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Synthesis and Study of Glycoluril Derivatives

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Abstract. Improve and illustrate the etherification of tetramethylol glycoluril using excess of methyl and ethyl alcohols in the presence of acid catalyst like HCl and HNO_3 under temperature not exceeding 55 °C. Furthermore, attempts to obtain 1,4-diphenyl 1,2-dimethylol glycoluril which is a new compound from the condensation of 1,4 diphenyl glycoluril with formaldehyde in the presence of water under mild temperature. The techniques used to identify the compounds of the present study are: FTIR spectroscopy, HPLC and ^{13}C NMR spectroscopy.

INTRODUCTION

At the present time investigation of the properties, as well as the synthesis of derivatives of glycoluril, which is a representative of bicyclic bisurea, remains one of the rapidly developing areas of modern heterocyclic chemistry. However, information on the reactivity of this class of compounds is limited, also glycoluril can act as a synthon in the synthesis of new azaheterocycles followed by investigation of their physiological and biological activities. All these properties of glycoluril prove that this object is under the scrutiny of scientists due to the disclosed potential of compounds of this class, and the development of all sorts of modification reactions of glycoluril is undoubtedly an urgent task.

The glycolurils have been received a great deal of attention due to their practical applications, such as fertilizers [1], polymer cross-linking [2, 3], explosives [4], stabilizers of organic compounds against photodegradation [5], combinatorial chemistry [6], catalysts, bleaching activators [7-9], and the monomer in supramolecular chemistry [10].

Glycoluril based amino resins (GF) have greater flexibility at similar crosslinking density compared to other amino resins and are favoured products for coil and can coatings applications.

Compared to other amino resins GF provide improved chemical resistance, hardness, flexibility and adhesion to metal substrate. Less formaldehyde is evolved during GF curing compared to other amino resins [11].

Alkylated glycolurils exhibit varying degrees of psychotropic behaviour [12]. The type and egree of the pharmacological activity of these alkyl glycolurils depends on the nature and the number of substituents on the glycoluril structure, tetra-N-alkylated compounds are the most active, and activity decreases rapidly with decreases in the number of alkyl substituents.

In this study our aim is to illustrate and to improve the methods of preparation of tetra methoxy methyl glycoluril and tetra ethoxy methyl glycoluril, which are used as crosslinkers in powder coating and to synthesize of 1,4 diphenyl 2,3 dimethylol glycoluril, which is new glycoluril derivative from 1,4 diphenyl glycoluril with good yield.

METHODS AND MATERIALS

All commercially available chemicals were purchased from Aldrich and used without further purification.

Melting points were measured on a Meltemp apparatus in open capillary tubes.

IR spectra (KBr pellet) were recorded by using an FTIR Bruker Alpha spectrometer in the 400–4000 cm^{-1} range.

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High performance liquid chromatography (HPLC) was performed in the isocratic mode. A C18 symmetry analytical column from waters with the size of 3.9 x 150 mm, 5 mm particle size was used. The mobile phase consisted of a mixture of acetonitrile, water solution (65:35, v/v). The flow rate was set to 0.75 ml/min, and the oven temperature 25°C. The injection volume was 5 µl, and the detection wavelength was set at 220 nm.

^{13}C NMR spectra was recorded in DMSO-d_6 with Bruker Avance 400 spectrometer.

The synthesis of the tetramethylol glycoluril has already been reported from the condensation of glycoluril with paraformaldehyde [13].

Preparation of Tetramethoxy Methyl Glycoluril using Nitric Acid

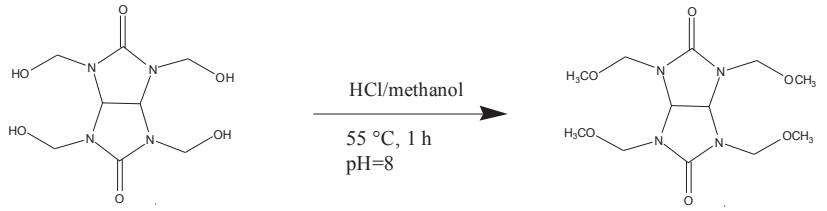
Into a suitable reaction vessel equipped with stirrer, thermometer, and condenser were charged 74 g (2.30 moles) of methanol and 3 ml of 70 % con. nitric acid. To this acidic methanol, 30 g (0.11 moles) of tetramethylol glycoluril were charged, and the reaction mixture was heated to 55 °C with stirring. In about 1 hour, all of the tetramethylol glycoluril went into solution. When the reaction mixture became clear, it was cooled to 22 °C, and 20 % sodium hydroxide solution were added to neutralize the reaction mixture to a pH of 7-8. The neutralized clear solution was heated to 50-55 °C and 50 ml of methanol were removed under slightly reduced pressure. The residue in the flask crystallized on standing for a few hours. The cyrstalline solids were filtered and washed with a small amount of water. The filtrate was then vacuum stripped at 70-80 °C to remove all the water.

The solid residue was then dissolved in benzene and the undissolved salt was removed by filtration. The benzene solution was mixed with the first crop of solid crystals and dissolved with additional benzene and was filtered again. On removal of benzene, tetramethoxy methyl glycoluril (2) was obtained. The yield was 95 %. It was recrystallized from benzene. The recrystallized product had the melting point of 116-118 °C. The structure of (2) was confirmed by IR.

Preparation of Tetramethoxy Methyl Glycoluril (2) Using Hydrochloric Acid

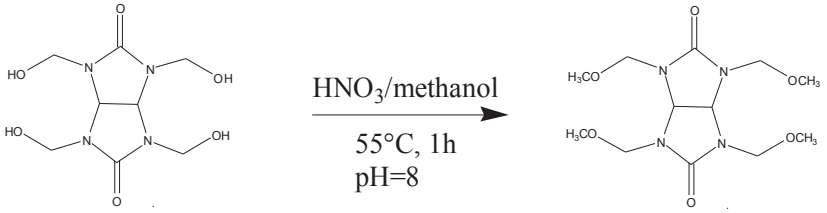
Into a suitable reaction vessel equipped with a stirrer, thermometer, and reflux condenser there was introduced 74 g (2.30 moles) of methanol and 3 ml of concentrated hydrochloric acid. To this mixture, 30 g (0.11 moles) of tetramethylol glycoluril were added and the reaction mixture was stirred at 55 °C. In about 1 hour, all the tetramethylol glycoluril went into solution. After half an hour, the reaction mixture was neutralized with a solution of sodium hydroxide 25 % at 22-23 °C. The pH after neutralization was about 8. The salt was filtered. The filtrate was concentrated at 60 °C under reduced pressure; the white crystalline precipitate was filtered and dried.

It was recrystallized from benzene. The recrystallized product had the melting point of 116-118 °C and with yield of 50 %.



1 **2** (50 %)

FIGURE 1. Etherification of tetramethylol glycoluril in HCl methanol based solutions.



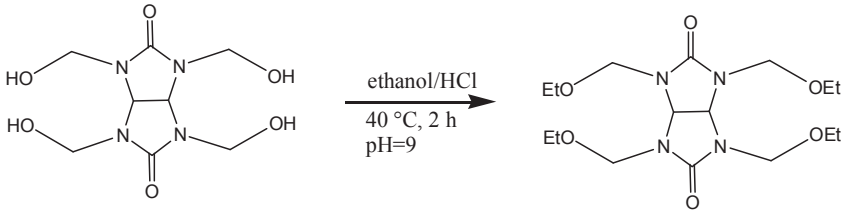
1 **2** (95 %)

FIGURE 2. Synthesis of tetramethoxy methyl glycoluril in the presence of HNO_3.

Preparation of Tetraethoxy Methyl Glycoluril (3)

Into a suitable reaction vessel equipped with a stirrer, thermometer, and refux condenser there was introduced 53 g (1.15 moles) of ethanol and 1.15 g of concentrated nitric acid. To this mixture was added 15 g (0.047 moles) of tetramethylol glycoluril and the reaction mixture was stirred at 40 °C for 2 hours. The reaction mixture became a clear solution. It is then distilled at reduced pressure between 45-50 °C to remove the ethanol/water azeotrope mixture. After removing the maximum of the ethanol/water mixture, 13.5 g of ethanol were added to the clear solution at room temperature. The solution was neutralized with 25 % caustic to a pH 9-10, followed by removal of more of ethanol/water mixture under reduced pressure.

The residue was filtered with a filter aid. The resulting yellow syrup was 95 % monomeric. The IR spectrum of the product confirmed the structure of the monomer to be tetraethoxy methyl glycoluril.

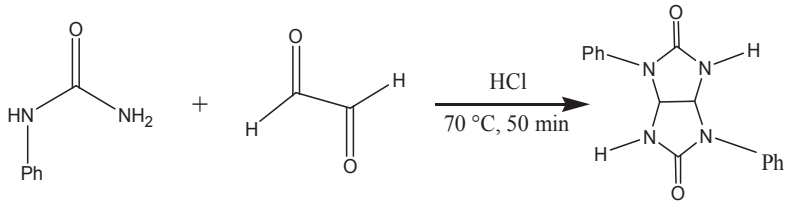


3 (95 %)

FIGURE 3. Synthesis of tetraethoxy methyl glycoluril.

Praparation of 1,4-Diphenyl Glycoluril (4)

Commercial 30 % glyoxal solution 10 g (0.05 moles), phenyl urea 13.6 g (0.1 moles), water (100 ml) and 70 % concentrated hydrochloric acid (2-3 ml) are maintained at 75 °C for 50 minutes. After cooling the formation of white cream contains brown solid as impurities, the cream is filtered and extracted three times with 150 ml portions of boiling ethanol to remove the brown solid. The dry, cream-colored product melting at 232 °C with yield of 47 %.

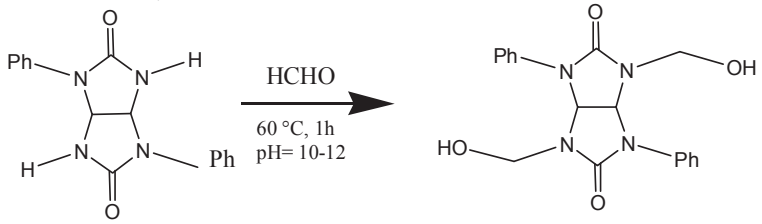


4 (47 %)

FIGURE 4. Synthesis of 1,4 diphenyl glycoluril.

Preparation of 1,4-Diphenyl 2,3-Dimethylol Glycoluril (5)

71 g (0.5 moles) of (4) was added to a stirred suspension of 66 g (2.2 moles) of paraformaldehyde in 150 ml of water. The pH of the suspension was adjusted to between 10 and 12 by the addition of alkali, and the suspension heated slowly to 50-60 °C for 1 hour. Without allowing the syrup to cool to a temperature 'which would induce crystallization, 300 ml of methanol was added, with vigorous stirring. The syrup went into solution and within a few minutes diphenyl dimethylol glycoluril separated as white powder these were filtered off, washed with 30 ml of methanol, and dried. Yield of 53 % of the theoretical.



5 (53 %)

FIGURE 5. Synthesis of 1,4 diphenyl 2,3 dimethyl glycoluril.

RESULTS AND DISCUSSION

Etherification reactions are acid catalyzed. Excess acid is added so as to neutralize the base catalyst of the methylolation stage. Usually etherification is carried out in the presence of excess alcohol to supress competing polymerization reactions, which take place under acidic conditions. When alcohol is lower boiling compared to water and water miscible, larger excess (1.6 per mole methylol) is required. The reaction mixture is refluxed under the influence of heat. Water of the reaction is removed at specified rate, the distillate is condensed remove water and excess of alcohol.

Complete etherification is carried out, resulting one product. The extent of etherification depends upon pH, reaction temperature and amount of alcohol. Low temperature and excess alcohol favours complete etherification. Usually alcohol for etherification must be the solvent for tetramethylol glycoluril and it should react readily to from methylol ethers.

IR and HPLC Analysis of Compound (2)

Tetrahydroxy methyl glycoluril (1) have been transformed into the corresponding (2) tetramethoxy methyl glycoluril [14] and during this preparation we fell in case of the formation of hyrdochloride sodium like indesirable salt, and to avoid this problem we have thought to use nitric acid instead hydrochloric acid, also to increase the yield of tetramethoxy methyl glycoluril from 50 % to 95 %. The formation of compound (2) was comfirmed by using IR analysis (Fig. 6) along with HPLC (Fig.7).

The structure of compound (2) was indicated by the absence of the characteristic O-H stretching vibration at 3200-3600 cm $^{-1}$, in addition the absorption bands of the C-O at 1170 cm $^{-1}$ and 1220 cm $^{-1}$.

HPLC chromatogram of compound (2) indicated the presence of byproducts with it due to the water used as solvent with acetonitrile, which led to the partial hydrolysis of compounds (2) to mono, di and trimethoxy methyl glycoluril. The purity of compound (2) was 86.66 %.

TABLE 1. Basic IR Absorptions of Compound (2).

Wave number (cm $^{-1}$)	Type of vibration	Nature of functional group
2944	CH3 stretching	Alkane
1435,1330	CH3 bending	Alkane
1470	CH2 bending	Alkane
1220,1170	C–O stretching	Ether
1710	C=O stretching	Carbonyl

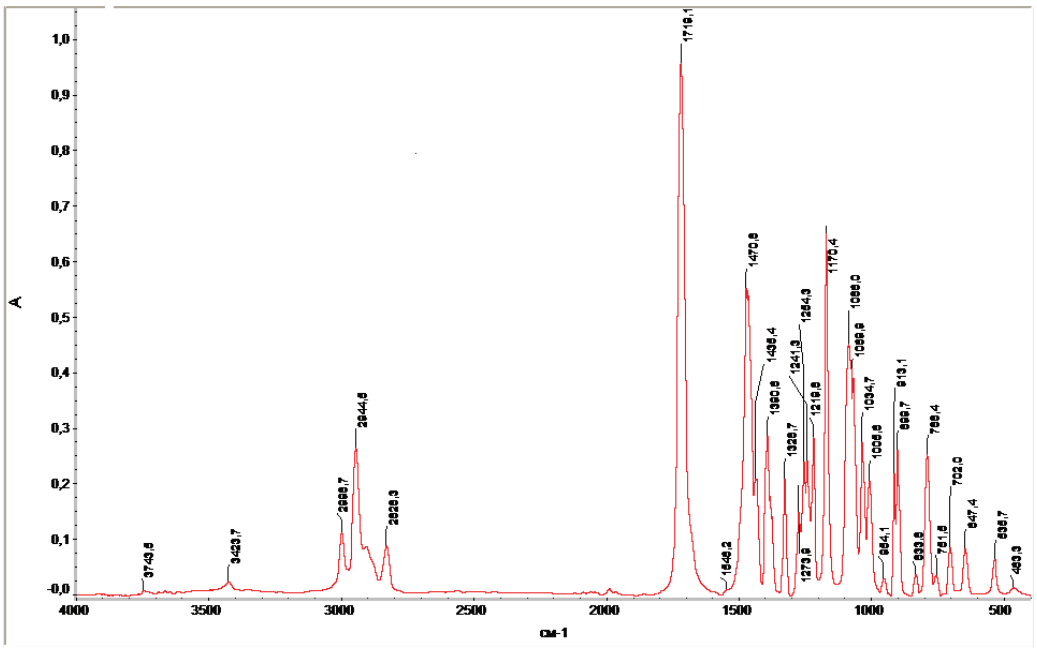


FIGURE 6. IR Spectrum of Compound (2).

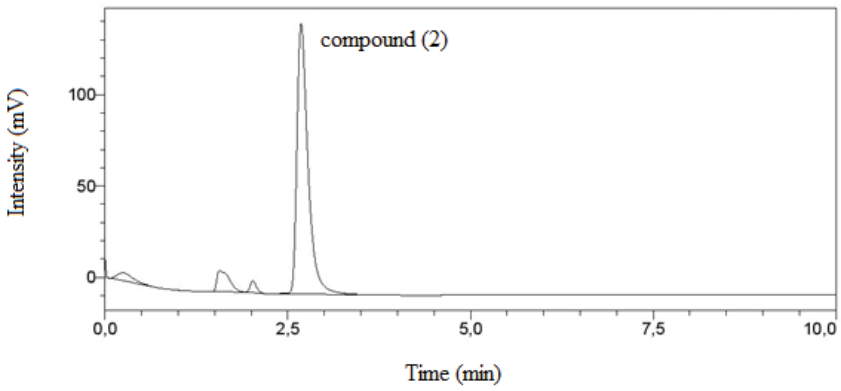


FIGURE 7. HPLC Chromatogram of Compound (2).

^{13}C NMR Analysis of Compound (2)

^{13}C NMR (400 MHz, DMSO-d_6): δ=158.07 (C=O glycoluril), 74.54 (CH), 66.85 (CH2-O), 55.59 (CH3-O).

The structure of compound (2) was confirmed by the presence of CH2-O peak at 66.85 and CH3-O peak at 55.59, which indicated the formation of ether.

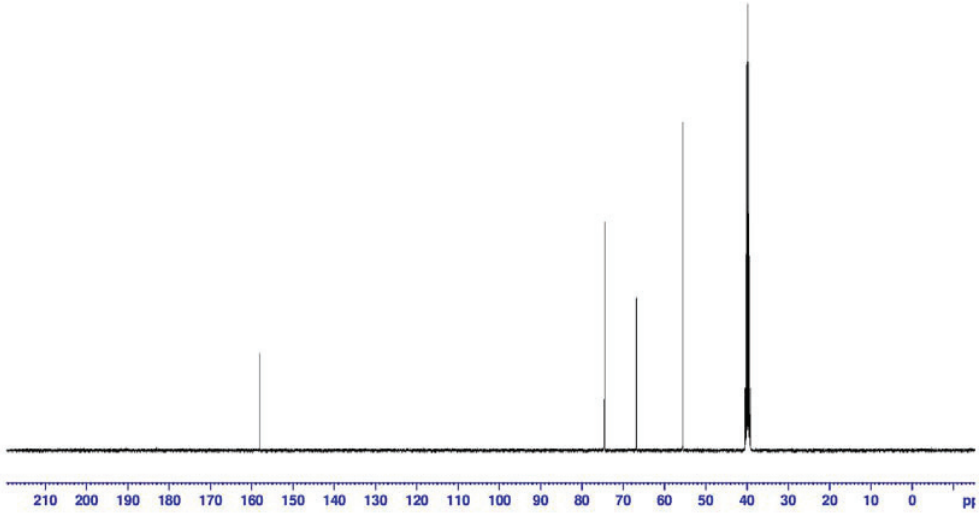


FIGURE 8. C-13 NMR Spectrum of Compound (3).

IR and HPLC Analysis of Compound (3)

We investigated the reaction between the compound (1) and ethanol in the presence of nitric acid (HNO_3), which was proven useful for the synthesis of the compound (3) as yellow oil with yield of 72 % (Fig.3), which was identified as only product by HPLC with purity of 99 % (Fig.10), as was evident by infra red spectrum (Fig.9), which indicated the absence O-H stretching band and the presence of CH3 bending absorptions at 1435 cm $^{-1}$ and 1330 cm $^{-1}$ besides the absorption of C=O at 1710 cm $^{-1}$.

TABLE 2. Basic IR Absorptions of Compound (3).

Wave number (cm $^{-1}$)	Type of vibration	Nature of functional group
2944	CH3 stretching	Alkane
1435,1330	CH3 bending	Alkane
1470	CH2 bending	Alkane
1220,1170	C–O stretching	Ether
1710	C=O stretching	Carbonyl

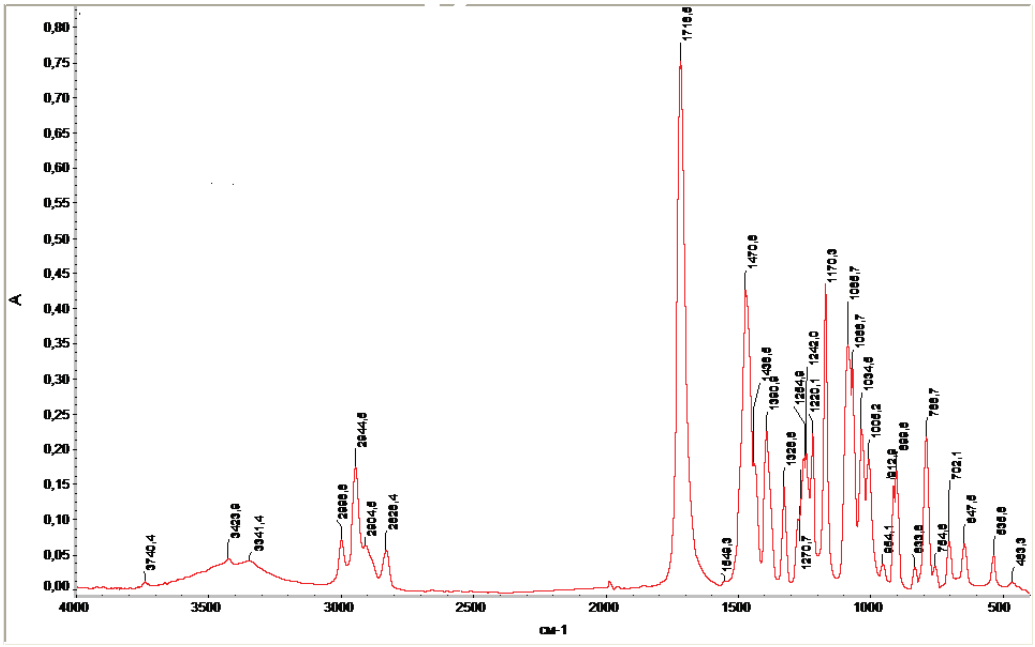


FIGURE 9. IR Spectrum of Compound (3).

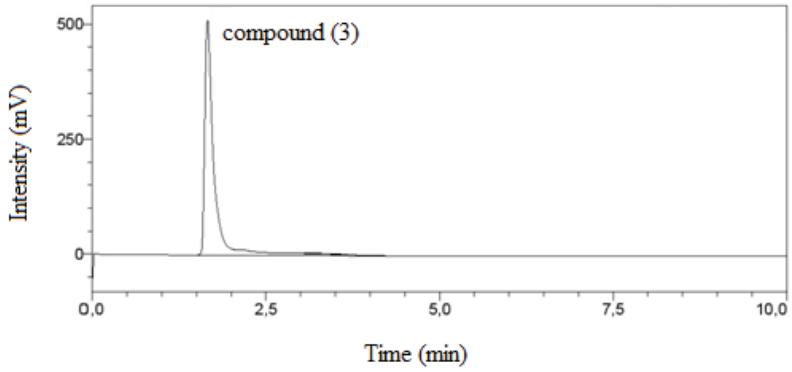


FIGURE 10. HPLC Chromatogram of Compound (3).

IR and HPLC Analysis of Compound (4)

The condensation of urea with glyoxal under acidic conditions (Fig.4) leads to the synthesis of compound (4) [15], which is the nitrogen analog of glycoluril, which was laterally used to synthesize the compound (5), whereas the reported melting point of the compound (4) was not found to be correct, also we acheived the higher % age yield of compound (4) i.e. from 35 % to 47 %, and by using IR spectroscopic technique (Fig.11).

The IR spectrum of compound (4) exhibited a NH stretching vibration at 3160-3410 cm $^{-1}$ which confirmed the formation of the secondary amide and C=C absorptions at 1620 cm $^{-1}$ and 1445 cm $^{-1}$, that confirmed the presence of aromatic ring..

TABLE 3. Basic Absorptions of Compound (4).

Wave number (cm $^{-1}$)	Type of vibration	Nature of functional group
3160,3410	N-H stretching	amide
1710	C=O stretching	carbonyl
1620,1445	C=C stretching	alkene
1148	C–N stretching	amide

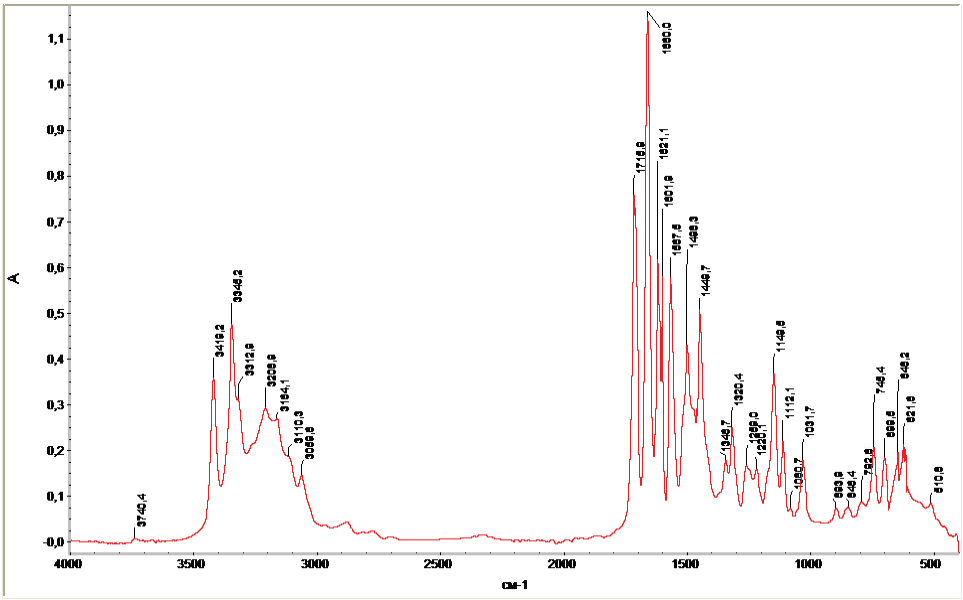


FIGURE 11. IR Spectrum of Compound (4).

^{13}C NMR Analysis of Compound (4)

^{13}C NMR (75 MHz, DMSO-d6): δ=157.09 (C=O glycoluril), 118.1 (CH arom), 121.96 (CH arom), 123.29 (CH arom), 123.62 (CH arom), 128.91 (C arom), 79.32 (CH), 59.34 (CH).

The peaks at 118-129 were affirmed the presence of the aromatic ring in the compound (4), which confirmed the synthesis of this latter.

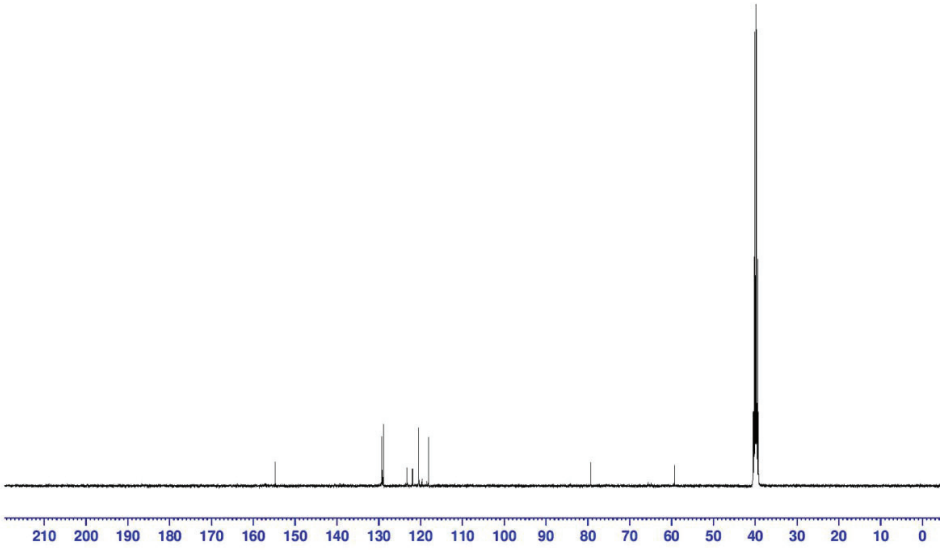


FIGURE 12. C-13 NMR Spectrum of Compound (4).

IR and HPLC Analysis of Compound (5)

To synthesize compound (5), we treated compound (4) with formaldehyde in the presence of hydroxide sodium, which led to the synthesis of compound (5) with yield of 87 % (Fig.5), and was evident by using both HPLC and IR techniques (Fig.13), which confirmed its synthesis with purity of 95 % (Fig.14).

The IR spectrum of compound (5) displayed the disappearance of the NH stretching vibration with presence of an OH absorption band at 3300-3600 cm $^{-1}$, in addition to the presence of C-O stretching vibration at 1148 cm $^{-1}$.

TABLE 4. Basic Absorption of Compound (5).

Wave number (cm $^{-1}$)	Type of vibration	Nature of functional group
3200-3600	OH Stretching	Alcohol
1695	C=O stretching	Carbonyl
1620	C=C stretching	Alkene
1465	CH2 bending	Alkane
1148	O-CH2 stretching	Ether

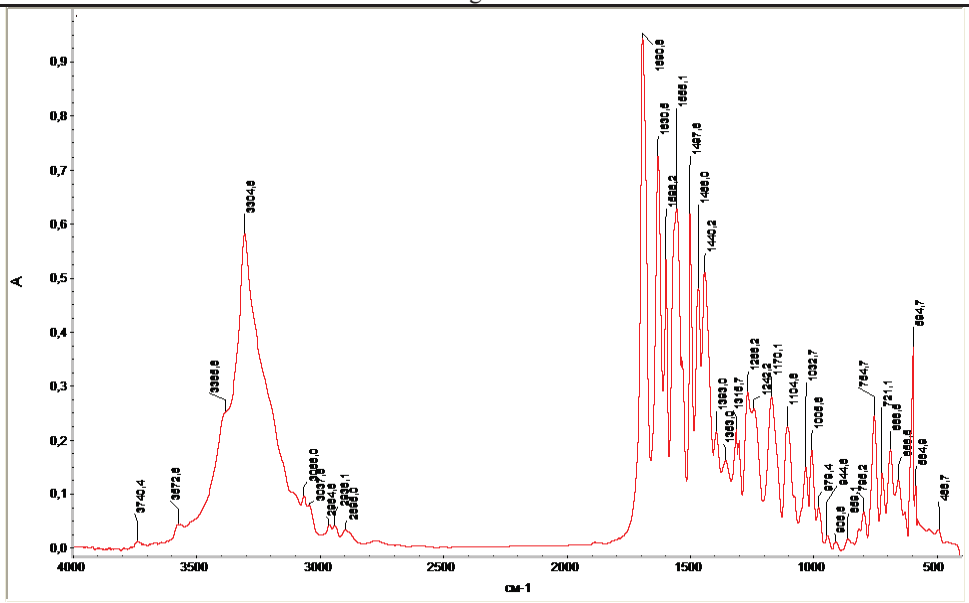


FIGURE 13. IR Spectrum of Compound (5).

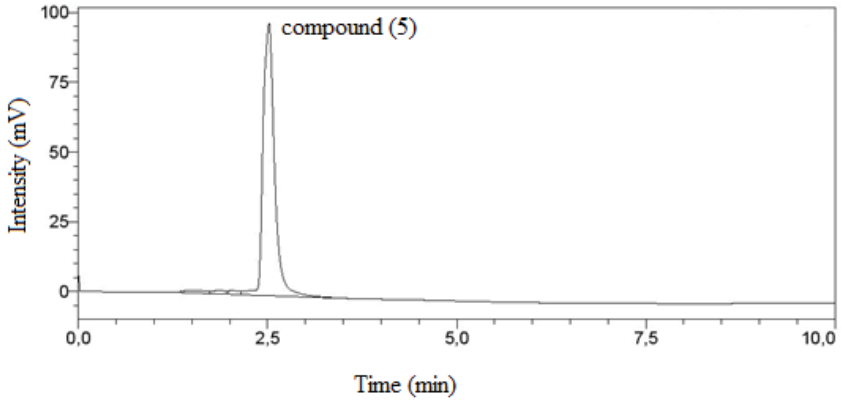


FIGURE 14. HPLC Chromatogram of Compound (5).

^{13}C NMR Analysis of Compound (5)

^{13}C NMR (75 MHz, DMSO-d6): δ=155.98 (C=O glycoluril), 129.54 (C arom), 118.27 (CH arom), 120.88 (CH arom), 123.83 (CH arom), 125.58 (CH arom), 77.54 (CH), 64.19 (CH2-O), 60.64 (CH).

The ^{13}C NMR spectrum of the compound (5) displayed the presence of CH of aromatic ring at 118-129, in addition the peak of the bond (CH2-O) at 64.64, which affirmed the presence of OH group.

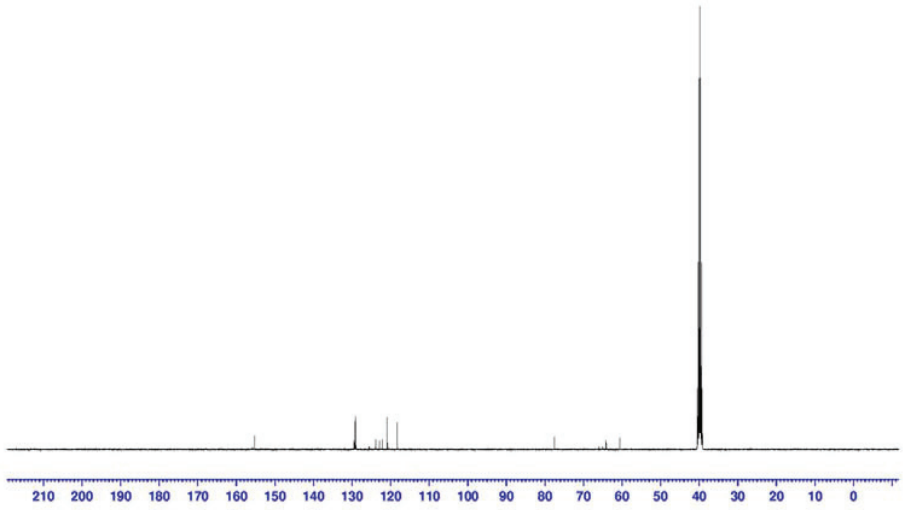


FIGURE 15. C-13 NMR Spectrum of Compound (5).

SUMMARY

The tetraethoxy glycoluril of the present study is a new class of cross-linking agents in powder coating, also we have introduced the synthesis of 1,4-diphenyl 2,3-dimethylol glycoluril, which is new glycoluril derivative through simple method via the condensation of 1,4-diphenyl glycoluril with formaldehyde in the presence of sodium hydroxide, the advantages of the presented syntheses are efficiency, high yield, short reaction time, cleaner reaction profile, simplicity not requiring highly specialized equipment and expensive reagents.

The identification of the derivatives was done by FTIR spectroscopy, HPLC and ^{13}C NMR spectroscopy.

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