

Synthesis and structure of a new aminal intermediate in the indirect reductive amination of terephthalaldehyde with aqueous ammonia

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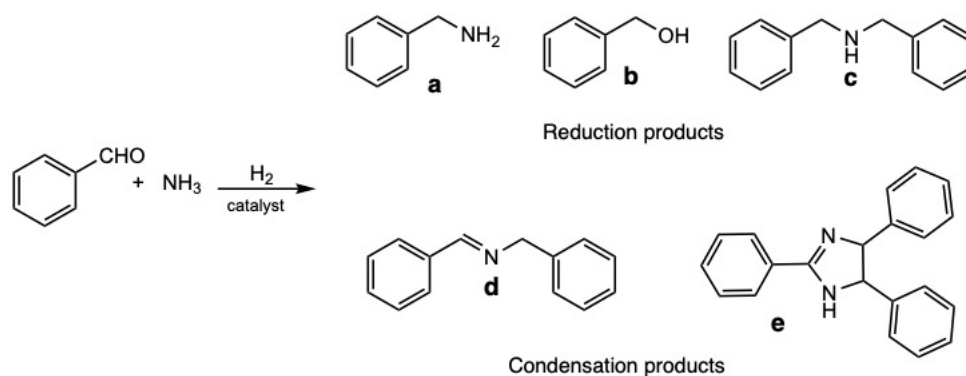
ABSTRACT

In this work, the indirect reductive amination of terephthalaldehyde with aqueous ammonia was studied. The condensation of terephthalaldehyde with ammonia afforded a new compound containing two aldehyde groups (CHO), one imino group (C=N), and an aminal carbon (N-CH-N). Reaction of this compound with sodium borohydride resulted in the reduction of the aldehyde groups, the imino carbon, and the aminal carbon. Analysis of the condensed Fukui functions and the LUMO orbital allowed us to propose a mechanism that explains this reactivity. Furthermore, a general mechanism for the condensation of aromatic aldehydes with aqueous ammonia is presented.

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1. Introduction

Reductive amination of carbonyl compounds is a useful synthetic strategy for obtaining secondary amines. This method consists of the condensation of primary amines with carbonyl compounds to produce imines or iminium ions, followed by reduction of the carbon–nitrogen double bond by catalytic hydrogenation or hydride reagents.¹



Scheme 1. Products of direct reductive amination of benzaldehyde with ammonia. **a.** benzylamine, **b.** benzyl alcohol, **c.** dibenzylamine, **d.** *N*-benzylidene(phenyl)methanamine, **e.** 2,4,5-triphenyl-4,5-dihydroimidazole.¹⁴⁻²⁵

Reductive amination is considered direct when the carbonyl compound, the amine, and the reducing agent are mixed without prior formation of the imine or iminium ion. In this case, the reducing agent must be selective, reducing the imine or iminium species without affecting the carbonyl compound. In contrast, reductive amination is indirect when it involves

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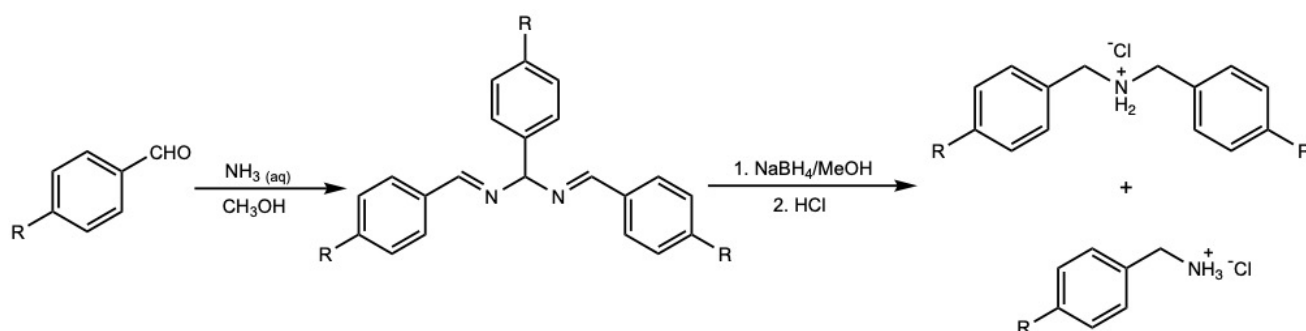
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the prior formation of an imine intermediate, followed by the addition of the reducing agent. This process can be carried out in a one-pot or two-step manner. Sodium borohydride (NaBH_4) is commonly used as the reducing agent.²⁻⁴

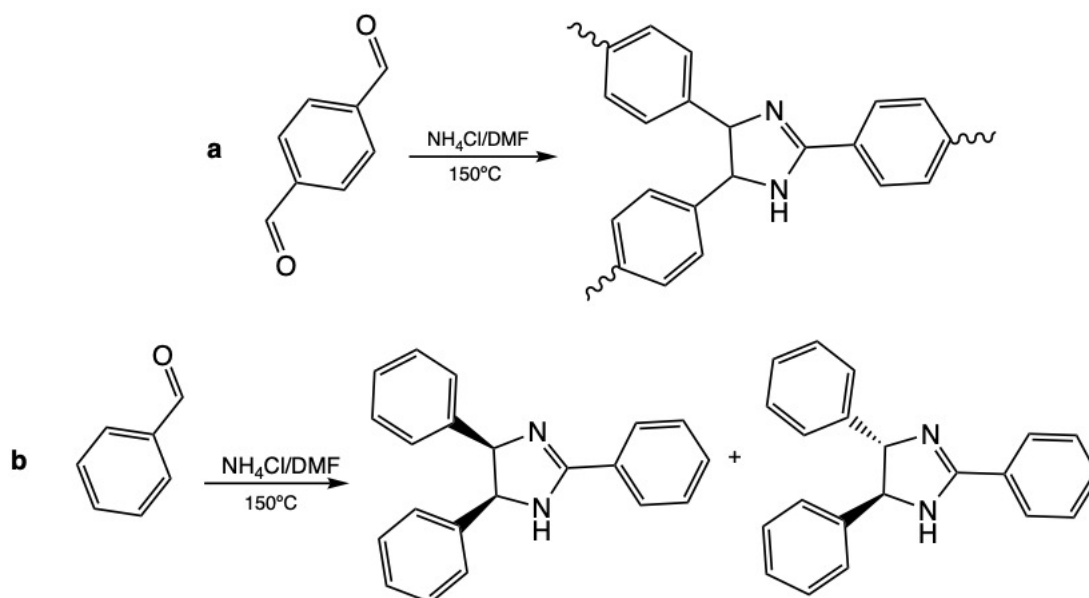
Benzylamines are amines of significant chemical interest due to their use as precursors for pharmaceuticals, agrochemicals, biomolecules, and natural products.⁵⁻⁹ Reductive amination of aromatic aldehydes with primary amines is the most common synthetic strategy for obtaining secondary benzylamines.¹⁰⁻¹⁵ When ammonia is used as the nitrogen source, complex mixtures of variable composition are typically obtained, consisting of benzyl alcohols, primary and secondary benzylamines, imines, and imidazolines (**Scheme 1**).¹⁴⁻²⁵

The reaction between aqueous ammonia and aromatic aldehydes affords hydroamides (*N,N'*-(phenylmethylene)*bis*(1-phenylmethanimines)), which are symmetrical compounds containing two imino groups and an aminated carbon center, formed by the condensation of three aldehyde molecules with two ammonia molecules (Scheme 2).²⁶⁻²⁸ It has recently been reported that these hydroamides can be reduced with sodium borohydride to produce equimolar mixtures of the corresponding primary and secondary amines (**Scheme 2**).²⁹ This strategy is useful for the synthesis of benzylamines and provides an explanation for the formation of product mixtures observed in the direct reductive amination of aromatic aldehydes with ammonia in the presence of hydrogen and metal catalysts.



Scheme 2. Indirect reductive amination of aromatic aldehydes with aqueous ammonia.

To the best of our knowledge, no studies have been reported on the reaction of terephthalaldehyde with aqueous ammonia. It has been reported that the reaction of terephthalaldehyde with ammonium halides in DMF at 150°C affords imidazoline network polymers. Under the same experimental conditions, the reaction of aromatic aldehydes with ammonium chloride has also been reported to produce mixtures of imidazoline stereoisomers (**Scheme 3**).³⁰⁻³²



Scheme 3. **a:** Reaction of terephthalaldehyde with aqueous ammonia in DMF at 150°C , **b.** Reaction of aromatic aldehydes with aqueous ammonia in DMF at 150°C .

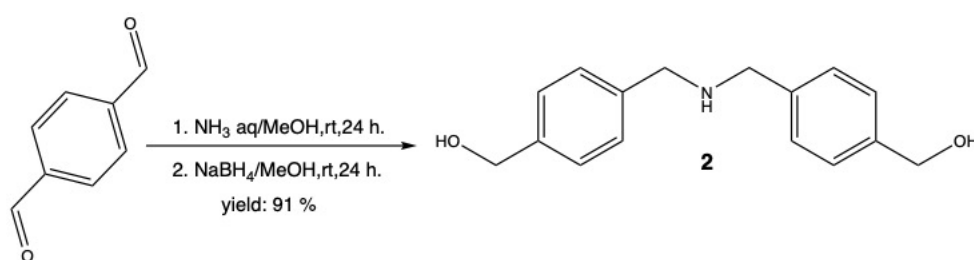
Herein, the indirect reductive amination of terephthalaldehyde using aqueous ammonia as the nitrogen source under mild experimental conditions is described. A new aminated product was isolated as the condensation product, and a secondary amine as the reduction product. The structures of these products are analysed, and a mechanism is proposed to explain the reactivity of aromatic aldehydes in the presence of aqueous ammonia.

2. Results and Discussion

The reaction of aromatic aldehydes with aqueous ammonia produces the corresponding hydroamides through the condensation of three aldehyde molecules with two ammonia molecules. These hydroamides contain two imine carbons and one aminal carbon in their structure, which are reduced with sodium borohydride to afford equimolar mixtures of the corresponding primary and secondary amines (**Scheme 2**). To the best of our knowledge, no reports have been described for the reaction of terephthalaldehyde with aqueous ammonia; however, its reaction with ammonium halides in DMF at 150 °C has been reported to yield imidazoline network polymers (**Scheme 3**).

Condensation of terephthalaldehyde dissolved in methanol with aqueous ammonia at room temperature afforded a yellow solid **1**, which was insoluble in all commonly used solvents. Compound **1** was suspended in methanol and reacted with sodium borohydride at room temperature for 24 h, yielding a beige solid **2**.

The ¹H NMR spectrum of **2** shows two doublets at 7.29 and 7.26 ppm in the aromatic region, characteristic of *p*-substituted aromatic rings. In addition to the aromatic signals, three singlets are observed in the aliphatic region at 4.48 ppm (Ar-CH₂-OH), 3.66 ppm (Ar-CH₂-NH-), and 3.65 ppm (Ar-CH₂-NH-). Analysis of the ¹³C NMR and HSQC spectra established that the obtained compound is the secondary amine ((azanediylbis(methylene))bis(4,1-phenylene))dimethanol **2**, which is formed by reductive amination of one carbonyl group of terephthalaldehyde and reduction of the other carbonyl group (**Scheme 4**).



Scheme 4. Reductive amination of terephthalaldehyde with aqueous ammonia.

Compound **2** does not correspond to the expected product of reduction of a hydroamide oligomer, as such a process would yield a mixture of benzylamine oligomers. If the condensation product were a hydroamide monomer, its reduction would afford an equimolar mixture of a primary and a secondary amine.²⁹ Compound **2** is also inconsistent with the possible reduction products of imidazolines, which are the reported products of the condensation of aromatic aldehydes with ammonium halides. Therefore, it was necessary to establish the structure of the condensation product formed between terephthalaldehyde and aqueous ammonia **1**, despite its insolubility.

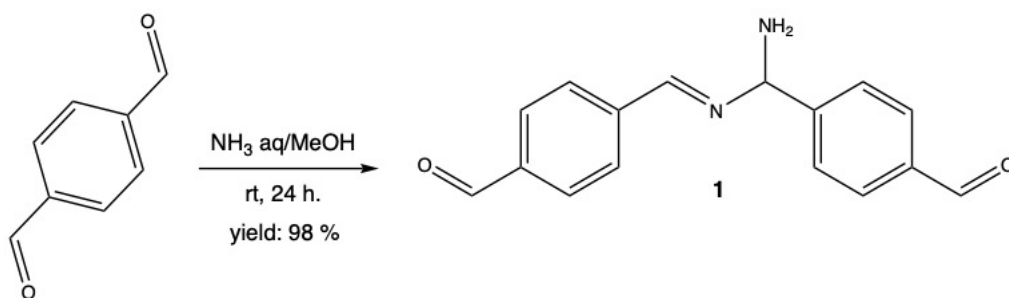
Upon heating, compound **1** could be dissolved in pyridine-*d*₅. The ¹H and ¹³C NMR spectra displayed the characteristic signals of terephthalaldehyde, indicating that product **1** is labile and readily hydrolyzed upon heating in solution. The presence of residual moisture in the deuterated pyridine likely promotes this hydrolysis.

Compound **1** was dissolved in DMSO-*d*₆ after prolonged heating in a water bath. The ¹H NMR spectrum shows a set of overlapping signals between 9.5 and 10.5 ppm, characteristic of aldehydic protons. Another group of signals appears between 7.0 and 8.4 ppm, corresponding to aromatic protons. Notably, no signals attributable to imino or aliphatic protons are observed. Within these signal regions, resonances corresponding to terephthalaldehyde are present, indicating that hydrolysis also occurs in DMSO. The ¹³C NMR spectrum shows signals corresponding to carbonyl and aromatic carbons.

Analysis of these spectra indicates that compound **1** undergoes transformation upon heating in solution in DMSO and that this process involves the carbon centers susceptible to reduction with sodium borohydride; therefore, a definitive structure could not be established based solely on the NMR data.

Finally, the high-resolution mass spectrum of compound **1** was recorded, showing an *m/z* value of 267.1131. Considering the starting reagents, the observed reductive amination product, and the measured *m/z* value, a structure corresponding to a compound formed by the reaction of two molecules of terephthalaldehyde with two molecules of ammonia was proposed. This species contains two carbonyl carbons, one imine carbon, and one aminal carbon (calcd. for C₁₆H₁₅N₂O₂ [M+H]⁺ 267.1128; **Scheme 5**).

It has been reported that, in molecules containing both imino groups and cyclic amins, chemoselective reduction of the imino carbon occurs upon reaction with sodium borohydride in ethanol. Additionally, some cyclic amins can be reduced by sodium borohydride in the presence of acetic acid. Furthermore, the reduction of these amins has been proposed to proceed via iminium ions, with a protic solvent being required for aminal opening.³³⁻³⁵



Scheme 5. Condensation of terephthalaldehyde with aqueous ammonia in methanol.

In this work, it was established that, in compound **1**, the sp^2 carbons (C=O and C=N) and the aminal carbon (sp^3 , N-CH-N) are reduced. To gain insight into the electrophilicity of these carbon centers, the structure of compound **1** was optimized and the frontier molecular orbitals (HOMO and LUMO) were calculated. The spatial distribution of the LUMO shows a high contribution from carbon 11, indicating that this is the most electrophilic position in the molecule (**Figure 1**). Carbon 9 also displays a significant contribution to this orbital, whereas carbons 16 and 29 show no contribution, indicating low electrophilic character.

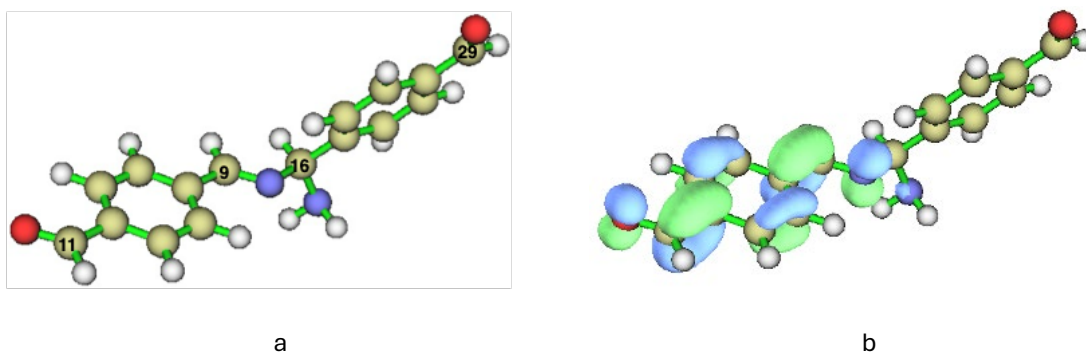


Fig. 1. Compound **1**: a. Optimized structure. b. LUMO.

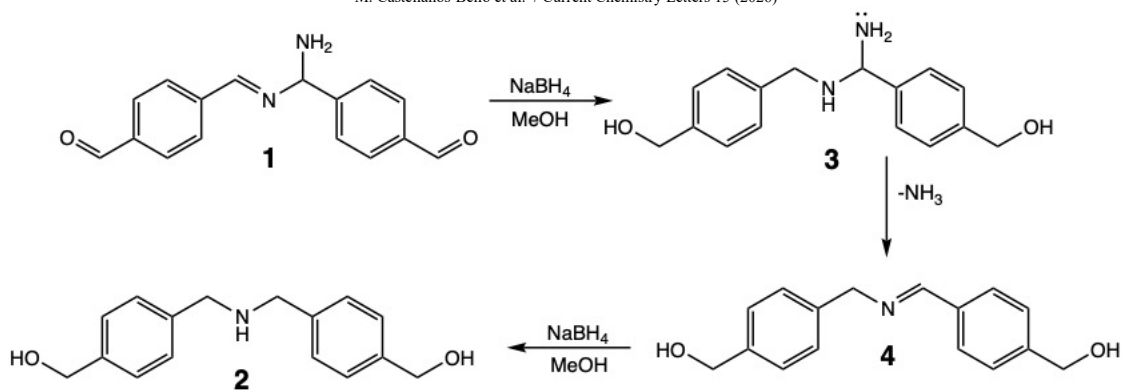
Condensed Fukui functions were calculated using the finite difference approach with Hirshfeld charges and subsequently normalized so that $\Sigma f = 1$, allowing direct comparison of local reactivity indices (**Table 1**). The electrophilic sites identified by the condensed Fukui function (f^+) correlate well with the spatial distribution of the LUMO. Among the four carbons analysed, C11 shows the highest local electrophilicity according to the normalized Fukui function ($f^+ = 0.08$), followed by C9 (0.05) and C29 (0.03), whereas C16 exhibits very low electrophilic character ($f^+ = 0.01$).³⁶⁻³⁷

Computational results indicate that the order of reactivity toward a nucleophile is $C11 > C9 > C29 \gg C16$, suggesting that nucleophilic attack at carbon 16 is electronically unfavourable. Therefore, in the presence of sodium borohydride, C16 (the aminal carbon) is unlikely to react directly, and reduction of this center must occur after a change in hybridization from sp^3 to sp^2 .

Table 1. Normalized condensed Fukui function (f^+) for C9, C11, C16 and C29.

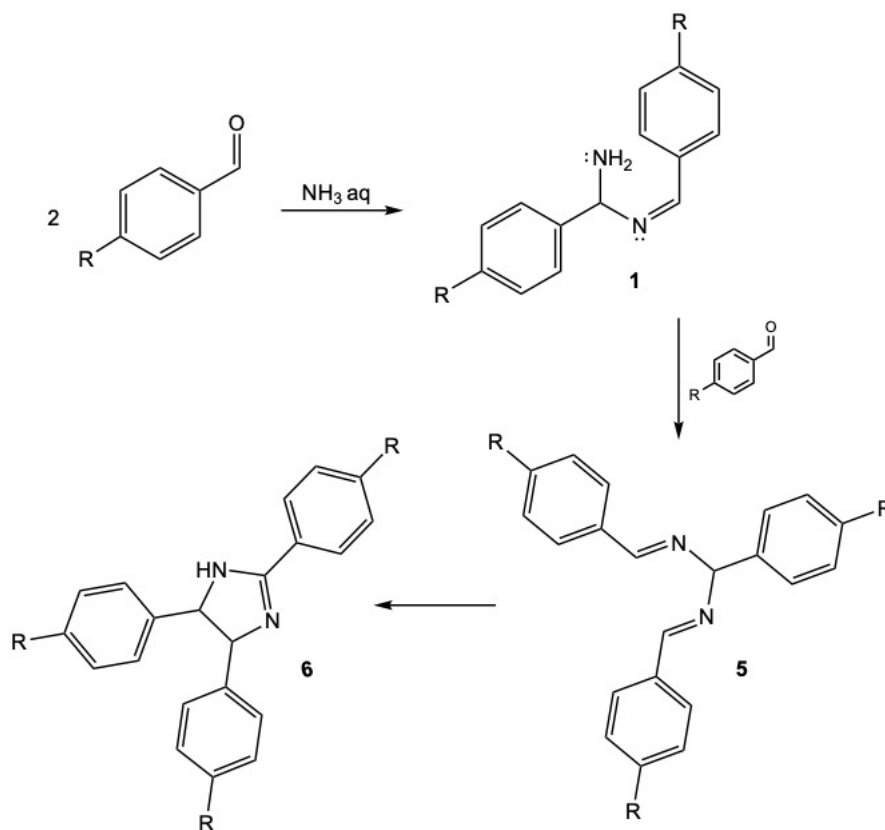
Atom	$f^+(\text{norm})$	Atom	$f^+(\text{norm})$
C9	0.05	C16	0.01
C11	0.08	C29	0.03

Based on DFT calculations, the following reaction mechanism is proposed to rationalize the reduction of compound **1**. Initial reduction of the most electrophilic sp^2 carbon centers (C=O and C=N) occurs, leading to the formation of a new aminal, **3**. It has been reported that the reduction of aminals proceeds via imines or iminium ions; therefore, an elimination step to form imine **4** is proposed.³³ The formation of this imine is favoured by the presence of benzyl groups bearing electron-donating substituents on the aromatic ring, as well as by stabilization through conjugation with the aromatic ring. This imine is subsequently reduced by sodium borohydride (**Scheme 6**).^{34,35}



Scheme 6. A possible general reduction mechanism of compound **1** with sodium borohydride in methanol.

The structure of compound **1** allows the proposal of a general reaction of aromatic aldehydes with aqueous ammonia. Initially, an imine is formed by reaction of the aromatic aldehyde with ammonia. Two imine molecules then undergo nucleophilic addition to form compound **1**. In the case of terephthalaldehyde, compound **1** is insoluble and precipitates from the reaction medium. For other aromatic aldehydes, compound **1** remains in solution and reacts with another imine or with an aldehyde to produce the corresponding hydroamide **5**, which precipitates when the reaction is carried out at room temperature.²⁹ Upon heating, cyclization can occur to afford the corresponding imidazoline **6** (Scheme 7).³⁰⁻³²



Scheme 7. A proposed sequence for the reaction of aromatic aldehydes with aqueous ammonia.

3. Conclusions

The indirect reductive amination of terephthalaldehyde with aqueous ammonia was investigated. The results established that two molecules of terephthalaldehyde react with two molecules of ammonia to afford a new compound, 4-(amino((4-formylbenzylidene)amino)methyl)benzaldehyde **1**. This compound contains two aldehyde carbonyl groups, one imine carbon, and one aminal carbon in its structure. Reaction of **1** with sodium borohydride in methanol produced the secondary amine ((azanediylbis(methylene))bis(4,1-phenylene))dimethanol **2** through reduction of the three *sp*²-hybridized carbons and the *sp*³-hybridized aminal carbon. Additionally, the synthesis of compound **1** enabled the proposal of a general mechanism for the reaction of aromatic aldehydes with aqueous ammonia.

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4. Experimental

4.1. Materials and Methods

Chemical reagents and solvents were purchased from Merck or Panreac and were used without further purification. All the reactions were conducted with continuous magnetic stirring and monitored by TLC using silica gel-coated glass plates (Merck Kieselgel 60). The plates were visualized under iodine vapors. The nuclear magnetic resonance (NMR) ^1H and ^{13}C spectra were collected using a Bruker Avance 400 spectrometer (400 MHz for ^1H , 100 MHz for ^{13}C) using the residual signal of solvent as a reference. A Chromolith RP-18e column (Merck, Kenilworth, NJ, 50 mm) was used for UPLC analysis, using an Agilent 1200 Liquid Chromatograph (Agilent, Omaha, NE). The products were analysed on a Bruker Impact II LC Q-TOF MS equipped with electrospray ionisation (ESI) in positive mode. DFT calculations were performed ORCA program package version 6.0.1.³⁸⁻⁴² Density functional theory (DFT) employed the PBE0 hybrid exchange correlation functional and def2-svpd basis set, this level of theory has been demonstrated to yield accurate geometries and spectroscopic properties.^{43,44} Multiwfn 3.8 software was used for calculating condensed Fukui functions.⁴⁵

4.2. Reaction of terephthalaldehyde with aqueous ammonia

Aqueous ammonia (25%, 10 mL, 150 mmol) was added to a solution of terephthalaldehyde (5.003 g, 37.3 mmol) in methanol (50 mL). The resulting mixture was stirred at room temperature for 24 h. The solid obtained was filtered and washed with methanol. 4-(amino((4-formylbenzylidene)amino) methyl)benzaldehyde **1**, Insoluble yellow solid (4.906 g, 18.4 mmol), does not melt, decomposes above 300 °C, yield: 98.6%. IR (KBr): (cm^{-1}) 3364 (N-H---N), 2786 and 2722 (Fermi resonance CHO), 1693 (C=O), 1607 and 1574 (C=C). HRMS (ESI) m/z : calcd. for $\text{C}_{16}\text{H}_{15}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 267.1128, found: $[\text{M}+\text{H}]^+$: 267.1131.

4.3. Reduction of 4-(amino((4-formylbenzylidene)amino)methyl)benzaldehyde **1**.

To a suspension of 0.828 g (3.1 mmol) of **1** in methanol (20 mL) were added 0.621 mg (16.4 mmol) of sodium borohydride. The reaction mixture was stirred at room temperature for 24 h., after which the solvent was allowed to evaporate at room temperature. The resulting solid was suspended in water, filtered, and washed. ((azanediylbis(methylene))bis(4,1-phenylene))dimethanol **2**, Beige solid (0.743 g, 2.9 mmol), does not melt, decomposes above 320 °C, yield: 92.9%. IR (ATR): (cm^{-1}) 3500-3100 (O-H associate and N-H), 2840 (aliphatic C-H) 1639 and 1606 (C=C). ^1H NMR (DMSO- d_6), δ /ppm: 7.29 (Ar-H,d,2H,J= 8Hz), 7.26 (Ar-H,d,2H,J= 8Hz), 4.48 (Ar-CH₂-OH,s,4H), 3.66 (Ar-CH₂-NH-,s,4H), 3.65 (Ar-CH₂-NH-,s,4H). ^{13}C NMR (DMSO- d_6), δ /ppm: 140.9 (C_{4Ar}), 140.8 (C_{4'Ar}), 139.2 (C_{1Ar}), 139.0 (C_{1'Ar}), 127.8 (C_{3Ar}, C_{5Ar}, C_{3'Ar} and C_{5'Ar}), 126.4 (C_{2Ar} and C_{6Ar}), 126.3 (C_{2'Ar} and C_{6'Ar}), 62.8 (-CH₂-OH), 52.0 (-CH₂-N), 51.9 (-CH₂-N). HRMS (ESI) m/z : calcd. for $\text{C}_{16}\text{H}_{19}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 258.1489, found: $[\text{M}+\text{H}]^+$: 258.1490.

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