with our research aimed at developing new pharmacophore site(s) leading us to efficient and selective antitubercular,<sup>9</sup> antitumoral<sup>10</sup> or anti-HIV drugs,<sup>11</sup> we became interested in the pharmacomodulation of parent drugs, as like the ethambutol; a clinical antitubercular agent.

## Results and Discussion

### Synthesis of compound (3)

The title compound 4-[(2-{{(1*E*)-1-methyl-3-oxobutylidene}amino}ethyl)imino]pentan-2-one (**3**) was prepared with slight modifications of the procedure described previously.<sup>12,13</sup> A mixture of 2:1 mole ratio of acetylacetone (**2**) and 1,2-diamino-ethane (**1**) were refluxed overnight in ethanol. Product, obtained by evaporating the solvent, was recrystallized from ethanol and was verified by its melting point and proton NMR spectra.

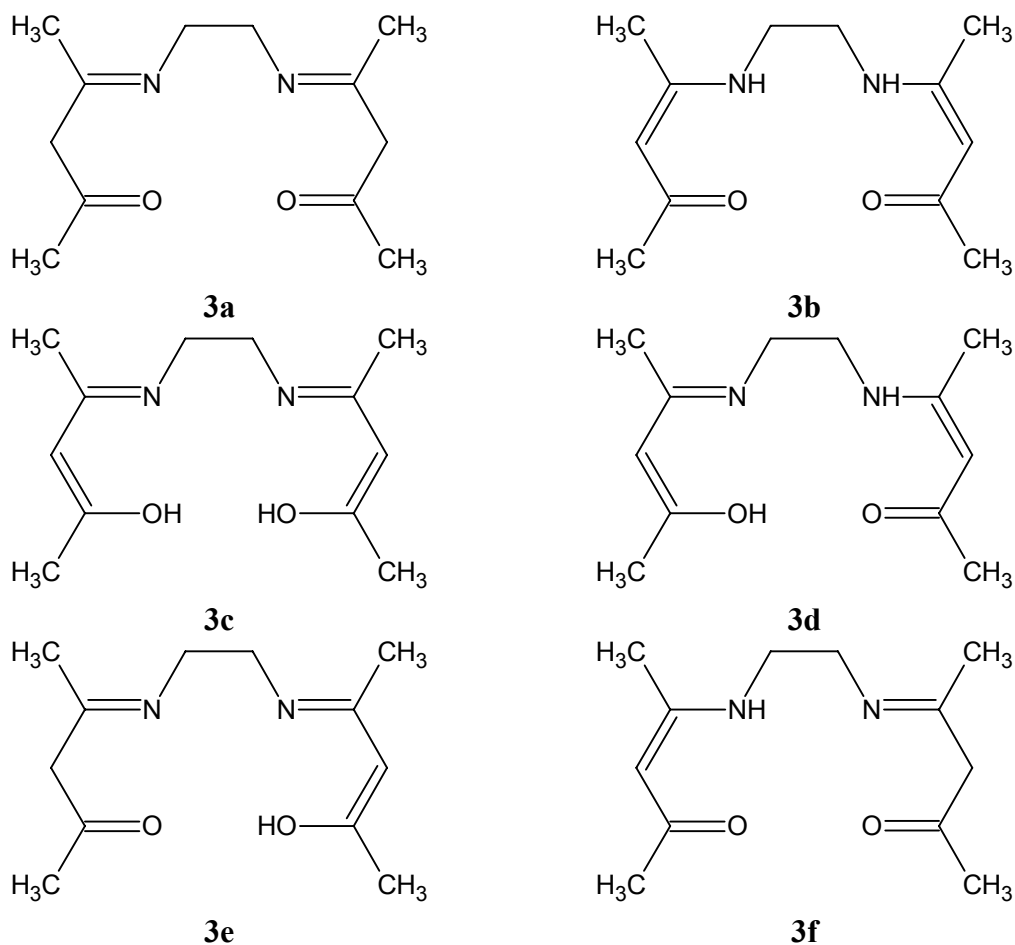


**Scheme 1.** Synthesis of tetradentate O,N,N,O-ligand **3**.

The title compound (**3**) is a Schiff base. Compound (**3**) is a well known Schiff base 4,9-dimethyl-5,8-diazadodeca-4,8-diene-2,11-dione, more commonly known as bis-(acetyl-acetone)ethylenediimine and abbreviated as **H<sub>2</sub>baen**. Compounds of this type can exist in six tautomeric forms (see scheme 2 below), *i.e.* a non-hydrogen-bonded keto-imine, a hydrogen-bonded enol-imine and a hydrogen-bonded keto-amine and mixed forms. It has been shown by IR and <sup>1</sup>H-NMR evidence that in the solid state and in most common organic solvents **H<sub>2</sub>baen** exists completely as the hydrogen-bonded tautomers with at least 80% contribution from the keto-amine form.<sup>14</sup>

### Tautomerism in compound 3

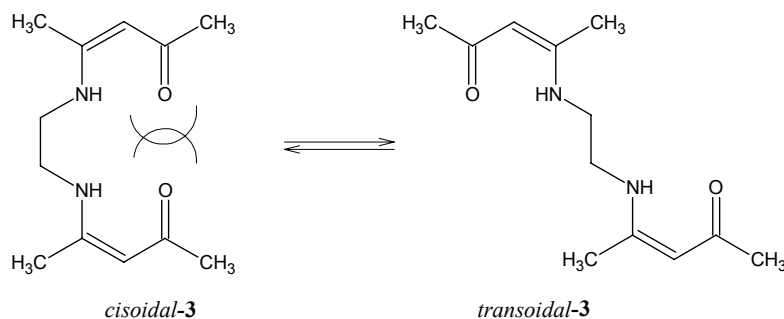
The 4,4'-(1,4-phenylene-bis-(azanediy))dipent-3-en-2-one (**3**), reported in this paper could be described as a symmetric an bis-Keto-imine form (**3a**), bis-keto-en-amine form (**3b**), bis-enol-imine form (**3c**); as a dissymmetric an enol-imine/Keto-en-amine form (**3d**), or Keto-imine/enol-imine form (**3e**) or an Keto-en-amine/keto-imine forms (**3f**). But in our knowledge, there is no study which confirms the exact arrangement around the central ethylenic (-CH<sub>2</sub>-CH<sub>2</sub>-) group. So it is of particular interest to know the preferred tautomeric form of compound (**3**).



**Scheme 2.** Different possible tautomeric forms of *Salen* ligand **3**.

<sup>1</sup>H-NMR resonance for the ethylenediamine (N-CH<sub>2</sub>-CH<sub>2</sub>-N) group (at  $\delta$  3.4) is not a singlet as expected, but rather is a multiplet due to spin-spin coupling with the amine H atom present in the keto-amine tautomer (**3b**). Similar conclusions have been drawn for one analogue compound; the 3,10-di-[2-(2-pyridyl)-ethyl]-*bis*-(acetyl-acetone)ethylenediimine.<sup>15</sup>

It was of interest to compare the structural features of compound **3** implied by the spectral data with that actually existing in crystalline form to see which geometric conformer is dominant (*cisoidal* or *transoidal* conformers) as described in Scheme 3.



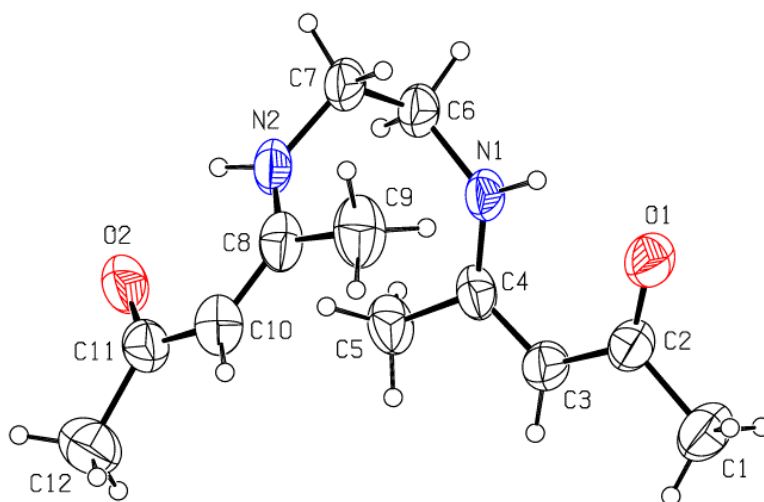
**Scheme 3.** Different possible geometric conformers of *Salen* ligand **3**.

Since the spectroscopic properties of the compound **3** were limited to (NH-C=C-C=O) moieties, it was difficult to attribute or separate the two possible conformers. To have a clear idea about the conformational aspect of compound **3**, see Figures 1 and 2.

### Crystallographic structure of compound **3**

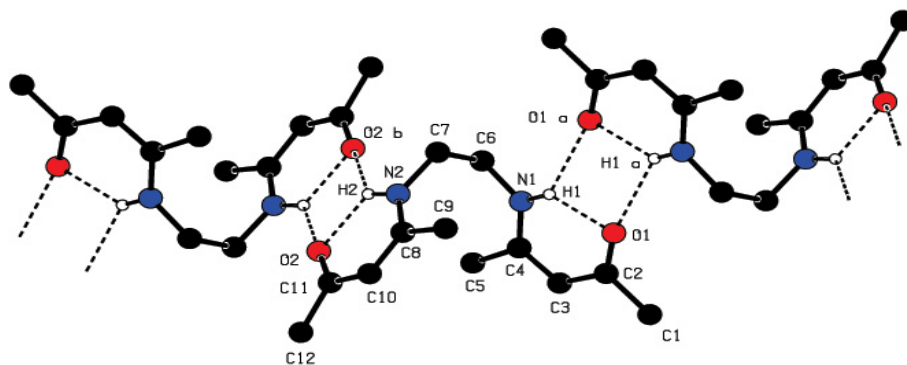
A light yellow prismatic crystal of **3** was mounted on a glass fiber and used for data collection. Cell constants and an orientation matrix for data collection were obtained by least-squares refinement of the diffraction data from 18126 reflections in the range of  $2.20 < \theta < 27.98^\circ$  on an Stoe IPDS 2 diffractometer. Data were collected at 296 K using MoK $_{\alpha}$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ) and the  $\omega$ -scan technique, and corrected for Lorentz and polarization effects. A semi-empirical absorption correction (integration) was made.<sup>16</sup>

Compound **3** has been structurally characterized by single crystal X-ray crystallography. The figure 1 shows a *transoidal* conformation around the ethylenic (-C<sup>6</sup>H<sub>2</sub>-C<sup>7</sup>H<sub>2</sub>-) band. The absence of the keto-imine tautomer is confirmed by (i) the  $128.3(2)^\circ$  bond angle of (C4—N1—C6) and  $127.3(2)^\circ$  for (C7—N2—C8), and (ii) the planarity of the C1/C2/C3/C4 and C8/C10/C11/C12.



**Figure 1.** An ORTEP drawing of compound **3**, showing atom labeling and 30% probability displacement ellipsoids.

The presence of the keto-amine tautomer is demonstrated by (i) the presence of H1(N1) and H2(N2) with N—H bond lengths of 0.86 Å, and (ii) the C2=O1, C11=O2, O1 $\cdots$ H1(N1) and O1<sup>a</sup> $\cdots$ H1<sup>a</sup>(N1<sup>a</sup>) [symmetry code: (a) 1-x, 1-y, 1-z] distances of 1.241(4), 1.251(4), 2.020 and 2.350 Å, respectively. The structure is stabilized by intra- and intermolecular N—H  $\cdots$  O hydrogen bonding interactions (Figure 2).



**Figure 2.** View of the hydrogen bonding of compound **3**, showing inter and intramolecular N—H $\cdots$ O hydrogen bonds as dashed lines. H atoms not involved in hydrogen bonding have been omitted. [Symmetry codes : (a) 1-x, 1-y, 1-z ; (b) -x, 1-y, 1-z].

## Thermodynamic Calculations

In addition to the experiments we did theoretical calculations. All calculations in this work were carried out with the AM1 level of theory using the GAUSSIAN 03 suite of programs.<sup>17</sup> More information about these methods is available elsewhere.<sup>18,19</sup>

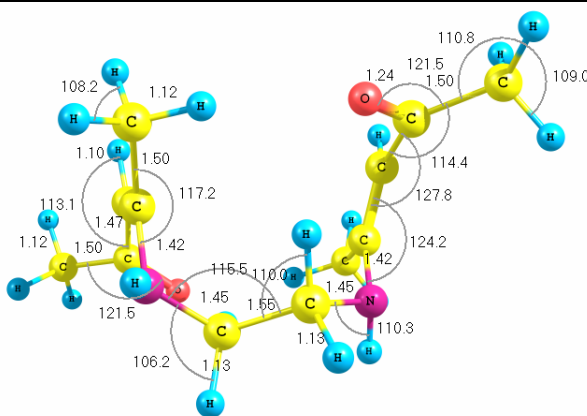
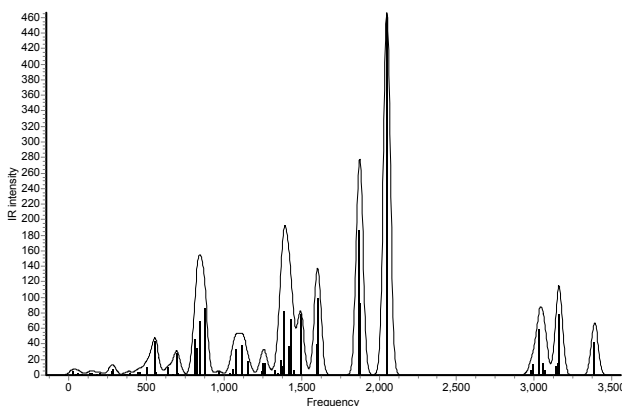
Table 1 summarizes our results. The table shows the thermodynamic parameters for the product (**3**) where T (temperature in K), S (entropy in J mol<sup>-1</sup> K<sup>-1</sup>), C<sub>p</sub> (heat capacity at constant pressure in kJ mol<sup>-1</sup> K<sup>-1</sup>), and  $\Delta H = H^\circ - H^\circ_{298.15}$  (enthalpy content, in kJ mol<sup>-1</sup>), T<sub>1</sub>=100 K, T<sub>2</sub>=298.15 K, and T<sub>3</sub>=1000 K calculated AM1 frequencies. The theoretical vibrational spectrum and structure are shown above. In the structure, all bond lengths are in angstroms (Å) and bond angles are in degrees (°) and the frequencies are in cm<sup>-1</sup>, and the IR intensities in KM/mol (broadened by the Doppler method). These calculations are useful for future thermodynamic studies as well as for NIST database indexing.

## Supplementary Information

Crystallographic data for the structural analysis have been deposited with the Cambridge crystallographic Data Centre, CCDC 661940 for compound **3**. Copies of this information can be

obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk) or <http://www.ccdc.cam.ac.uk>).

**Table 1.** Physical Properties of the molecule as well as vibrational spectra and structure computed at the AM1 level of theory



	<i>Fitted Thermodynamic Equation (T/1000=t)</i>	100 K	298.15 K	1000 K
$C_p$	$18.15545 + 991.06411 * t - 354.43068 * t^2 - 14.01517 * t^3 + 0.34365 * t^2$	147.73	283.21	642.37
S	$4.96793 * \ln(t) + 1031.43134 * t - 381.14603 * t^2 / 2 - 18.61589 * t^3 / 3 - 0.59027 / (2 * t^2) + 347.80663$	408.09	629.02	1182.24
$\Delta H$	$-18.81629 * t + 1150.6777 * t^2 / 2 - 578.22049 * t^3 / 3 + 85.76673 * t^4 / 4 - 0.82111 / t + 14.47319$	9.95	52.38	398.90

## Experimental Section

**General Procedures.** A mixture of 6.3 g (105 mmol) of ethylenediamine **1** and 21 g (210 mmol) of acetylacetone **2** was stirred in absolute ethanol (100 ml) at room temperature. The

mixture was stirred and room temperature for 48 h until TLC indicated complete disappearance of substrates. After removing ethanol, the crude products were filtered and then washed respectively by water and hexane. The solid was dissolved completely in ethanol and filtered. Crystals were grown from dichloromethane/hexane **3** in good yield of 73%. M.p. = 114-115.  $R_f$  = 0.5 (hexane/ dichloromethane = 1/ 2). IR (KBr)  $\nu$   $\text{cm}^{-1}$ : 3168; 2359; 1599; 1571; 1516; 1437; 1371; 1279; 1224; 1084; 975; 841; 734; 667. RMN  $^1\text{H}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 10.8 (s, 2H, NH); 5.1 (s, 2H, CH); 3.4-3.4 (m, 4H,  $\text{CH}_2$ ); 2 (s, 6H,  $\text{CH}_3\text{CO-}$ ); 1.91 (s, 6H,  $\text{CH}_3\text{C (N) =C}$ ).  $^{13}\text{C}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 195.6; 162.8; 96.1; 43.5; 28.9; 18.7. SM(IC,  $\text{CH}_4$ ): m/z: (MH) $^+$  = 225.

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