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Methods of analysis of glycoluril and its derivatives

The present work provides the literature data generalization concerning analysis of glycoluril, its derivatives and related compounds that allows obtaining information about the structure and properties of these compounds. Basic methods for analysis of glycoluril and substances on the basis thereof are considered, advantages and disadvantages of these methods are described. The generalized results of the methods of analysis of glycoluril and its derivatives show that the majority of carried studies are focused on the revealing of purity and identification of related impurities for compounds that found practical application (drugs, monomers and polymers on the basis thereof). Consistent trend to active search of new methods to analyze macrocyclic and supramolecular systems synthesized on the basis of glycoluril is observed. The aim of the present review is to take attention of chemists to the most advanced methods of analysis of glycoluril and its derivatives with reference to promotion of further research. The literature analysis will be useful for researchers dealing with designing of new molecules based on glycoluril with given properties where the methods of process control and analysis of target compounds has a decisive importance.

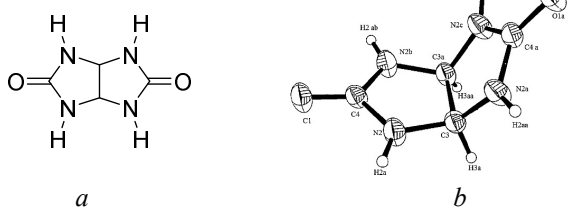
Keywords: glycoluril, N-substituted glycoluril, supramolecules, analysis, spectroscopy, HPLC, isomers.

Introduction

Bicyclic bisureas (glycolurils) belong to well-known azaheterocycles among which many valuable substances were founded and some of them are manufactured industrially. With that, there is no detailed information on the impurity profile in the glycoluril synthesis as well as on its assay procedures. Besides there is no literature data on the reliable methods of assay of glycoluril and its derivatives. Based on the aforesaid, this review aims to draw the attention of chemists and specialists in related fields to the methods of analysis of glycoluril and its derivatives.

1. General information about glycoluril

In the chemistry of nitrogen-containing heterocyclic compounds bicyclic bisureas occupy a special place, and 2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (glycoluril) **1** and its derivatives (Fig. 1) are among the most interesting of them.



a *b*

Figure 1. Structural formula of glycoluril **1** (1a) and its spatial configuration in the crystal (1b)

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The chemistry of glycolurils, primarily due to the multifunctionality of their structure, has undergone a rapid development reflected in the creation of valuable substances on the basis thereof for various fields of human activity: antitumor drugs [1–4], their derivatives are used as stabilizers and antipyretics in production of rubbers [5], crosslinking agents [6], fibre modifiers in the manufacturing of fabrics [7], preservatives and bactericidal agents [8, 9] and modifiers of wood properties [10]. Currently, glycoluril **1** is an essential component for the manufacturing of a number of macrocyclic compounds: molecular clips, bambus[n]urils, tiara[n]urils, and several classes of cucurbit[n]urils [11]. Some glycoluril derivatives have found application in genetic research [12, 13] for the rapid analysis of glycolipids [14] and biogenic amines [15]. N-methylol derivatives of glycoluril are used in the production of organic thin-film components of microelectronics [16]. Based on the supramolecular derivatives of glycoluril, new promising targeted antitumor [17], antibacterial [18] and other [19] drugs are being developed. Moreover, porous ungrafted [20] and grafted adsorbents [21], explosives [22–25], organic regioselective catalysts [26, 27] are made on the basis of glycoluril. Glycoluril is used as a catalyst for selective peroxidation in the fine organic synthesis of biologically active substances [28]. The undoubted advantage of glycoluril **1** is that it is nontoxic and not carcinogenic in the absence of impurities [29, 30].

Glycoluril **1** is a multifunctional compound having the urea fragment that indeed determines the properties of molecule 1 caused by the presence of two reactive centers in the molecule, namely, four electron donating (NH) groups and two electron withdrawing (C=O) groups. Direct methods for the analysis of glycoluril **1** are based on its properties of a highly active n-nucleophile and a substantially deactivated p-nucleophile. On the other hand, molecule 1 has two symmetry planes, namely, σ_1 and σ_2 (Fig. 2), that pass along the methine CH–CH bridge and two carbonyl oxygen atoms, respectively [31].

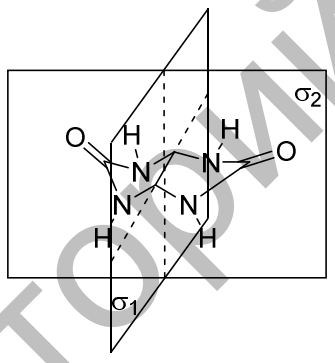


Figure 2. Symmetry planes σ_1 and σ_2 in glycoluril molecule

However, when studying the crystal structure of glycoluril **1** by X-ray structural analysis (Fig. 1b), it was found for the first time that, in addition to symmetry, the conformation of the bicyclic skeleton 1 due to the rigidity of the cis-coupling of annelated imidazolidinone rings has a folded structure in the form of a "half-opened book" [32], where the dihedral angle between the imidazolinone rings in molecule 1 is 124.1°. Moreover, it was found that nitrogen atoms in the molecule 1 are equidistant from each other. Hydrogen atoms with methine carbon are cis-oriented, and imidazolidinone rings are characterized by an almost flat structure with a slight deviation of the carbonyl groups from the middle plane.

A significant limiting condition for the effective analytical determination of glycoluril is its low solubility in water and organic solvents, although most of its N-substituted derivatives are already free of this disadvantage (see Table 1 for the example of N,N,N,N-tetraacetylglycoluril).

In addition, due to the widespread use of glycoluril **1** and its derivatives, there is a need for analytical methods to determine glycoluril and its related impurities. It is reliably known that targeted glycoluril **1** may contain closely related substances, such as hydantoin [33] and other unidentified impurities that accompany them after synthesis [34]. Moreover, in the open literature, there is no complete information about the profile of impurities and methods for their quantitative determination. The publications do not also provide reliable methods for the quantitative determination of glycoluril. Manufacturers and suppliers of glycoluril normalize only the elemental composition (%C, %N) [35] that is insufficient since the related glycoluril impurities often have similar elemental composition, therefore, elemental analysis cannot serve to unambiguously assess the purity of the desired compound.

Table 1

Comparative physical-chemical properties of glycoluril 1 and N,N,N,N-tetraacetylglycoluril

Compound	Glycoluril (**1**)	Tetraacetylglycoluril
Melting point	360 °C (with decomposition)	236–238 °C
Solubility	Insoluble in halocarbons, alcohols, ketones, esters, upon heating it is soluble in DMSO, DMF, HCOOH, AcOH, Ac_2O	Insoluble in H_2O, alcohols, soluble in CH_2Cl_2, $CHCl_3$, HCOOH, AcOH, Ac_2O, MeCN
IR spectrum, ν, cm^{-1}	(KBr): 3209 (NH), 1675 (C=O)	(Nujol): 1753, 1733 (C=O), 1695 (C=O)
NMR ^1H (400 MHz, δ, DMSO-d_6, ppm)	5.24 (c, 2H, CH), 7.16 (c, 4H, NH)	6.38 (c, 2H, CH), 2.38 (c, 12H, CH_3)
NMR ^{13}C (100 MHz, δ, DMSO-d_6, ppm)	160.30 (C=O), 64.60 (CH)	169.42 (C=O acetyl), 151.48 (C=O), 62.61 (CH), 25.11 (CH_3)

Currently, to analyze glycoluril **1**, its N- and C-derivatives and their related compounds, a number of analysis methods are used that allow obtaining a significant amount of information about the structure and properties of these substances. Below we present the main methods for the analysis of glycolurils and compounds synthesized on the basis thereof. We discuss and critically examine the advantages and disadvantages of the methods proposed.

2. Spectral analysis methods

Spectral analysis methods are widely used to investigate and analyse glycoluril **1** and its derivatives. To study the structure and properties of glycoluril, various spectral analysis methods are used: spectroscopy in the ultraviolet (UV), visible, and infrared (IR) regions, nuclear magnetic resonance spectroscopy (NMR), mass spectrometry (MS) and, less commonly, other methods of spectral analysis.

2.1. Infrared spectroscopy

One of the most widely used methods to analyze glycolurils is the IR spectroscopy method that is most often used in the middle spectral region, i.e. from 2,500 to 25,000 nm (400 to 4000 cm^{-1}). IR spectroscopy is used to identify and confirm the structure of glycoluril [36, 37], its oligomers [38, 39], polymers [40], macrocyclic derivatives cucurbiturils [41], N-alkyl derivatives [42], N-acyl derivatives [43], C-phenyl glycolurils [44], C-amino derivatives [45], organosilicon [46], phosphorylated [47] and mercapto derivatives [48] as well as multifunctional glycoluril derivatives of complex composition [49]. There are known examples of the analysis of the confirmation of various N nitro derivatives of glycoluril: mono-, di-, tri-, tetranitroglycolurils and nitrophenyl derivatives [50, 51] by IR spectroscopy in a disk of potassium bromide and by IR spectroscopy of diamond attenuated total reflectance (DATR FTIR).

The IR spectrum of glycoluril derivatives contains characteristic signals of vibrations of chemical bonds included in the structure of glycoluril (Table 2).

Table 2

Characteristic absorption bands in the IR spectra of glycolurils

Wavenumber, cm^{-1}	Bond, type of vibrations	Comment
3350–3200	N–H, stretching	No signal in N-tetrasubstituted derivatives
3000–2048	C–H, stretching	
1680	C=O, stretching	Carbonyl group of N-unsubstituted fragment
1640	C=O, stretching	Carbonyl group of N-substituted fragment
1500	C–H, bending	
1100	C–N, stretching	

As can be seen from the data (Table 2), the infrared spectroscopy method allows identifying and confirming the structure of glycoluril derivatives. The method allows obtaining the information about the presence of several types of bonds and functional groups in the structure of glycolurils shown in the table. Moreover, IR spectroscopy can be used to identify target compounds by the "fingerprints" principle, when the IR

spectra of the two glycoluril derivatives completely coincide, one can conclude that they are completely identical.

The disadvantages of this method are its comparative insufficient specificity, low resolution, and inability to analyse mixtures of substances with a similar structure. IR spectroscopy of glycolurils is practically unsuitable for quantitative analysis and features low sensitivity to the water content in the sample.

2.2. UV-Vis spectroscopy

The method of spectrophotometry in the visible region is limitedly used for the indirect quantitative determination of glycoluril [52]. Thus, a method is known based on the photometric determination of the reaction product of glycoluril, sodium arsenite and sodium nitroprusside in the presence of Trilon B. However, the reaction chemistry is not given in the work that significantly complicates the interpretation of the results. At the same time, the proposed method does not provide chemoselectivity of the ongoing processes and does not allow analysing the glycoluril content in the solution in the presence of its precursors, namely, urea and hydantoin.

In the structure of unsubstituted glycoluril **1** there are no chromophoric groups that provide an intense absorption in the UV spectrum with a wavelength above 200–220 nm. First of all, because of this, the UV spectroscopy is used to analyse the modified glycolurils, e.g., phenyl [53], pyridyl [54], and naphthyl derivatives [55], due to the presence of analytical signals in the spectra of the corresponding glycoluril derivatives caused by the interaction of aromatic fragments of the molecules with the irradiation.

The nature of the analytical signal in the direct spectrophotometric determination of aromatic derivatives of glycoluril is determined primarily by the spectral properties of aromatic substituents and, to a lesser extent, by the properties that arise from p-π conjugation of the fragments of substituted glycolurils. At the same time, the bicyclic glycoluril fragment has practically no effect on the absorption: the general view of the spectrum and the absorption maxima of 3-methyl-6-phenylglycoluril and the precursor, phenylurea, practically coincide (Table 3).

Table 3

Comparison of absorption maxima positions in the UV range for 3-methyl-6-phenylglycoluril and phenylurea

Compound	Absorption maxima, nm
Phenylurea [56]	232 274
3-Methyl-6-phenylglycoluril [53]	217 230 274

Thus, it is obvious that the UV spectroscopy is not a specific method for derivatives and predecessors of glycoluril, namely, acyclic ureas since it does not allow selective assessment of the concentration and properties of the corresponding substances with their possible simultaneous presence in the mixture. The low specificity of the UV spectrophotometry makes it unsuitable for confirmation, identification, and quantification of glycoluril **1** and its derivatives without preliminary sample preparation, e.g., those associated with the separation of mixtures of closely related substances.

The method of fluorimetry differs from the absorption spectroscopy by significantly higher sensitivity and specificity that is used in the analysis of some glycoluril derivatives. Fluorimetry is widely used to analyze glycoluril derivatives capable of fluorescence or its quenching [57]. For instance, the fluorescence parameters of bis-tolane glycoluril derivatives were studied and the excitation and emission spectra were obtained [58]. The absorption region of the glycoluril derivatives under consideration is in the range from 200 nm to 350 nm, the absorption maximum is at 300 nm (π→π* transition), the emission region is 400–600 nm, the emission maxima are 406 and 432 nm. In the course of the studies, a selective fluorescence quenching of bis-tolan glycoluril derivatives in the presence of nitrophenols was shown. The mechanism of the observed effect, as indicated in the work, can be presumably associated with the simultaneous occurrence of hydrogen bonds between the hydroxyl group of nitrophenol and the carbonyl group of glycoluril as well as the π-π-stacking interaction [59]. Interestingly, the phenols that do not contain nitro groups in the structure do not affect the changes in the fluorescence intensity.

The ability of dansyl glycoluril derivatives to fluorescence was studied in the presence of a wide range of metal ions: Ag^{+}, Na^{+}, Li^{+}, Fe^{3+}, Cr^{3+}, Cu^{2+}, Pb^{2+}, Ni^{2+}, Zn^{2+}, Co^{2+}, Cd^{2+}, and Hg^{2+} [60]. The authors showed

that there is a dependence of the intensity of the light emitted by the complex on the metal nature. For instance, it was found that the addition of Cu^{2+} or Hg^{2+} ions leads to a decrease in the fluorescence intensity, while Pb^{2+} had practically no effect, and the remaining ions increase the fluorescence intensity of the dansyl glycoluril derivatives. Presumably, these properties are associated with the structure of the electron shell of metal atoms, their ionic radius, and the ability to complexation.

The opportunity for indirect fluorimetric determination of macrocyclic derivatives of glycoluril, namely, cucurbit[7]uril and cucurbit[8]uril, was demonstrated [61–64]. Cucurbit[n]urils specifically affect the fluorescence intensity of proflavin, pyronin, oxonin, Congo red, methylene blue, and other organic dyes. Thus, when interacting with the glycoluril-based macrocyclic compounds, the fluorescence intensity changes, e.g., at different pH, the acridine red fluorescence intensity increases naturally with the addition of cucurbit[7]uril.

A similar indirect method of fluorimetric determination was proposed to confirm the formation of a complex of cucurbit[n]urils with camptothecin [65]. Since the change in the fluorescence intensity of camptothecin with the addition of an equimolar amount of cucurbit[8]uril linearly decreases with the increasing concentration of the added cucurbit[8]uril until the point at which the molar ratio of the reagents is 1:1, the authors suggest the formation of a "guest-host" complex with the molar ratio of cucurbit[8]uril and camptothecin of 1:1 ratio.

The fluorimetric quantitative determination of cetylpyridinium in blood and urine with a limit of quantitation of 7 μg/l [66] is based on the differences in the emission spectra of complexes of cucurbit[7]uril-palmitin and free palmitin: the palmitin alkaloid is displaced by cetylpyridinium from the guest-host complex in this case, and a new emission maximum corresponding to free palmitin appears on the fluorescence spectrum. Due to the high selectivity of the fluorimetry method and the high affinity of the components of the "guest-host" complexes, high specificity of the method is achieved: the determination of cetylpyridinium does not interfere with the blood plasma components, anionic surfactants, amino acids, metal cations, many remedies, etc.

Using fluorimetric titration, a controlled transition was studied at different pH values of the rotaxane-like complex of cucurbit[6]uril with diaminobutane in various forms that differ in the position of the macrocyclic ring relative to the diaminobutane fragment of the molecule (Fig. 3) [67, 68].

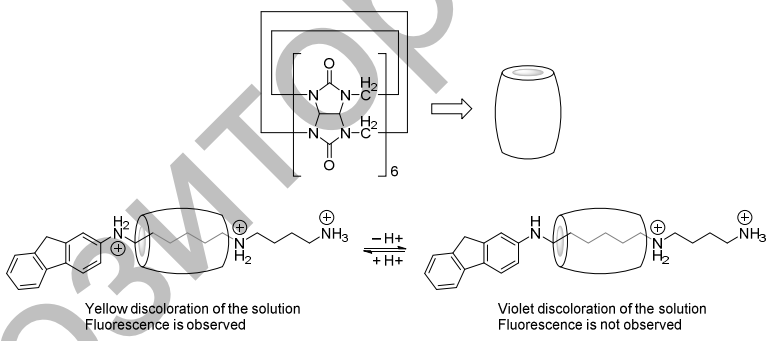


Figure 3. Dependence of the fluorescence of the "guest-host" complex on the relative position of the cucurbit[6]uril fragment in the structure

The authors found that with an increase in pH, the fluorescence intensity decreases, while at a pH value of 8.1, the fluorescence of the complex completely disappears indicating a quantitative transition of the complex to a non-fluorescent state.

The found fluorescence effects of such compounds can be used for the selective quantitative determination of "guest-host" complexes based on cucurbit[n]urils.

It is noteworthy that the fluorimetry is the most specific method for the direct determination of glycoluril derivatives containing conjugated aromatic fragments in the structure with the ability to fluorescence. The key advantages of the method are high sensitivity (the minimum detection limit is ~10–17 g), the availability of equipment, the speed of analysis, and the safety of the structure of the substances being determined.

The main disadvantages of this method are the inability to obtain an analytical signal for non-fluorescent compounds, strict sample preparation requirements (the analytical signal is affected by the impurities in solvents, etc.) as well as the lack of flexibility of the method: the emission wavelength is an individual characteristic of the substance and cannot be changed. Thus, when two related compounds with close

emission wavelengths are in the sample, it is extremely difficult to achieve analysis selectivity without using preliminary separation of the sample components.

2.3. NMR spectroscopy

NMR spectroscopy is one of the most widely used methods in the analysis of glycoluril derivatives. An investigation of the NMR spectra of glycolurils makes it possible to determine accurately the spatial configurations of molecular symmetry when the hydrogen and carbon atoms of the bicyclic framework are expressed by equivalent signals. Using chemical shifts ^{1}H and ^{13}C in the NMR spectra of N-substituted glycolurils, it is possible to identify the type of substituent.

An analysis of chemical shifts in the ^{1}H and ^{13}C NMR spectra of glycoluril and its derivatives (library of 86 compounds) was carried out to determine the influence of the donor-acceptor nature of substituents on changes in the electron density in the bicyclic framework from the position of symmetry and asymmetry [69]. The range of changes in the chemical shifts of key atoms in the glycoluril series includes NH protons (7.49–9.96 ppm); CH–CH (5.14–6.63 ppm); carbon C=O (151.40–161.79 ppm); CH–CH (61.55–74.86 ppm). A general analysis of the ^{1}H and ^{13}C NMR spectra of the studied glycolurils allowed the authors to accurately identify the spatial symmetry configurations of the molecules, where the enantiotopic hydrogen and carbon atoms of the bicyclic framework (σ1 and/or σ2, Fig. 2) appear as equivalent signals. It was established that according to the ^{1}H and ^{13}C chemical shifts in the NMR spectra of the N-substituted glycoluril framework, glycolurils with electron-withdrawing substituents for the screening of carbon atoms of C=O groups and electron-donating substituents for de-screening of CH–CH carbons can be distinguished. This is due to the redistribution of electron density and the occurrence of local paramagnetic contributions due to anisotropy.

In the course of a general analysis of the ^{1}H and ^{13}C NMR spectra of the studied glycolurils, it was concluded that screening of the carbonyl atom C=O in the imidazolidinone fragment of the molecule is observed for any type of N- or C-substitution. The generalizations made allow clearly distinguishing between symmetric and asymmetric molecules and distinguish impurity signals that can often accompany the synthesis of glycolurils and compounds on the basis thereof. According to the ^{1}H and ^{13}C NMR spectra, glycolurils can be clearly distinguished with electron-withdrawing N-substituents by screening the signals of the carbon atom of C=O groups, and electron-donating N-substituents by de-screening of CH–CH carbon.

In another review paper [70], a comprehensive systematic analysis of chemical shifts in the ^{31}P and ^{13}C NMR spectra of 89 phosphorus- and urea-containing heterocycles that differ in the valence state of the phosphorus atom, the size of the cycle, and the method of connection of the cycles was carried out. A comparative analysis of the chemical shifts of the phosphorus atom in phosphorus- and urea-containing heterocycles with five-coordinated phosphorus showed that they mainly undergo a negative shift, and their location mainly depends on the hybrid state of P in the cycle and the way the cycles are connected. An attempt of a comparative analysis of the chemical shifts of the –C=O carbonyl group in phosphorus- and urea-containing heterocycles did not reveal the significant differences due to their changes in a narrow range of values (151–156 ppm), regardless of the valence state of the phosphorus atom in the cycle and the way of connection of the cycles (e.g., in spiro- and bicyclic compounds). Of interest is only some screening of the C=O group in phosphorus- and urea-containing heterocycles compared to urea itself (159.5 ppm) and octane-bicyclic bisurea glycoluril **1** (161.9 ppm). This observed effect is apparently determined by an increase in steric stresses (compression) in phosphorus- and urea-containing heterocycles due to limitations in the flexibility of their skeleton, and, hence, an increase in the order of the amide bond. The informativity of analysis of the NMR spectra of phosphorus- and urea-containing heterocycles to some extent is reduced by the absence of chemical shifts of NH groups, but this circumstance is because almost all synthesized and identified phosphazacycles listed in the work contain substituents at nitrogen atoms.

Apparently, due to the low content of natural ^{15}N and ^{17}O isotopes and high complexity of the analysis, there is practically no information in the literature on the use of NMR on ^{17}O nuclei for several glycolurils, and to obtain the information on the position of chemical shifts of ^{15}N glycoluril **1** and its derivatives the 2D heterocorrelations of the ^{1}H–^{15}N spectra [71] and the establishment of the direct coupling constant ^{15}N–^{1}H are usually used [72].

Thus, NMR spectroscopy is a serious tool to identify and confirm the structure of glycoluril derivatives. This method is the most reliable way to study the structure of substituted glycolurils, i.e., the position, amount, and type of N-substituents. A particular advantage of NMR spectroscopy is that the method allows establishing the spatial configuration of the glycoluril symmetry with high accuracy. A number of studies

have demonstrated the opportunity to use NMR spectroscopy for the analysis of glycoluril-based supramolecular systems. Thus, a detailed analysis of ^{13}C NMR spectra was performed for the identification of a series of cucurbit[5–8]urils [73]. In Ref. [74] during the simulation of the binding process of the SF5 complex with cucurbit[6]uril, the NMR shifts of the formation of the inclusion system were calculated and compared with the experimental values. It was proposed to include the prochiral dimethyl sulfonic derivatives of biphenyls in the cucurbit[7,8]uril cavity that allows recording the proton chemical shifts due to the splitting of signals of a pair of methyl groups [75].

A key disadvantage of NMR spectroscopy as a method of analysis of glycoluril derivatives is its non-selectivity for related compounds when substances are present in the sample as a mixture. In addition, an important disadvantage is the relatively high cost of NMR spectrometers and the need to use deuterated solvents.

2.4. X-Ray structural analysis

The geometric features of glycolurils (Figs. 1 and 2) essentially determine the opportunity to synthesize and study supramolecular compounds on the basis thereof. In the course of such studies, it was found that glycolurils acted as building blocks of such polycyclic condensed systems as cucurbit[n]urils [76–78] and bambus[n]urils [79, 80] that have a number of unique physical & chemical properties.

A study of the spatial arrangement of molecules determined by intermolecular interaction and polarization of bonds in synthons often provides initial information on the organization of supramolecules on the basis thereof. The obtained information on the structure of molecular ensembles extracted from the crystal structures of synthons is used to judge on the structure of liquids and solutions, molecular clusters, and other supramolecular structures.

Taking into account the above, the analysis of the results of X-ray structural studies of glycoluril **1** and its derivatives (a library of 39 compounds) was carried out [81] and the structural features of these compounds were revealed, namely, the effect of substituents and their types on the geometry of molecules, and the formation of hydrogen bonds in crystals that ultimately determines the ability of glycolurils to form complexes, macro- and supramolecules. The result of the generalization of X-ray structural studies of a wide range of glycolurils made it possible to determine the centers of formation of hydrogen bonds and those participating in complexing since in these cases it is the elongation of precisely those bond lengths that are involved in intermolecular binding.

An analysis of the structural parameters of N-alkyl glycolurils and metal complexes showed the presence of conformational similarity of the molecular scaffolds of the compounds studied. It was shown that N-alkyl substituted glycolurils are potentially polydentate ligands (due to the contribution to the coordination of four nitrogen atoms and two oxygen atoms) and can fulfill both a monodentate and a bidentate bridging function with d-metals via binding of urea fragments through C=O groups depending on the coordination number of the metal atom.

For complexation, oxygen and nitrogen atoms are the most possible coordination centers in glycolurils, however, coordination through nitrogen atoms is usually sterically hindered due to its predominant pyramidal structure, especially since this center has a reduced electron density with respect to oxygen.

The basic geometric parameters of the bicyclic framework for N-arylalkyl glycolurils are similar to those for N-alkyl glycolurils. When a substituent with a strong electron-withdrawing property is introduced into the glycoluril skeleton, the bond lengths of the C–N amide fragment increase causing a decrease in the nature of doubling and an increase in the nature of the C=O double bond. This fact can be explained by more efficient hybridization of carbonyl carbon atoms to the sp^2 state and to the sp^3 state in the C–N fragment occurring for these compounds.

When considering the dihedral angles of the studied glycolurils together, it was concluded that for any type of substitution (C- or N-) in the glycoluril framework, the values of the dihedral angles change towards their reduction, i.e., the effect of "collapsing" of annelated imiadazolidinone cycles is observed. However, when considering C1–C5 substituted glycolurils, a progressive decrease in the dihedral angle in these molecules occurs with an increase in the size of the hydrophobic substituent (H>Me>Ph compounds). The same pattern is observed in a series of compounds in the presence of an electron-withdrawing functional group ($H>NH_2>CO_2Et$) in C1–C5-substituted glycolurils.

The performed studies on the structure of glycolurils by X-ray structural analysis turned out to be useful for researchers involved in the designing of new molecules based on glycoluril **1** with predetermined properties in the synthesis of biologically active compounds, molecular clips, and supramolecular systems.

2.5. Mass-spectrometry

Mass spectrometry also finds its place in the study of glycoluril derivatives. The "direct input" mass spectrometry is most often used when a mixture of substances is introduced into the ionization source of the mass spectrometer without prior separation by chromatographic methods. A method of mass spectrometry with electrospray ionization (ESI-MS) of N-alkylated glycoluril dimers without their preliminary chromatographic separation was proposed [82] In the given mass spectrum, three signals of molecular ions of a mixture of glycoluril dimers were observed (Fig. 4).

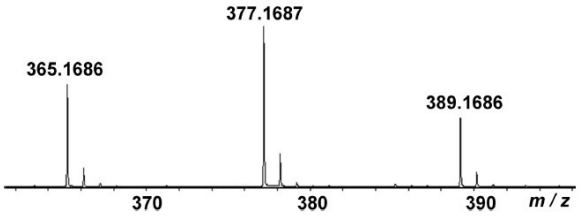


Figure 4. Mass spectrum of the mixture of glycoluril dimers without decomposition

The electron-ionization mass spectrometry (EI-MS) is widely used to confirm the structure of low molecular weight glycoluril derivatives [83]. Using this ionization method during mass spectrometric studies of synthesized samples, mass spectra of a large number of N-alkylated and N-acylated glycoluril derivatives are described. However, the EI-MS ionization mode used in mass spectrometers is de facto incompatible with liquid chromatography: modern EI-HPLC solutions do not provide sensitivity comparable to atmospheric pressure ionization modes (API). Thus, this method cannot be used to study and analyse mixtures of non-volatile compounds that is characteristic of many glycoluril derivatives.

Mass spectrometry was used to study the composition and decomposition paths of glycoluril nitro derivatives. It was shown that dinitroglycoluril, when introduced into the ion source of electronic ionization, is characterized by a number of ions m/z=232, 231, 215, 183, 142, etc., on the mass spectrum [23]. The key ionization pathways are related to the breaking of C–N and N–H bonds as well as OH group losses. A number of signals in the mass spectrum may not be associated with dinitroglycoluril, and their source may be connected with possible impurities formed during the synthesis of glycoluril. Dinitroglycoluril labeled with 2D and ^{15}N atoms was shown to undergo similar fragmentation without significant differences in the intensity of the fragment ions.

In Ref. [84], mass spectra were obtained from a study of the isolated samples for a number of isomeric dimethylglycolurils **3–5** by GC-MS (Fig. 5).

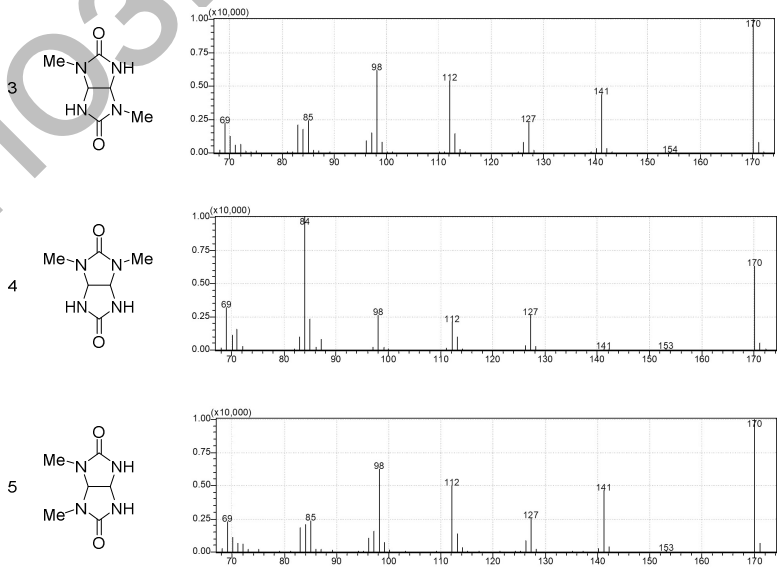


Figure 5 Structural formulas and mass spectra for isomers of N-dimethylglycolurils

As can be seen from the mass spectra of these compounds, the m/z values of the fragment ions of substances **3** and **5** are absolutely identical, therefore, gas chromatography-mass spectrometry can only be used to identify isomer **4**. The authors assumed that the absence of visible differences in fragmentation **3** and **5** are associated with similar trajectories of possible fragmentation paths **3** and **5** and the difference in the proposed mechanism of fragmentation of substance **4** (Fig. 6).

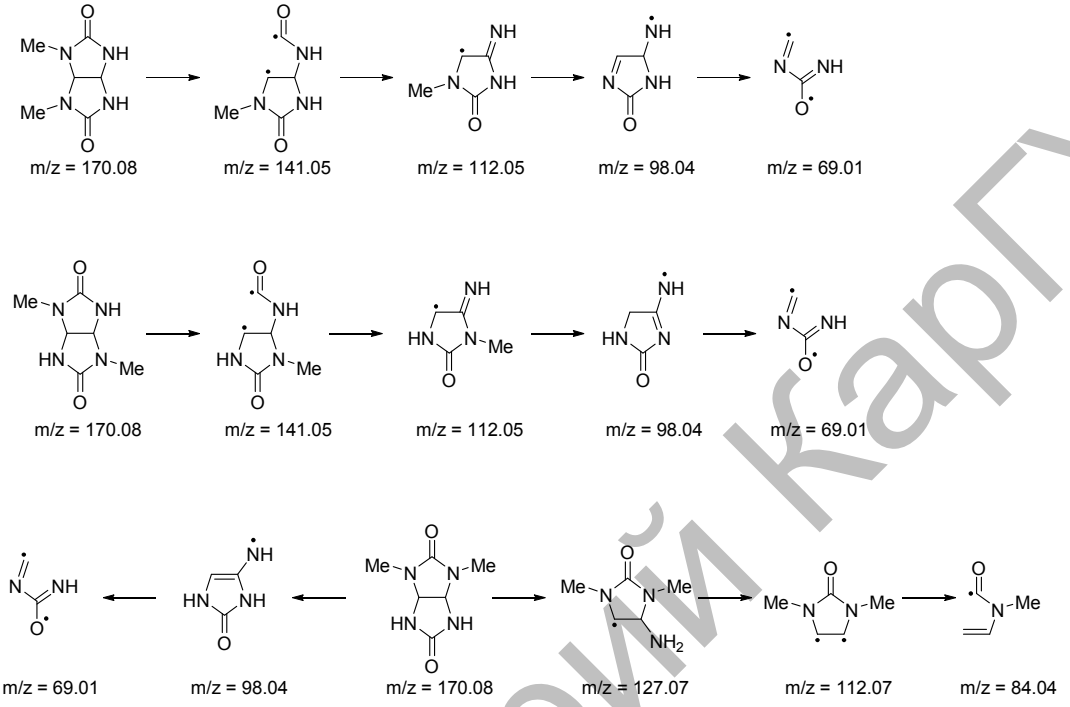


Figure 6. Tentative scheme of fragmentation of molecules 3, 4, and 5 during electron ionization

The proposed fragmentation scheme shows that substances **3** and **5**, when they are electronically ionized, form a series of successive ion radicals with similar m/z values. Contrary, during ionization, substance **4** forms two sequences of radical ions, and this mechanism excludes the possibility of the formation of a radical ion with a value of m/z=141. By the presence of this ion, it is possible to judge whether a particular N-dimethylglycoluril belongs to isomer **4** or one of isomers **3** or **5**. The results of the studies allow reliable identification of isomeric dimethylglycolurils **3**–**5**.

Refs. [85, 86] describe the use of the ESI-TOF-MS high-resolution mass spectrometry method to study the glycoluril derivatives. However, mass spectrometry was used without prior chromatographic separation to confirm the structure of oligomeric glycoluril derivatives. The authors of the work showed that the "Negative" ionization method can be used to obtain the analytical signal, while the formation of a number of adducts of the expected composition was observed, e.g., $[M^{+}Br]^{-}$, $[M^{+}Cl]^{-}$, $[M^{+}F]^{-}$, $[M^{+1}H\text{-}3Na]^{2-}$.

The direct ionization mass spectrometry "Positive" is used to identify monomeric glycolurils, in particular, to identify phosphorylated derivatives of glycoluril [26], N,N′-diacetylglycolurils and N,N′-dibenzylglycoluril [87]. In both cases, molecular ions of the corresponding glycolurils with the composition $[M^{+}H]^{+}$ were detected; the fragmentation mechanism was not described by the authors.

To study the composition and quantitative determination of glycoluril derivatives by mass spectrometry, the method of matrix-associated laser desorption and ionization (MALDI-MS) was proposed [88]. The method is based on the soft ionization of molecules under the influence of laser radiation in the presence of acids or bases. The MALDI-MS allows the analysis of supramolecular glycoluril derivatives in matrices of complex composition, e.g., biological objects, without preliminary sample preparation and separation into components. Moreover, the advantages of the method are the high sensitivity (minimal detection limit is $\sim 10^{-15}$ g) and the ability to analyze compounds with high molecular weights (up to 150 kDa).

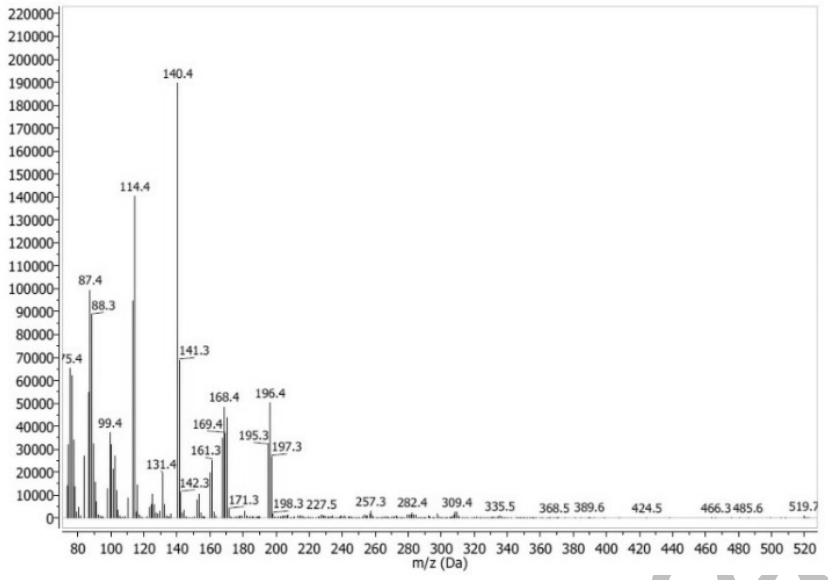


Figure 7. An example of mass spectrum of glycoluril derivative [26]

The widespread use of liquid mass spectrometry is largely hindered by the high cost of the equipment for the study as well as the complexity of the method and the requirements for the purity of the sample and the reagents and materials used.

2.6. Other spectroscopic methods

The method of nuclear gamma resonance spectroscopy (Mössbauer spectroscopy) is limitedly used to analyse glycoluril derivatives containing iron atoms in the structure: cucurbit[n]uril ferrocenes [89] and other glycoluril-based supramolecular complexes [90].

Raman spectroscopy is also used to a limited extent in the study of glycoluril derivatives, in particular, to control the course of reactions and study the structure of some glycoluril derivatives, namely, guest–host complexes. In particular, the difference between the signals on the spectra of new glycoluril-based complexes and those of their components was shown [91–93]. In particular, when using this type of spectroscopy, the spectrum cannot be deciphered in details, it is used only to monitor the synthesis and subsequently identify the compounds by the "fingerprints" principle.

EXAFS spectroscopy is a spectroscopic method based on the interpretation of the fine structure of X-ray absorption spectra. The Refs. [94–96] show examples of deciphering the 3D structure of cucurbit[n]uril complexes and metal compounds: Cu(II), U(VI), and Eu(III) (Fig. 8). The EXAFS spectroscopy method allows determining the interatomic distances, coordination numbers, valence states of atoms, and other parameters. The rarity of use of this method with respect to glycoluril derivatives is explained by the high cost of equipment and the inability to determine the spectral parameters of compounds that do not contain elements with a molecular weight below 20 in the structure.

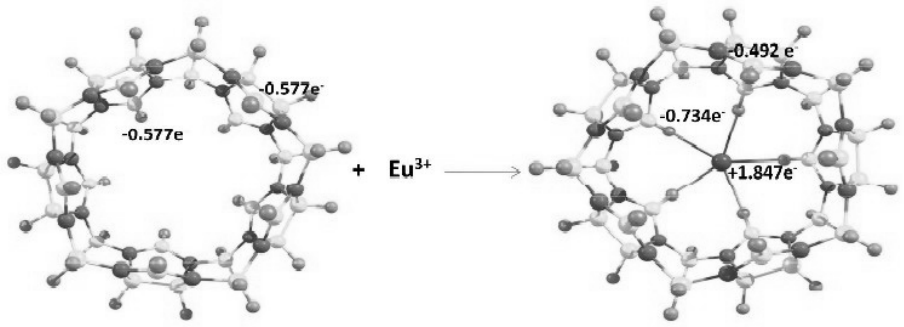


Figure 8. An example of visualization of EXAFS spectra of a complex of cucurbit[5]uril and Eu(III) [96]

3. Electrochemical methods of analysis

Electrochemical methods to analyze glycolurils are presented in very rare cases. Thus, the voltammetry method is limitedly used for the direct determination of glycoluril derivatives, e.g., for analysis of guest-host complexes based on cucurbit[7]uril and substituted metallocenes: ferrocene and cobaltocene [97, 98], and only due to the electrochemical activity of metals in these compounds.

Glycoluril derivatives are used as electrode modifiers. To analyze cholesterol in blood plasma and food products, the authors of Refs. [99,100] applied the electrode modification to a phosphorylated glycoluril derivative that does not have its own electrochemical activity.

The opportunity to study macrocyclic complexes of glycoluril with zinc, manganese, cobalt, nickel, and cadmium by polarography with a dropping mercury electrode was studied [101, 102]. The relationship between the analytical signal, the concentration of metal, cucurbit[n]uril, and the interaction constant of the components of the guest-host complex was shown.

Electrochemical methods of analysis are rarely used to study and analyse glycoluril derivatives. Obviously, this phenomenon is associated with their direct physical-chemical properties, namely, with low solubility and high chemical inertness.

4. Chemical methods of analysis

Currently, glycoluril derivatives are rarely analysed using "traditional" chemical methods of analysis. The study of the decomposition products of cucurbit[n]urils was carried out using a combination of instrumental physical-chemical and chemical analysis methods [103] in the latter case, using qualitative reactions. The evolution of ammonia and the formation of sodium carbonate during the boiling of glycoluril derivatives in a 30 % sodium hydroxide solution was confirmed by the colouring of the indicator paper.

The quantitative determination of N-alkylated glycoluril derivatives can be carried out using the Kjeldahl method [104]. To quantitatively determine the N,N,N,N-tetramethylglycoluril, the methods of cerimetric and iodometric titration can also be used [105]. These analysis methods are non-selective in nature and are suitable only for analysis of the mass fraction of the main substance provided that the impurities are identified and analysed by another method, e.g., chromatography.

5. Chromatographic methods of analysis

5.1. Gas chromatography (GC)

Several examples of the gas chromatographic analysis of glycoluril derivatives are known. For instance, it was proposed to separate fully alkylated glycoluril derivatives: N,N,N,N-tetramethylglycoluril, N,N,N,N-tetraethylglycoluril, N,N,N,N-dimethyldiethylglycoluril, and N,N,N,N-isopropyltrimethylglycoluril using a one-meter-long packed chromatographic column filled with stationary phase G3 OV-17 (50 % diphenyl-, 50 % dimethylpolysiloxane) [104].

A method to analyse the content of N,N,N,N-tetramethylglycoluril in biological fluids after extraction with chloroform was proposed [106]. The method consists in gas chromatographic separation of N,N,N,N-tetramethylglycoluril from the matrix components using a steel packed column filled with chromosorb-G, modified with 3 % diphenyldimethylpolysiloxane OV-17. The carrier gas is nitrogen, isothermal chromatography is carried out at 240 °C, the gas flow rate at the column outlet is 35 ml×min^{-1}. The injection volume of the solution is 2 μl.

The method of analysis of N,N,N,N-tetraethylglycoluril by gas chromatography using a capillary chromatographic column was recommended [107]. Analysis conditions: glass column 0.26 mm × 25 m, stationary phase was Xe-60 (cyanoethyl methylsiloxane), isothermal analysis, column temperature was 185 °C, carrier gas flow rate was 2 ml min-1; stream division was 1/20. The internal standard was N,N-dimethyl-N,N-diethylglycoluril. Using this method, the retention times for N,N,N,N-tetraethylglycoluril and N-dimethyl-N-diethylglycoluril were 20 and 24 min, respectively.

5.2. Thin-layer chromatograhy

The chromatography method to separate and analyze glycoluril derivatives is used less frequently than spectral analysis methods. Most often, in the publications concerning glycoluril derivatives, the authors note that the reaction progress is monitored by TLC [36, 108–111]. However, a fairly common case is that the conditions for chromatographic analysis and typical chromatograms and photographs of TLC plates are not provided.

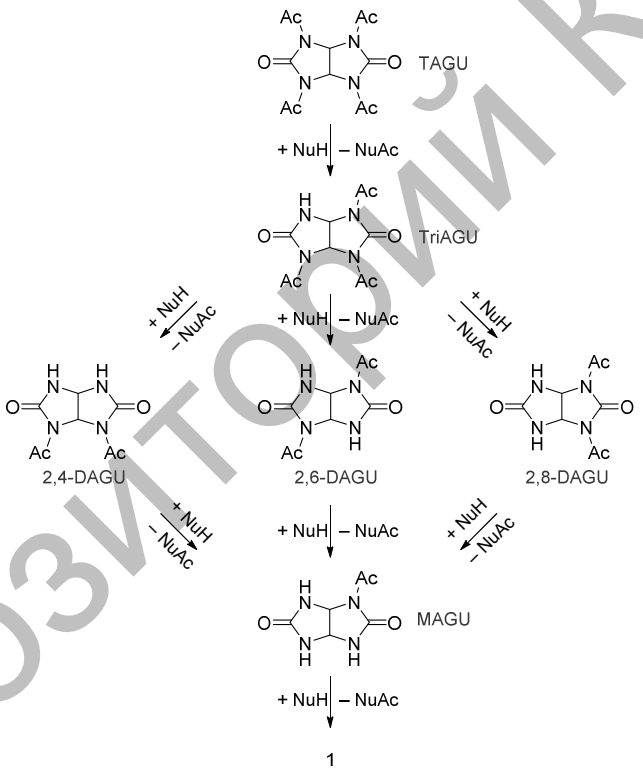
The hydrolysis of tetraacetylglycoluril under the action of various nucleophilic reagents at room temperature and pH=10 in an aqueous-alcoholic medium was studied in details (Fig. 9) [112].

The authors found that the hydrolysis of compound 2 occurs stepwise through the formation of a series of N-acetylglycolurils: triacetyl derivative; isomeric diacetylglycolurils; monoacetyl derivative and finally glycoluril **1**. The TLC is carried out on tetraacetylglycoluril hydrolyzate on kieselguhr plates, the eluent is chloroform-methanol-ethyl acetate (7:2:2) followed by the development with hydroxylamine and ferric chloride that allowed separating and establishing the Rf values for the acylated glycolurils (Table 4).

Table 4

The R_f values for products of tetraacetylglycoluril hydrolysis

Substance	R_f
1	0.04
TAGU	0.84
TriAGU	0.76
2,6-DAGU	0.68
2,4-DAGU	0.35
2,8-DAGU	0.61
MAGU	0.21



TAGU = TetraAcetylGlycolUril, TriAGU = TriAcetylGlycolUril, DAGU = DiAcetylGlycolUril, MAGU = MonoAcetylGlycolUril

Figure 9. Scheme of tetraacetylglycoluril hydrolysis

Individual acetylglycolurils were characterized using NMR and mass spectrometry.

The TLC method was used to confirm the structure and content of impurities of N,N,N,N-tetramethyl glycoluril, the active substance of the remedy "Adaptol" (JSC "Olainfarm", Latvia) [113]. The identities of other alkylated glycoluril derivatives were also controlled by TLC [114]. The separation was carried out using "Silufol" plates as the stationary phase. The plates were chromatographed using supported samples with an ascending method with a solvent mixture of acetone-hexane in a volume ratio of 5:2. The plates were developed by keeping in the iodine chamber for 1–2 min. Under these conditions, the R_f values for N,N-dimethyl-N,N-diethylglycoluril and N,N,N,N-tetraethyl glycoluril were 0.41 and 0.49, respectively.

Similar chromatographic conditions for the analysis of N-dimethyl-N-diethylglycoluril and its impurities, N-monomethyl-N-diethylglycoluril, were proposed [105]. The stationary phase was "Silufol", the mobile phase was a mixture of chloroform and methanol in a ratio of 8:1 v/v. The development was carried out by spraying with a 10 % alcohol solution of the phosphoromolybdic acid followed by heating the plate to a temperature of 140 °C. When using this chromatographic system, the R_f values for N,N-dimethyl-N,N-diethylglycoluril and monomethyl-N,N-diethylglycoluril were 0.55 and 0.37, respectively.

In the vast majority of cases, TLC separation of glycoluril derivatives is realized using normal-phase mode on silica gel. The compositions of mobile phases for TLC were studied, and the separation of N,N,N,N-tetramethylglycoluril (Mebicar) from a number of drugs with similar pharmacological activity (chlorprothixene, imiprazine, clozapine, etc.) was carried out [115].

The normal-phase TLC mode was used for the separation and further preparative isolation of the "molecular clamps" based on glycoluril **1** [116], i.e., aromatic glycoluril derivatives with a complex composition. The authors proposed the use of silica gel as the stationary phase, and a mixture of methanol, ethyl acetate, and chloroform in various ratios as the mobile phase until optimal retention was achieved depending on the type of silica gel. Almost similar chromatographic conditions for C-substituted glycoluril derivatives were proposed [117, 118]. The stationary phase was unmodified silica gel with a particle size of 63–20 μm, the mobile phase was chloroform-ethyl acetate (8:2 v/v). The photograph given by the authors (Fig. 10) showed that when using this method, complete separation of the mixture was not achieved. Similar conditions were proposed to control the progress of the reaction of N, N, N, N-tetramethylolglycoluril with arylamines [119]. As a stationary phase, TLC plates based on silica gel-G Sorbfil-254 were used; the mobile phase was benzene-ethanol (8:2 v/v).

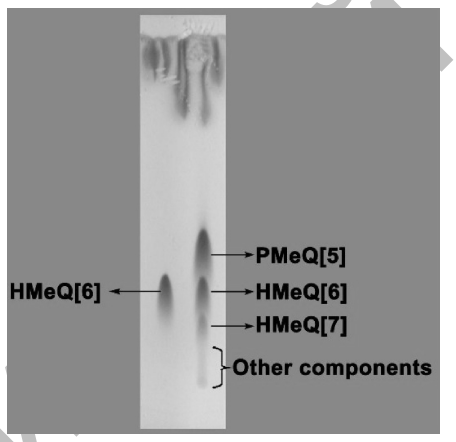


Figure 10. An image of TLC plate after separation of C-methylcucurbiturils [120]

The authors used a universal method to control the N,N,N,N-tetramethylolglycoluril derivatives by TLC using the mobile phase of chloroform-methanol (9:1 v/v) on aluminum plates coated with silica gel-G Silufol 254 [120, 121].

The authors of Ref. [122] described a method to identify and analyze the N,N,N,N-tetramethylglycoluril in blood plasma by TLC in an open unsaturated evaporation chamber. The stationary phase was silica gel-G produced by Sorbfil, the mobile phase was acetone.

Chromatography on paper is currently rarely used to separate the low molecular weight substances due to the high complexity. Ref. [123] describes a method for chromatographic separation of unsubstituted glycoluril **1** and its related concomitant substances, such as allantoin, hydantoin, and hydantoic acid. The mobile phase when the maximal separation of the components was achieved comprised n-butanol-acetic acid-water in a ratio of 100:22:5 v/v/v. After separation, the paper was dried, sprayed with a 0.25 % alcohol solution of mercury (II) acetate, redried, sprayed with a 0.05 % solution of diphenylcarbazone in ethanol and heated to a temperature of 90 °C. Glycoluril **1** and its related compounds were claimed to form light blue spots on the paper.

5.3. Column liquid chromatography (LC)

The column chromatography is used less frequently than the TLC to separate and analyze glycoluril derivatives. Ref. [124] presents an example of the separation by a method of low-pressure liquid chromatog-

raphy of a mixture of glycoluril derivatives. Thus, C, C′-diphenyl-N,N′-dibenzylglycoluril, the initial and by-products of the synthesis, were separated and isolated by normal-phase chromatography using spherical silica gel with a particle size of 50 μm as a stationary phase, and a mixture of chloroform-methanol (50:1 v/v) as a mobile phase.

The composition of the reaction products between formaldehyde and glycoluril **1** was studied by reverse phase chromatography with spectrometric detection in the UV region [125]. The best separation of the peaks of glycoluril **1** and the products of its interaction with formaldehyde was achieved using the stationary phase Hypersil MOS 5 μm 200 × 4.6 mm and water as the mobile phase. However, according to the results of the study, the authors found various products of glycoluril methylation with formaldehyde. The compounds were not identified, moreover, a complete chromatographic separation of the components of the mixture was not achieved: the resolution between the peaks did not exceed the value RS=1.2 even with a retention time of the most retained component t_R=34.3 min.

The purity and yield of carboxylated glycoluril derivatives were evaluated by RP-HPLC using the stationary phase Kromasil C18 (spherical endcapped octadecylsilylated porous silica gel) [126]. The mobile phase was a water-methanol mixture (6:4 v/v). The isocratic elution was applied. The optical purity of glycoluril derivatives was evaluated by chiral chromatography using a stationary Astec Chirobiotic T phase based on the macrocyclic glycopeptide antibiotic teicoplanin grafted onto silica gel. A similar approach to the separation of enantiomers of glycoluril derivatives was described [127, 128]. The authors used similar sorbents as stationary phases to analyze the optical purity, i.e., silica gels modified with teicoplanin aglycon (Astec Chirobiotic TAG).

The diastereomers of the macrocyclic aromatic derivatives of glycoluril, xylenebambusurils, were separated using preparative reverse-phase gradient flash chromatography on a Grace C18 sorbent using a mixture of water and acetonitrile in volume ratios from 80:20 to 0:100 as a mobile phase [129]. The target diastereomers were found partially separated and eluted from the cartridge in 27–30 min.

According to Ref. [130], quantitative determination of N,N,N,N-tetramethylglycoluril (Mebicar) in the composition of drugs, in tablets, granules and capsules was carried out by HPLC, but the authors did not disclose the analysis conditions. In addition, some manufacturers of N,N,N,N-tetramethylglycoluril declared that the mass fraction of the main substance in their products was monitored by HPLC, however, the analysis methods were not publicly available.

Ref. [131] shows the opportunity for chromatographic determination of N,N,N,N-tetramethylglycoluril by the method of microcolumn HPLC using a chromatographic column filled with a ProntoSil 120-5-C18 Aq (Knauer) reversed phase spherical adsorbent (Knauer) was shown to be chromatographic. Mobile phase A was 200 mM lithium perchlorate solution, adjusted with a 5 mM perchloric acid solution to pH=2.8; mobile phase 2 was acetonitrile. Elution mode comprised a linear gradient from 5 % to 70 % acetonitrile. The retention time of N,N,N,N-tetramethylglycoluril was ~7 min; the total analysis time was 40 min.

Unlike unsubstituted glycoluril **1**, its N-methyl derivatives **2–6** are soluble in many polar organic solvents, including water. This circumstance served as the basis to study the chromatographic separation of N-methyl derivatives of glycoluril in several modes differing in the expected retention mechanism and selectivity: reverse phase chromatography and hydrophilic chromatography [84]. The development of chromatographic separation of N-methyl derivatives of glycoluril was carried out using the following samples of substances (Table 5).

Table 5

Model glycolurils used in Ref. [84]

Number of compound	Name
1	Glycoluril
2	2-Methylglycoluril
3	2,6-Dimethylglycoluril
4	2,8-Dimethylglycoluril
5	2,4-Dimethylglycoluril
6	2,4,6,8-Tetramethylglycoluril

In the reverse phase mode, the retentions of N-methyl derivatives of glycoluril were found to increase with an increase in the number of alkyl substituents. Tetramethylglycoluril did not elute from the column

when a 1 % solution of acetonitrile in water was used as a mobile phase, and the L1 PerfectSil Target ODS-3 HD spherical porous silica gel with a particle size of 5 μm was used as a stationary phase (MZ-Analysentechnik GmbH). When 5 % acetonitrile was added to the composition of the mobile phase, substance 6 was eluted from the column, while in the reverse phase mode for substance 1, the minimal required retention was ensured to resolve the critical group of peaks (Fig. 11).

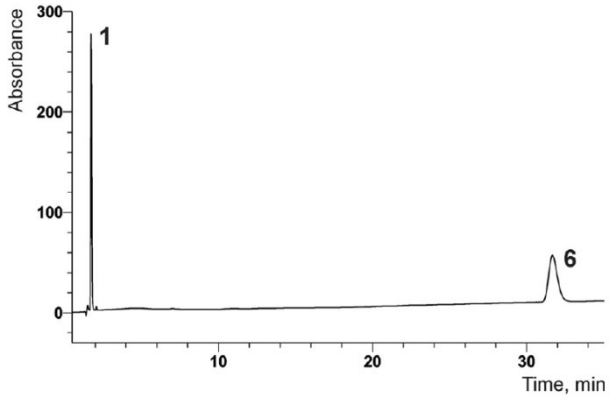


Figure 11. Chromatogram of a solution of mixture of glycoluril and tetramethylglycoluril

Since it is impossible to achieve sufficient chromatographic separation of weakly retained components 1–2 in the reverse phase chromatography under elution conditions of tetramethylglycoluril 6, it was assumed that the complete chromatographic resolution and elution of substances 1–6 in a short time was possible using the gradient elution mode comprising a continuous sequential increase in the eluting solvent strength. In order to verify this thesis, a series of experiments was carried out. For this, substances 1–6 were chromatographed under the following conditions: a column with the size of 150 × 4.6 mm L100 Zorbax SB Aq, with a sorbent particle size of 5 μm (Agilent Technologies); mobile phase A was 5 % solution of acetonitrile in water; mobile phase B was 25 % solution of acetonitrile in water; gradient profile: 0.0 min — 0 % PF B, 1.5 min — 25 % PF B; volumetric flow rate F=1.5 ml×min^{-1}; column thermostat temperature was 30 °C; injection volume was 5 μl.

Fig. 12 shows that the substances 3–6 are eluted from the column with the shortest time, and sufficient retention of substances 1–2 is observed; however, dimethyl glycoluril isomers **3–4** are not completely separated ($R_{S3/4}$=1.35) making up a critical pair of peaks due to insufficient chromatographic selectivity system.

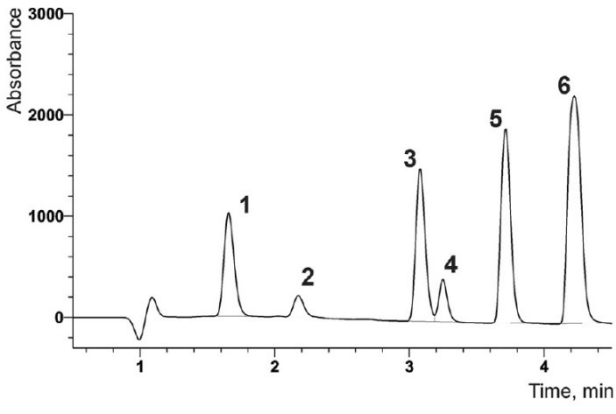


Figure 12. Chromatogram of a solution of a mixture of 1 and its derivatives **2–6** obtained using the stationary phase Zorbax SB-Aq. For this stationary phase, the separation conditions were practically not optimized

Thus, when optimizing the resolution using the approach of increasing N by extending the chromatographic column or by increasing the overall retention of the chromatographic system, the minimal resolution can be achieved by increasing the analysis time.

It has been suggested that the selectivity for structural isomers of dimethylglycoluril **3–4** can be increased by using the stationary phase with grafted "planar" polar fragments. Such stationary phases are char-

acterized by specificity with respect to structural isomers, i.e., "shape selectivity". In addition, a decrease in the selectivity of the chromatographic system with an increase in the retention coefficient in the reverse phase chromatography mechanism realized due to dispersion (hydrophobic) interactions is possible by combining gradient elution (linear increase in the eluting force of the mobile phase) and using a stationary phase containing a grafted linker layer short-chain fragment. Presumably, all of these requirements can be met using halogenated phenylalkylsilylated silica gels such as dimethyl(3-(pentafluorophenyl)propyl)silyl silica gel (F5, PFP, etc.) [85].

When using such stationary phases, according to the authors, a complex retention mechanism is realized by combining hydrophobic interactions between methyl and methine groups of glycolurils, dipole-dipole interactions, hydrogen bonds, and steric shape selectivity due to "flat" grafted selectors that are fragmentarily shown in Fig. 13.

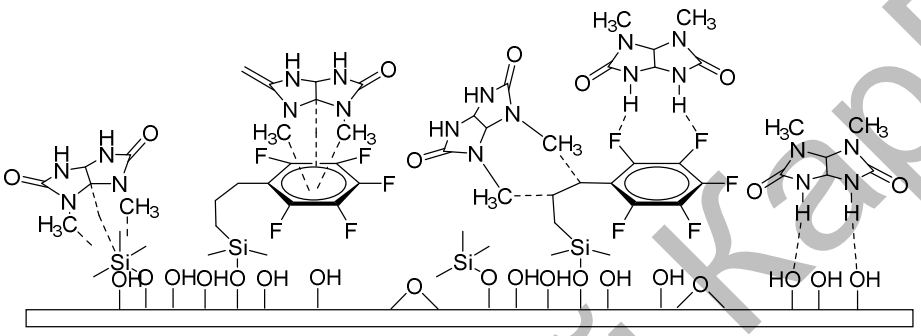


Figure 13. Simplified proposed multiple interactions between N-methyl derivatives of glycoluril (using 2,4-dimethylglycoluril as an example) and the stationary phase with a "flat" selector PFP; the dotted line indicates the intermolecular interactions

To verify the possibility of complete separation of methylglycolurils, a prefilled column with the size 150×4.6 mm filled with spherical endcapped pentafluorophenylpropylsilyl silica gel L43 — Luna 5u PFP (2) 100 Å with a particle size of 5 μm (Phenomenex) was used. Chromatographic conditions: mobile phase A was 5 % solution of acetonitrile in water; mobile phase B was 25 % solution of acetonitrile in water; gradient profile: 0.0 min — 0 % PF B, 1.5 min — 25 % PF B; volumetric flow rate F=1.5 ml×min^{-1}; column thermostat temperature was 30 °C; 5 μl injection volume was used.

When using this stationary phase in the gradient elution mode, complete chromatographic separation of substances **1–6** was achieved in less than 4 min (Fig. 16) with a minimum resolution of R_S=1.6.

Thus, the approach allowed achieving effective chromatographic separation of glycoluril **1** and its methyl derivatives **2–6**, including isomeric dimethylglycolurils **3–5**.

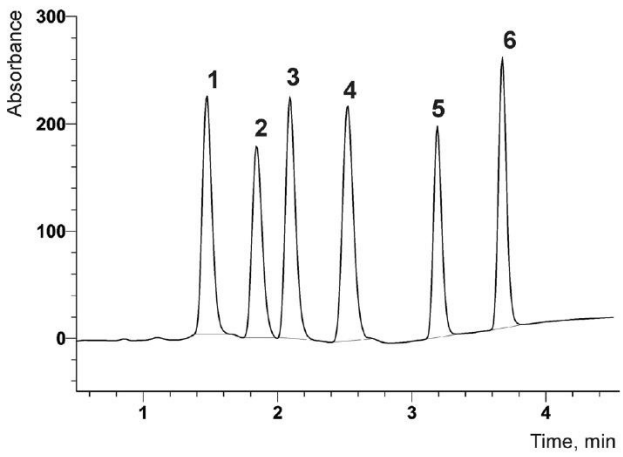


Figure 14. Chromatogram of a solution of a mixture of glycoluril **1** and its N-methyl derivatives **2–6** under optimized conditions using stationary phase Luna PFP(2) 5u

Aromatic derivatives of glycoluril (1,6-bis(p-methoxybenzyl)-7,8-di-p-tolyl glycoluril, 1,6-dibenzyl glycoluril) were isolated from the reaction mass by flash chromatography [132]. Dry unmodified silica gels were used as the stationary phase, mixtures of ethyl acetate with n-hexane with an ethyl acetate content of 30 % to 50 %, and methanol with methylene chloride in a ratio of 1:10 v/v were used as the mobile phase.

Ion exchange and ligand exchange chromatography methods are used to a limited extent to isolate glycoluril derivatives. For instance, the sodium complexes of glycoluril oligomers (decamers) were isolated from the reaction mass by ligand exchange preparative chromatography [133].

Size exclusion chromatography is used to analyze the molecular weight of glycoluril-based polymers. The gel permeation chromatography (GPC) mode was used to determine the molecular weight of water-insoluble glycoluril-based polymers [134, 135]. The stationary phase in this mode was a porous, hyper-crosslinked polystyrene polymer; the mobile phase was most often chloroform or dimethylformamide.

The molecular weight of water-soluble glycoluril-based polymers is most often analyzed using size exclusion chromatography (SEC). For instance, water-soluble polymers based on glycoluril, epichlorohydrin, and formaldehyde were studied by the SEC method [136].

Ref. [137] showed the use of HPLC method to confirm the hypothesis of the formation of a guest-host supramolecular complex (Fig. 15). As the authors suggested, when cucurbit[n]urils were added to the lipophilic compounds, the retention time of the compound in the reverse phase mode was reduced. The analysis was performed under the following conditions: column was Agilent XDB-C18 (4.6 mm × 150 mm, 5 μm), elution was gradient water → acetonitrile in a v/v ratio of 95:5 to 5:95 in 18 min, flow rate was 1 ml×min^{-1}. The mobile phase was acidified with 0.1 % trifluoroacetic acid to suppress secondary interactions in the column.

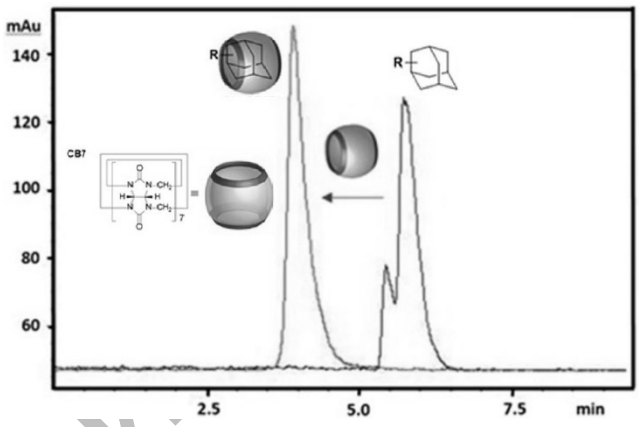


Figure 15. Chromatogram of the starting compound (blue curve) and its guest-host complex with cucurbit[7]uril (red curve)

Using preparative chromatography with the stationary C18 phase, it was proposed to isolate substituted macrocyclic glycoluril derivatives from the reaction mass, but the authors did not present the separation conditions and chromatograms [138].

N,N-Diglycidyl derivatives of glycoluril used as crosslinking agents for the production of high-purity polymeric materials were purified from the related impurities by preparative chromatography [139]. Unmodified silica gel was used as a sorbent; eluent was a mixture of chloroform and methanol 10:1 v/v.

The authors of Refs. [140–143] indicated that the analysis of glycolurils was carried out by HPLC, but the conditions of analysis and chromatograms were not provided.

Conclusions

Thus, chromatographic methods are the most promising and informative for the analysis of glycoluril **1** and its related compounds, since they allow rapid separation of complex mixtures of organic substances simultaneously with a quantitative determination. In addition, chromatographic separation can be adapted for preparative isolation of individual glycoluril derivatives in pure form as well as for combination with other analysis methods: UV and mass spectroscopy, fluorimetry, electrochemical analysis methods, etc.

However, chromatography-based separation and analysis methods are applied to glycoluril derivatives to a limited extent: for instance, the open literature does not show the fundamental opportunity to analyze

glycoluril by chromatography. In most studies, the chromatographic analyses of glycoluril derivatives are limited to the determination of its supramolecular guest-host compounds, while the purity of the starting compounds is not controlled. However, since the content of related glycoluril compounds in the synthesis of supramolecular compounds on the basis thereof is undesirable due to the possible formation of macromolecules that differ in properties from the given ones, it is necessary to control the purity of low molecular weight glycoluril derivatives, especially with respect to specific impurities, i.e. spatial isomers.

Summarizing the generalized results of the methods of analysis of glycoluril and its derivatives, we can point out that most of the studies conducted aimed at establishing the purity of the sample and identification of the related impurities for substances that have found practical use (drugs, monomers, and polymers on the basis thereof). The search for new methods to analyze macrocyclic and supramolecular systems synthesized based on glycolurils is carried out most intensively due to the unique properties found for such molecules.

Acknowledgement

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Гликолурил және оның туындыларын талдау әдістері

Мақалада гликолурилді, оның туындыларын және олардың байланысты қосылыстарын талдау әдістерінің әдеби мәліметтерін жалпылау жүргізілді, бұл осы заттардың құрылымы мен қасиеттері туралы ақпаратты біріктірілген түрде алуға мүмкіндік береді. Гликолурилдер мен олардың негізінде синтезделген қосылыстарды талдаудың негізгі әдістері зерттелген, оларды ұсыну барысында ұсынылған әдістердің артықшылықтары мен кемшіліктері сыни қарастырылған. Гликолурил мен оның туындыларын талдау әдістерінің жалпыланған нәтижелері көрсеткендей, жүргізілген зерттеулердің көпшілігі үлгінің тазалығын анықтауға және практикалық қолданысқа ие заттарға (дәрі-дәрмектер, мономерлер және олардың негізіндегі полимерлер) байланысты қоспаларды анықтауға бағытталған. Гликолурилдер негізінде синтезделген макроциклді және супрамолекулалық жүйелерді талдаудың жаңа әдістерін қарқынды іздеудің тұрақты үрдісі байқалады. Осы шолудың мақсаты — химия саласындағы мамандардың назарын гликолурил мен оның туындыларын талдаудың қолданыстағы әдістеріне аудару және одан әрі осындай зерттеулерді ынталандыру. Жүргізілген әдеби талдау алдынала анықталған қасиеттері бар гликолурил негізіндегі жаңа молекулаларды жасаумен айналысатын зерттеушілер үшін пайдалы, оның барысында процестерді бақылау және мақсатты қосылыстарды талдау әдістері өте маңызды.

Кілт сөздер: гликолурил, N-алмастырылған гликолурилдер, супрамолекулалар, талдау, спектроскопия, тиімділігі жоғары сұйық хроматография, изомерлер.

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Методы анализа гликолурила и его производных

В статье проведено обобщение литературных сведений о методах анализа гликолурила, его производных и их родственных соединениях, позволяющих получить информацию о структуре и свойствах этих веществ в интегрированном виде. Рассмотрены основные методы анализа гликолурилов и соединений, синтезируемых на их основе, в ходе изложения которых критически рассмотрены достоинства и недостатки предлагаемых методов. Обобщенные результаты методов анализа гликолурила и его производных говорят о том, что большинство проведенных исследований направлено в сторону установления чистоты образца и идентификации родственных примесей для веществ, нашедших практическое применение (лекарственные препараты, мономеры и полимеры на их основе). Наблюдается устойчивая тенденция к интенсивному поиску новых методов анализа макроциклических и супрамолекулярных систем, синтезируемых на основе гликолурилов. Цель настоящего обзора — привлечение внимания химиков к существующим методам анализа гликолурила и его производных и дальнейшее стимулирование подобных исследований. Проведенный авторами литературный анализ будет полезным для исследователей, занимающихся конструированием новых молекул на основе гликолурила с заранее заданными свойствами, в ходе которых методы контроля процессов и анализа целевых соединений имеют решающее значение.

Ключевые слова: гликолурил, N-замещённые гликолурилы, супрамолекулы, анализ, спектроскопия, высокоэффективная жидкостная хроматография, изомеры.

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