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## Study of glycoluril and its derivatives by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy

Bicyclic bisureas, especially 2,4,6,8-tetraazabicyclo[3.3.0]octan-3,7-dione (glycoluril), have a special place in chemistry of heterocyclic compounds. The carbamide fragment in glycoluril structure determines the properties of the molecule, which are due to the presence of two reaction centers (NH-groups and C=O-groups) in the molecule. In this work, we analyzed the proton and carbon chemical shifts of glycoluril and its derivatives (86 compounds) in the NMR spectra to reveal the effect of the donor-acceptor substituents on the changes in the electron density in the bicyclic framework from the position of symmetry and asymmetry. A general analysis of the <sup>1</sup>H and <sup>13</sup>C NMR spectra of glycolurils makes it possible to accurately determine the spatial configurations of molecular symmetry, in the presence of which ( $\sigma_1$  and / or  $\sigma_2$ ) the enantiotopic hydrogen and carbon atoms of the bicyclic framework are manifested by equivalent signals. Also, according to the <sup>1</sup>H and <sup>13</sup>C chemical shifts in the NMR spectra, glycolurils with electron-acceptor substituents can be clearly distinguished by the shielding of carbon atoms of C=O-groups, and with electron-donating substituents by the deshielding of CH-CH-carbons, due to the rearrangement of electron density and the occurrence of local paramagnetic contributions owing to anisotropy

**Keywords:** glycoluril, NMR, chemical shifts, symmetry, enantiotopic atoms, shielding, deshielding, X-ray diffraction.

### Introduction

In the chemistry of heterocyclic compounds, bicyclic ureas have a special place, among which the greatest interest are 2,4,6,8-tetraazabicyclo[3.3.0]octan-3,7-dione **1** (glycoluril) (Fig. 1) and its derivatives. The history of glycoluril chemistry dates back to the second half of the 19<sup>th</sup> century, when a number of researchers succeeded in synthesizing the progenitor **1** of this class of compounds. Since then, the chemistry of glycolurils, first of all, due to polyfunctionality of their structure, has developed rapidly. It was reflected in the creation of valuable substances in various fields of human activity such as disinfectants [1, 2], medicines [3; 86, 4], polymer stabilizers [5], independent explosives or their components [6–8] and other important substances and materials based on these compounds.

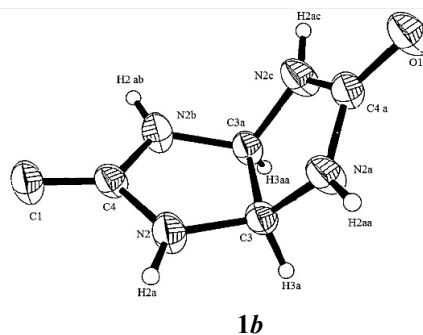
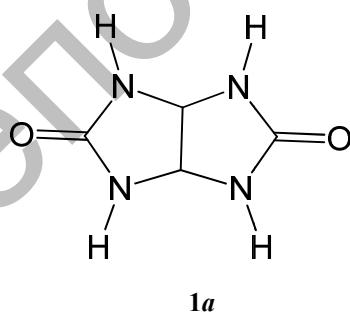


Figure 1. The structural formula of glycoluril **1** (**1a**) and its spatial configuration in the crystal (**1b**)

Glycoluril **1** is a polyfunctional compound in which the carbamide fragment (Fig. 2) essentially determines the properties of the molecule **1** being resulted from the presence of two reaction centers (4 donor groups (–NH) and 2 acceptor groups (C=O)) in the molecule. Glycoluril **1** has the properties of a highly ac-

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tive N-nucleophile and a significantly deactivated p-nucleophile. Despite its weak basicity, glycoluril **1** is rather difficult to protonate, but it is capable of N-alkylation, N-acylation, N-halogenation, N-nitration, N-nitrosation, N-hydroxyalkylation reactions, etc. [9; 126–129].

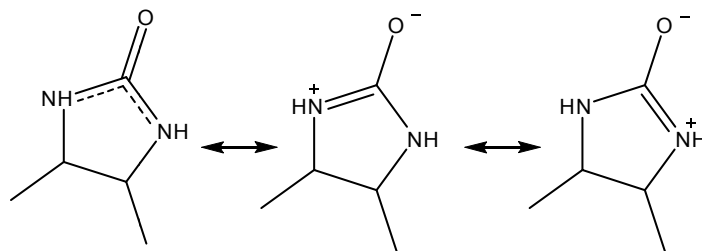


Figure 2. Resonance structures of the carbamide fragment of the glycoluril molecule **1**

The synthesis and study of the chemical properties of bicyclic bisureas allows creating of new classes of nitrogen-containing heterocyclic compounds with other practically useful properties. For example, polycyclic condensed systems such as cucurbit[n]urils [10–12] and bambus[n]urils [13, 14], the building blocks of which is glycoluril **1**.

Due to the complex structure of glycoluril derivatives, the problem arises of the precise identification of the studied compounds, where the most convenient method for solving structural problems is the method of nuclear magnetic resonance spectroscopy (NMR).

The molecule of glycoluril **1** contains nitrogen, oxygen, carbon and hydrogen atoms, for the analysis of the bonds of which it is convenient to record the spectra on  $^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{15}\text{N}$ ,  $^{17}\text{O}$  nuclei. NMR spectroscopy on these nuclei can provide enough information to determine the structure of a molecule, its electronic and conformational features. Due to the low content of natural isotopes  $^{15}\text{N}$  and  $^{17}\text{O}$ , there is no information in the literature on the use of NMR on  $^{17}\text{O}$  nuclei for a number of glycolurils. To obtain information of the position of the  $^{15}\text{N}$  chemical shifts of glycoluril **1** and its derivatives 2D heterocorrelation of the  $^1\text{H}$ – $^{15}\text{N}$  spectra [15] and the establishment of the direct coupling constant  $^{15}\text{N}$ – $^1\text{H}$  [16] are most often used. Therefore, in this work, we analyzed the chemical shifts (further in the text, CS) of the NMR of glycoluril **1** and its derivatives **2-13**, recorded on  $^1\text{H}$  and  $^{13}\text{C}$  nuclei (Table 1-10).

Taking into account the specific and limited solubility of glycoluril **1** and its derivatives **2-13**, which depends on the presence of substituents, in practice, the universal solvents DMSO- $d_6$  and  $\text{D}_2\text{O}$  are most often used for analysis. N-acylderivatives of glycoluril **12** is convenient to analyze in a  $\text{CDCl}_3$  solvent to avoid overlapping signals of atoms.

When recording the NMR spectra of glycoluril **1**, it was found that in the proton magnetic resonance spectrum there are 2 CS in the regions of 5.24 ppm and 7.16 ppm, which correspond to signals of the CHCH and NH groups, and in the  $^{13}\text{C}$  spectrum, the carbons of the CH-CH and C=O groups resonate at 64.60 ppm, 160.30 ppm respectively. These data certainly indicate the spatial symmetry of glycoluril **1**. Indeed, in the molecule **1**, there are two planes of symmetry  $\sigma^1$  and  $\sigma^2$  (Fig. 3), where the plane  $\sigma^1$  passes along the methine CH–CH bridge, and the plane  $\sigma^2$  intersects two carbonyl oxygen atoms (Fig. 3) [17].

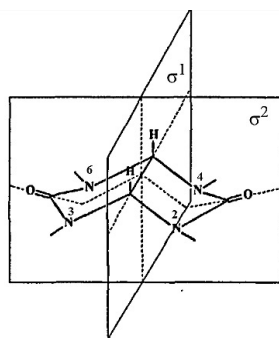


Figure 3. Symmetry planes  $\sigma^1$  and  $\sigma^2$  in the molecule of glycoluril **1**

However, when studying the crystal structure of glycoluril **1** by X-ray diffraction (Fig. 1b), it was first established [18] that, in addition to symmetry, the conformation of bicyclic framework **1** due to the rigidity

of the cis-joint of annelated imidazolidinone rings has a folded structure in the form of a «half-opened book». The dihedral angle between the imidazolidinone rings in molecule **1** is 124.1°. In addition, it was found that the nitrogen atoms in molecule **1** are located equidistant from each other. The hydrogen atoms of the CH-CH group are cis-oriented, and the imidazolidinone rings are characterized by an almost flat structure with a slight deviation of the C=O groups from the plane.

Thus, the goal of this work was to study CS of glycoluril **1** and its derivatives **2-13** to identify the effect of substituents on changes in electron density in the bicyclic framework, taking into account the symmetry and asymmetry of the 86 molecules considered.

### Experimental

The substances **2e-g**, **3c, d**, **4b-c**, **5d, e, g**, **6c-f** were synthesized in accordance with the methods of [9; 113]. NMR spectra for substances **2e-g**, **3c, d**, **4b-c**, **5d, e, g**, **6c-f** were recorded on a Bruker AVANCE III HD spectrometer (Bruker Corporation, Germany) with an operating frequency of 400 and 100 MHz for <sup>1</sup>H and <sup>13</sup>C nuclei respectively, in a solution of DMSO-d<sub>6</sub> with a concentration of 0.001 mol of the substance in 0.5 ml of solvent. The internal standard is tetramethylsilane (TMS).

### Results and Discussion

*N*-Monosubstituted glycolurils. First of all, it should be noted that with *N*-monosubstitution in the glycoluril framework, the symmetry of the molecule is violated (glycolurils **2a-g**). In the analyzed molecules **2a-g**, there are no symmetry planes  $\sigma^1$  and  $\sigma^2$ , which, as we have found, is reflected in the change of CS in the <sup>1</sup>H and <sup>13</sup>C NMR spectra (Table 1).

Table 1

Chemical shifts of *N*-monosubstituted glycolurils **2a-g**

№	Substituent	<sup>1</sup> H NMR, ppm, (J/Hz)		<sup>13</sup> C NMR, ppm	
		CH-CH	NH	CH-CH	C=O
<b>1</b> <sup>[19]</sup>	H	5.24 (s. 2H)	7.16 (s. 4H)	64.60	160.30
<b>2a</b> <sup>[19]</sup>	CH <sub>3</sub>	5.14 (d. 1H, J = 8.0) 5.19 (d. 1H, J = 8.0)	7.20 (s. 1H) 7.30 (s. 2H)	62.54 69.89	159.75 161.79
<b>2b</b> <sup>[20]</sup>	CH <sub>2</sub> CONHCH(CH <sub>3</sub> )C <sub>2</sub> H <sub>5</sub>	5.22 (d. 1H, J = 7.9) 5.29 (d. 1H, J = 7.9)	7.29 (s. 2H) 7.44 (s. 1H)	62.39 68.55	159.40 161.14
<b>2c</b> <sup>[21]</sup>	CH <sub>2</sub> CH <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	5.21 (d. 1H, J = 8.2) 5.32 (d. 1H, J = 8.2)	7.29 (s. 1H) 7.40 (s. 2H)	62.24 67.75	159.13 161.00
<b>2d</b> <sup>[21]</sup>	CH <sub>2</sub> CH <sub>2</sub> NHCOCH <sub>3</sub>	5.18 (d. 1H, J = 8.1) 5.31 (d. 1H, J = 8.1)	7.25, 7.30, 7.39 (3s. 3H)	62.33, 67.74	159.36 161.15
<b>2e</b>	CH <sub>2</sub> OH	5.45 (d. 1H, J = 8.0) 5.65 (d. 1H, J = 8.0)	7.17, 7.29, 7.22 (3s. 3H)	64.10 67.70	158.30 160.08
<b>2f</b>	COCH <sub>3</sub>	5.68 (d. 1H, J = 8.0) 5.23 (d. 1H, J = 8.0)	8.55, 7.57, 7.49 (3s. 3H)	61.55 63.24	151.40, 154.80
<b>2g</b>	NO	5.34 (d. 1H, J = 7.6) 5.66 (d. 1H, J = 7.6)	7.94, 7.97, 9.38 (3s. 3H)	62.11 63.48	152.30 160.68
Chemical shift range ( $\Delta$ )		5.14–5.68	7.17–9.38	61.55–69.89	151.40–161.79

An analysis of the NMR data for compounds **2a-g** shows that in the absence of planes of symmetry  $\sigma^1$  and  $\sigma^2$ , the protons and carbons of methine (CH-CH) groups appear to be non-equivalent peaks. In the PMR spectra, CH-protons resonate in pairs in the form of doublet signals in the region from 5.1 ppm to 5.7 ppm, and in the <sup>13</sup>C NMR spectra, shielding of signals of one CH up to 2 ppm (**2f**) and CH carbon deshielding from the substitution side up to 4.4 ppm (**2a**) relative to the CS of similar glycoluril atoms **1** are observed. The deshielding of CH atoms in substances **2a-e** is probably due to the positive inductive effect of electron-donating substituents on nitrogen atoms [22; 712], which makes its unshared electron pair more available for sharing with a five-membered ring. Such an effect of electron-donating groups makes C-C carbons on the substitution side partially sp<sup>2</sup>-hybridized atoms due to an increase in electron density, which shifts the CS of carbon CH to the fields of «molecular currents» or  $\pi$ -conjugated systems.

The CS of NH groups in compounds **2a-g** become unequal and resonate in the form of two or three singlets in the regions from 7.2 ppm to 9.4 ppm. In compounds **2a-e** with electron-donating substituents at nitrogen atoms, a shift in the CS of NH groups in the range of  $\pm 0.5$  ppm relatively to **1** is observed. These

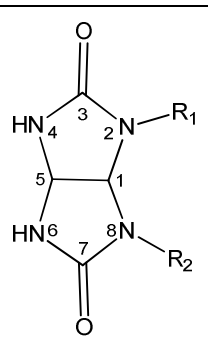
changes indicate a weak effect of the substituents on the inhibition of amide conjugation in the urea fragment of the molecules **2a–g** (Fig. 2). While in the case of substances **2f, g** with acceptor substituents, the CS of the NH group shifts to the low-field region by 2.2 ppm relatively to glycoluril **1**, due to the inductive effect of the substituent on the unshared pair of electrons of the neighboring unsubstituted amino group, which is isolated and not shared with the imidazolidine ring.

The CS of carbons of C=O groups are shielded in substituted imidazolinone rings in average up to 2.0 ppm (**2a–e**), and for compounds **2f, g** with electron-acceptor substituents (–NO, –COCH<sub>3</sub>) the carbonyl signals shift to the high-field region by 8.9 ppm. The observed effect of strong shielding of the C=O group in compounds **2f, g** is explained by the circulation of electron-acceptor substituents' electrons due to the presence of  $\pi$ -bonds, which leads to the appearance of a field additionally strengthening the external [23; 183] or «anisotropy cone» [24]. This effect is similar for 2,6-N-disubstituted compounds **5e–h** and is shown in Figure 4.

*2,8-N-disubstituted glycolurils.* The absence of plane of symmetry  $\sigma^2$  in 2,8-N-disubstituted glycoluril **3a–d** molecules can also be detected in the <sup>1</sup>H and <sup>13</sup>C NMR spectra (Table 2).

Table 2

**Chemical shifts of 2, 8-N-disubstituted glycoluril 3a–d**

	№	Substituent	<sup>1</sup> H NMR, ppm, (J/Hz)		<sup>13</sup> C NMR, ppm	
			R <sub>1</sub>	CH–CH	NH	CH–CH
	1 <sup>[19]</sup>	H	5.24 (s. 2H)	7.16 (s. 4H)	64.60	160.30
	3a <sup>[19]</sup>	CH <sub>3</sub>	5.15 (d. 1H, J = 8.4) 5.18 (d. 1H, J = 8.4)	7.39 (s. 2H)	60.63 75.63	160.19
	3b <sup>[25]</sup>	CH <sub>2</sub> Ph	4.98 (d. 1H, J = 8.5) 5.39 (d. 1H, J = 8.5)	7.64 (s. 2H)	60.40 70.70	159.70
	3c	CH <sub>2</sub> OH	5.41 (d. 1H, J = 8.0) 5.58 (d. 1H, J = 8.0)	7.39 (s. 2H)	64.10 67.70	160.90
	3d	COCH <sub>3</sub>	5.25 (d. 1H, J = 7.2) 6.44 (d. 1H, J = 7.2)	8.74 (s. 2H)	59.50 63.31	154.73
Chemical shift range ( $\Delta$ )			4.98–6.44	7.39–8.69	59.50–75.63	154.73–160.19

The CS of 2,8-N-disubstituted glycolurils **3a–d** indicates the equivalence of the C=O signals in the <sup>13</sup>C spectra and the NH groups in the <sup>1</sup>H NMR spectra due to the presence of the plane of symmetry  $\sigma^1$  of the molecules that passes through the C–C bond. The lack of symmetry along the  $\sigma^2$  plane is demonstrated by the nonequivalence of carbons and protons of methine groups (CH–CH) in such a way that the carbons resonate with pair signals in the regions of 59.5–75.6 ppm, and the protons appear doublets in the range of 4.9–6.4 ppm.

The CS of the NH groups in the compounds **3a–d** appear as singlet peaks, and, in the case of glycolurils **3a–c**, with a shift to a low-field of up to 0.5 ppm, and for 2,8-N-diacetyl glycoluril **3d** to 1.6 ppm relatively to **1**. The shielding of carbonyl carbon atoms for compounds **3a–c** is on average 1 ppm. For compound **3d** a shift of CS of the C=O groups to the high-field by 5.6 ppm relatively to the parent **1** is observed. The general character of the shift of the C=O groups signal for **3a–d** is similar to substances **2a–h**, but **2a–h** have in their structure only one substituted imidazolinone ring, and compounds **3a–d** combine the properties of two similarly substituted rings. In the structures of glycolurils **3a–d**, there is a synergistic effect of pairs of substituents on the electronic density of glycoluril framework, distribution of which is reflected in NMR spectra by stronger shielding and deshielding of the corresponding atoms relatively glycoluril **1**. So in <sup>13</sup>C NMR spectra of glycolurils **3a–d** there is the shielding of signals of one CH in **3d** (up to 5.1 ppm) and a significantly higher deshielding of CH carbon in **3a–c** from the substitution side (up to 11 ppm) relatively to CS of similar glycoluril atoms **1**. In the latter case, the found effect is due to the positive inductive effect of electron-donating groups to nitrogen atoms [22; 712], which determines the «pushing out» of unshared pairs of nitrogen electrons to C–C carbons from the substitution side, making them partially sp<sup>2</sup>-hybridized. This interpretation can explain the shift of CS of CH-carbons to fields of «molecular currents» or  $\pi$ -conjugated systems.

*2,4-N-Disubstituted glycolurils.* In the molecules of 2,4-N-disubstituted glycolurils **4a–e**, in the case of equivalent substituents, there is a symmetry corresponding to the  $\sigma^2$  plane. This fact is confirmed by the CS in the NMR spectra (Table 3), where the signals of protons of equivalent NH groups give singlet peaks in the region of 7.5–8.9 ppm, the CS of carbons (62.6–76.7 ppm) and protons (5.1–5.7 ppm) of the CH–CH groups appear in the form of single signals. The absence of symmetry along the  $\sigma^1$  plane is indicated by nonequivalent CS of C=O-groups.

Table 3

Chemical shifts of 2, 4-N-disubstituted glycolurils 4a–e

№	Substituent		<sup>1</sup> H NMR, ppm, (J/Hz)		<sup>13</sup> C NMR, ppm	
	R <sub>1</sub>	R <sub>2</sub>	CH–CH	NH	CH–CH	C=O
1 <sup>[19]</sup>	H	H	5.24	7.16 (s. 4H)	64.60	160.30
4a <sup>[19]</sup>	CH <sub>3</sub>	CH <sub>3</sub>	5.12 (s. 2H)	7.54 (s. 2H)	76.67	158.22 160.20
4b	CH <sub>2</sub> OH	CH <sub>2</sub> OH	5.55 (s. 2H)	7.47 (s. 2H)	66.86	158.01 161.47
4c	COCH <sub>3</sub>	COCH <sub>3</sub>	5.65 (s. 2H)	8.87 (s. 1H)	62.62	154.68 161.10
4d <sup>[21]</sup>	CH <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> NHCOCH <sub>3</sub>	5.10 (d. 1H, J = 8.1) 5.27 (d. 1H, J = 8.1)	7.49 (s. 1H) 7.56 (s. 1H)	66.16 67.93	158.36 161.61
4e <sup>[21]</sup>	Ph	CH <sub>2</sub> CH <sub>2</sub> NHCOCH <sub>3</sub>	5.41 (d. 1H, J = 8.3) 5.82 (d. 1H, J = 8.3)	7.71 (s. 1H) 7.87 (s. 1H)	65.11 66.24	155.17 161.11
Chemical shift range (Δ)			5.10–5.82	7.47–8.87	62.62– 76.67	154.68– 161.61

The structures of compounds **4a–e** combine the properties of unsubstituted and disubstituted by nitrogen atoms imidazolinone rings, where the CS of C=O groups for **4a, b, d** in the substituted fragment are shielded by an average of 2.0 ppm, and in the case of compounds **4c, e** with substituents of acceptor type — up to 5.5 ppm relatively to glycoluril **1**. In the unsubstituted cycle of compounds **4a–e**, on the contrary, carbonyl carbon atoms are deshielded up to 1.3 ppm compared to **1**.

For compounds **4a** and **4c**, the symbatic effect of two substituents is observed. Acetyl substituents (**4c**) lower the electron density of the adjacent annelated ring, this is reflected in the shift of the CS of NH groups by 1.7 ppm in a low-field relatively to **1**. Methyl substituents in **4a** increase the electron density in the disubstituted cycle, which affects the deshielding of signals of CH–CH groups by 12 ppm relatively to **1**.

In compounds **4a, b, d**, aminogroups are deshielded by an average of 0.5 ppm, which corresponds to the range of compounds **2, 3** considered above with electron-donating substituents at nitrogen atoms.

The presence of various functional groups at 2,4-N-positions in compounds **4d** and **4e** leads to asymmetry of the molecule and, accordingly, to a change in the number of signals in the NMR spectra for NH, C=O, and CH–CH groups. For the substance **4e**, the CS of unsubstituted NH groups also reflect a moderate acceptor effect of the phenyl substituent, which deshields NH by 0.7 ppm relatively to **1**.

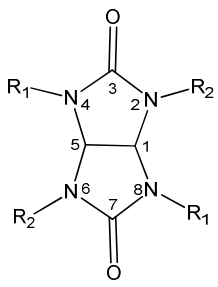
2,6-N-disubstituted glycolurils; and 2,4,6,8-N-tetrasubstituted glycolurils. Similarly to the glycoluril molecule **1**, 2,6-N-di- **5a–h** (Table 4) and 2,4,6,8-N-tetra-substituted compounds **6a–i** (Table 5) have two planes of symmetry ( $\sigma^1$  and  $\sigma^2$ ). In <sup>1</sup>H NMR spectra of substances **5a–h** and **6a–i**, we observe the equivalent singlets of protons of CH–CH groups of a bicyclic framework and in <sup>13</sup>C NMR spectra the equivalent CS of CH–CH and C=O groups, as well as singlet peaks of two unsubstituted NH-groups in **5a–h**.

Table 4

Chemical shifts of symmetric 2, 6-N-disubstituted glycoluril 5a–h

№	Substituent	<sup>1</sup> H NMR, ppm, (J/Hz)		<sup>13</sup> C NMR, ppm	
		CH–CH	NH	CH–CH	C=O
1 <sup>[19]</sup>	H	5.24 (s. 2H)	7.16 (s. 4H)	64.60	160.30
5a <sup>[19]</sup>	CH <sub>3</sub>	5.10 (s. 2H)	7.57 (s. 2H)	67.39	159.66
5b <sup>[26]</sup>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	5.04 (s. 2H)	7.81 (s. 2H)	64.88	158.86
5c <sup>[27]</sup>	CH <sub>2</sub> CH <sub>2</sub> NHCOCH <sub>3</sub>	5.25 (s. 2H)	7.49 (s. 2H)	65.40	159.20
5d	CH <sub>2</sub> OH	5.53 (s. 2H)	7.61 (s. 2H)	66.34	160.56
5e	COCH <sub>3</sub>	5.66 (s. 2H)	8.85 (s. 2H)	61.80	154.34
5f <sup>[28]</sup>	COCH <sub>2</sub> Cl	5.34 (s. 2H)	8.83 (s. 2H)	63.32	154.03
5g	NO	5.64 (s. 2H)	9.96 (s. 2H)	60.19	152.00
5h <sup>[29]</sup>	NO <sub>2</sub>	6.03 (s. 2H)	9.83 (s. 2H)	63.80	149.00
Chemical shift range (Δ)		5.10–6.03	7.49–9.96	60.19–67.39	149.00–160.56

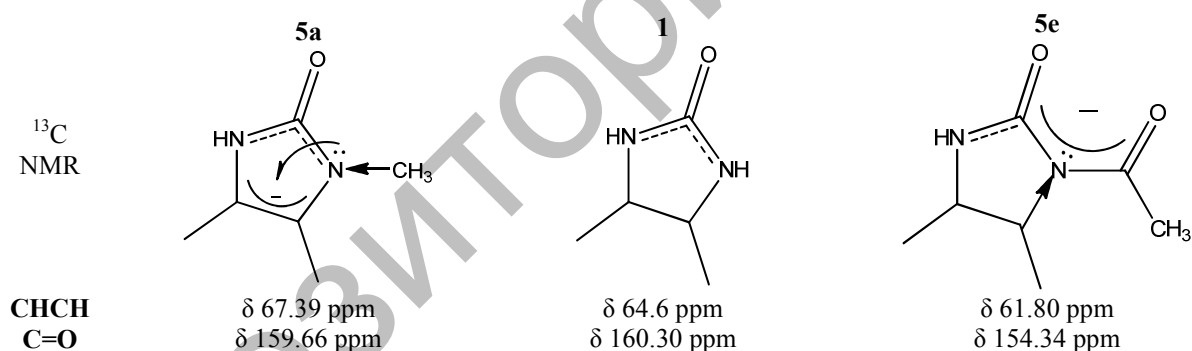
Chemical shifts of symmetric 2, 4, 6, 8-N-tetrasubstituted glycolurils 6a–i

	No	Substituent		<sup>1</sup> H NMR, ppm, (J/Hz)		<sup>13</sup> C NMR, ppm
		R <sub>1</sub>	R <sub>2</sub>	CHCH	CHCH	C=O
	1 <sup>[19]</sup>	H	H	5.24 (s. 2H)	64.60	160.30
6a <sup>[19]</sup>	CH <sub>3</sub>	CH <sub>3</sub>	5.06 (s. 2H)	71.92	159.05	
6b <sup>[26]</sup>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	4.84 (s. 2H)	67.71	159.54	
6c	CH <sub>2</sub> OH	CH <sub>2</sub> OH	5.59 (s. 2H)	70.65	158.62	
6d	CH <sub>2</sub> OCH <sub>3</sub>	CH <sub>2</sub> OCH <sub>3</sub>	5.52 (s. 2H)	74.86	158.45	
6e	Cl	Cl	5.48 (s. 2H)	72.72	160.51	
6f	COCH <sub>3</sub>	COCH <sub>3</sub>	6.33 (s. 2H)	62.69	151.58	
6g <sup>[31]</sup>	NO <sub>2</sub>	NO <sub>2</sub>	7.77 (s. 2H)	65.90	142.40	
6h <sup>[20]</sup>	CH <sub>3</sub>	CH <sub>2</sub> NHSO <sub>2</sub> Ph	4.70 (s. 2H)	66.75	156.80	
6i <sup>[20]</sup>	C <sub>2</sub> H <sub>5</sub>	CH <sub>2</sub> NHSO <sub>2</sub> Ts	4.65 (s. 2H)	65.38	156.85	
Chemical shift range (Δ)				4.65–7.77	62.69–74.86	142.40–163.81

Structures **5a–h** are two annelated monosubstituted imidazolinone rings with *anti*-arrangement of substituents relatively to each other.

The type of the action of the substituents on the shift of the signals of NH groups to a low-field for substances **5a–h** is similar to compounds **2, 3** considered above. In the substances **5a–d**, electron-donating substituents of nitrogen atoms deshield the nuclei of NH groups by 0.6 ppm, and acceptor substituents (**5e–h**) deshield the CS of NH groups at 2.8 ppm relatively to **1**.

The CS of C=O-group carbons undergo shielding on average up to 1.5 ppm (**5a–d**), and for compounds **5e–h** with electron-acceptor substituents on nitrogen atoms, a synergy of electronic effects with shielding of carbonyl signals by 11 ppm is observed, which is due to the formation of  $\pi$ -electron shielding regions (Fig. 4, **5e**).

Figure 4. Diagram of the distribution of electron density in the imidazolinone fragment of glycolurils **1, 5a, 5e**

It was found, that the CS of CH–CH protons in compound **5h** is most deshielded compared to **5a–g** and is shifted to the low-field region by 0.8 ppm relatively to **1**. This effect can be explained by the spatial intramolecular interaction of nitrogens with methine protons, which was discovered by studying the substance **5h** by X-ray diffraction analysis (Fig. 5, **5h**) [30], where it is reported that one of the oxygen atoms of the two nitrogens is maximally reversed towards the *cis*-protons of the methine bridge.

The structures of compounds **6a–i** combine the properties of two N-disubstituted imidazolidinone rings, where for substances **6f, g**, the synergic effect of 4 acceptor substituents is reflected in the spectral data. In this case, shielding of C=O groups to 17.9 ppm relative to **1** is observed. Electron-donating substituents in glycolurils **6a–e, h, i** increase the electron density in disubstituted imidazolinone rings, which is shown in <sup>13</sup>C NMR spectra by deshielding of CH–CH carbons to 10.2 ppm relatively to **1**.

In the PMR spectra of compounds **6f, g**, the singlets of protons CH–CH are most deshielded compared to the CS of the corresponding atoms of compounds **6a–e, h, i** and are shifted to a low-field by more than 1.1 ppm (**6f**) and 2.5 ppm (**6g**) relative to **1**. Intramolecular interactions between substituents (–COCH<sub>3</sub>, –NO<sub>2</sub>) and *cis*-protons of the CH–CH groups may be present in these compounds. In the case of tetraacetylsubstituted glycoluril **6f**, these interactions were recorded by X-ray diffraction [32] (Fig. 5, **6f**),

where it was shown that the oxygen atoms of the two most twisted acetyl groups are maximally turned toward the protons of the methine bridge.

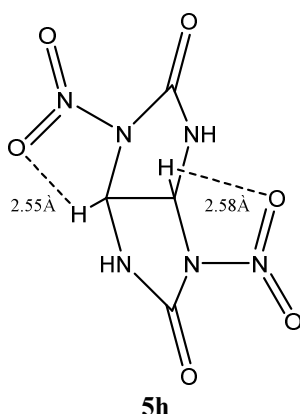


Figure 5. Intermolecular interactions between the oxygen atoms of the substituents and the protons of the methine bridge in 2,6-N-dinitroglycoluril **5h** according to X-ray diffraction data

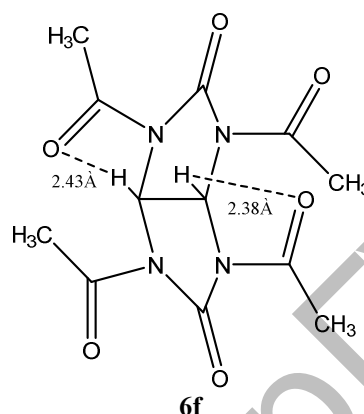


Figure 6. Intermolecular interactions between the oxygen atoms of the substituents and the protons of the methine bridge in 2,4,6,8-N-tetraacetyl glycoluril **6f** according to X-ray diffraction data

*2,4-N-Dimethyl derivatives of glycoluril.* Comparing CS of **1** and substances **2a**, **3a**, **4a**, **5a**, **6a**, it should be noted that the presence of CH<sub>3</sub> groups at nitrogen atoms causes deshielding of CH-carbon signals by an average of 10 ppm. Based on these data, CS in the series of asymmetric 2,4-N-dimethyl derivatives of glycolurils **7a–f** are further considered (Table 6).

Table 6

Chemical shifts of asymmetric 2,4-N-dimethyl derivatives of glycolurils **7a–f**

№	Substituting group	<sup>1</sup> H NMR, ppm, (J/Hz)		<sup>13</sup> C NMR, ppm	
		CH–CH	NH	CH–CH	C=O
<b>1</b> <sup>[19]</sup>	-	5.24 (s, 2H)	7.16 (s, 4H)	64.60	160.30
<b>4a</b> <sup>[19]</sup>	H	5.12 (s, 2H)	7.54 (s, 2H)	76.67	158.22
<b>7a</b> <sup>[19]</sup>	CH <sub>3</sub>	5.08 (d, 1H, J = 8.3)	7.62 (s, 2H)	65.30	158.07
		5.22 (d, 1H, J = 8.3)		72.92	159.54
<b>7b</b> <sup>[20]</sup>	CH <sub>2</sub> COOH	5.15 (d, 1H, J = 8.3)	7.90 (s, 1H)	65.93	158.08
		5.22 (d, 1H, J = 8.3)		71.85	160.05
<b>7c</b> <sup>[21]</sup>	C(CH <sub>3</sub> ) <sub>2</sub> COOH	5.18 (d, 1H, J = 8.1)	7.77 (s, 1H)	66.51	158.45
		5.41 (d, 1H, J = 8.1)		70.54	160.09
<b>7d</b> <sup>[21]</sup>	CH <sub>2</sub> CH <sub>2</sub> NH(CH <sub>3</sub> ) <sub>2</sub> Cl	5.16 (d, 1H, J = 9.5)	7.91 (s, 1H)	65.81	158.43
		5.34 (d, 1H, J = 9.5)		70.92	159.45
<b>7e</b> <sup>[21]</sup>	CH <sub>2</sub> CH <sub>2</sub> NHCOCH <sub>3</sub>	5.06 (d, 1H, J = 8.3)	7.65 (s, 1H)	65.65	158.25
		5.22 (d, 1H, J = 8.3)		71.31	159.51
<b>7f</b> <sup>[27]</sup>	N=CHPh	5.33 (d, 1H, J = 8.4)	8.43 (s, 1H)	63.10	156.70
		5.62 (d, 1H, J = 8.4)		72.10	157.60
Chemical shift range (Δ)		5.06–5.61	7.54–8.42	63.10–76.67	156.00–160.09

When analyzing the CS of 2,4-N-dimethylglycolurils **7a–f**, the asymmetry of the structures is clearly distinguished. The carbon atoms of the carbonyl groups of compounds **7a–e** shift toward a high-field in the range from 0.2 ppm up to 2.2 ppm relative to the CS C=O of glycoluril **1**. For compound **7f** shielding of the carbonyl group to 4.3 ppm, and the shift of the CS of NH groups to a low-field by 1.3 ppm relative to **1** are observed, which is probably due to the positive mesomeric and negative inductive effect of the N=CHPh substituent.

In the spectra of compounds **7a–f**, the highest deshielding of CH-carbons up to 8.3 ppm from the N-2,8-disubstitution of the molecule was recorded, and the CS of the neighboring CH carbons are manifested in NMR spectra with a shift of ±1.5 ppm relative to **1**.

*Tricycles and tetracycles.* It was interesting to trace the influence of the hard formation of substituents in polycyclic structures **8a–c** and **9a–c** on the CS of the reference atoms of NH, CH–CH, C=O groups of the glycoluril framework (Table 7).

Table 7

Chemical shifts of asymmetric tricyclic **8a–c** and symmetric tetracyclic structures **9a–c**, derivatives of glycoluril **1**

№	Substituting group		<sup>1</sup> H NMR, ppm, (J/Hz)		<sup>13</sup> C NMR, ppm	
	R <sub>1</sub>	R <sub>2</sub>	CH-CH	NH	CH-CH	C=O
<b>1</b> <sup>[19]</sup>			5.24 (s, 2H)	7.16 (s, 4H)	64.60	160.30
<b>8a</b> <sup>[20, 33]</sup>	t-Bu	C <sub>2</sub> H <sub>5</sub>	5.25 (d, 1H, J = 8.0) 5.52 (d, 1H, J = 8.0)	8.03 (s, 1H)	63.40 64.20	157.20 159.40
<b>8b</b> <sup>[20, 33]</sup>	t-Bu	Pr	5.20 (d, 1H, J = 8.0) 5.52 (d, 1H, J = 8.0)	8.00 (s, 1H)	63.40 64.30	157.30 159.50
<b>8c</b> <sup>[20, 33]</sup>	t-Bu	s-Bu	5.25 (d, 1H, J = 8.0) 5.51 (d, 1H, J = 8.0)	7.92 (s, 1H)	63.39 64.35	157.02 159.28
<b>9a</b> <sup>[20]</sup>	c-C <sub>6</sub> H <sub>11</sub>	c-C <sub>6</sub> H <sub>11</sub>	5.50 (s, 2H)	–	64.27	159.27
<b>9b</b> <sup>[20]</sup>	(CH <sub>2</sub> ) <sub>2</sub> COOH	(CH <sub>2</sub> ) <sub>2</sub> COOH	5.56 (s, 2H)	–	64.42	159.37
<b>9c</b> <sup>[20]</sup>	CON(CH <sub>3</sub> ) <sub>2</sub>	CON(CH <sub>3</sub> ) <sub>2</sub>	5.59 (s, 2H)	–	53.18	160.02
Chemical shift range (Δ)			5.20–5.59	7.92–8.03	53.18–64.42	157.02–160.02

Analysis of the CS of tricyclic pentaazabicyclo[5.3.1.0]undecane-1,5-diones **8a–c** and tetracyclic hexahydrohexaazacyclopeite[*def*]fluoren-4,8-diones **9a–c** made it possible to establish that these substances do not have significant differences in NMR signals for glycoluril scaffolds indicating the presence of polycyclic and a rigid frame. It was found that the CS of CH-CH carbons in the **9c** polycycle are shielded by 11 ppm, relative to **1**, which is probably due to the additional shielding field, created by the  $\pi$ -group of NCON(CH<sub>3</sub>)<sub>2</sub>.

The obtained values of CS make it possible to conclude that there is no symmetry in **8a–c** molecules and its presence in **9a–c** substances.

*1,5-C-Substituted glycolurils.* In comparison with N-substituted tetracycles **9a–c**, in the NMR spectra of 1,5-C-substituted glycolurils **10a–h** and their diester polycyclic derivatives **11a–d**, the influence of ether fragments on the CS of atoms of the glycoluril framework is noticeable (Table 8).

From the obtained data of <sup>13</sup>C NMR spectra of substances **10a–h**, **11a–d**, it is seen that the diester fragments shield the signals of the carbon of C–C and C=O groups by an average of 2 ppm.

In compounds **10a–d**, **11a**, **b**, **d**, the CS of C<sub>1</sub>–C<sub>5</sub> carbons, due to their «Quaternary», are shifted to the low-field up to 10 ppm on average and in the case of phenyl substituents at C<sub>1</sub>–C<sub>5</sub> atoms in substances **10e–g**, **11c** up to 15 ppm.

The drift of the CS of NH-groups of substances **10a–h** directly depends on the nature of the substituent at the C–C bond. Thus, electron-donating substituents in substances **10a–d** cause a displacement of the CS on average  $\pm$  0.5 ppm relative to **1**, and the inductive effect of electron-withdrawing substituents in substances **10e–h** deshields the nuclei of NH group protons by 0.6–1.6 ppm relative to **1**.

It is noteworthy, that acceptors at the 1, 5-C-substitution (**10e–h**) do not affect the shielding of C=O in <sup>13</sup>C NMR spectra as compared to the N-substitution (**2f**, **g**, **3d**, **4c**, **e**, **5e–h**, **6f**, **g**, **7f**), which probably indicates the absence in this case of the formation of  $\pi$ -electronic «anisotropy cones» with an additional shielding field.

Table 8

**Chemical shifts of symmetric 1,5-C-substituted glycolurils 10a–h and their diester polycyclic derivatives 11a–d**

№	Substituting group		<sup>1</sup> H NMR, ppm, (J/Hz)		<sup>13</sup> C NMR, ppm	
	R <sub>1</sub>	R <sub>2</sub>	CH-CH	NH	CH-CH	C=O
1 <sup>[19]</sup>			5.24	7.16 (s. 4H)	64.60	160.30
10a <sup>[34, 35]</sup>	CH <sub>3</sub>	CH <sub>3</sub>		7.10 (s. 4H)	75.20	159.30
10b <sup>[34]</sup>	H	CH <sub>3</sub>	4.8 (s. 1H)	7.10 (s. 2H) 7.20 (s. 2H)	69.80 73.10	160.30
10c <sup>[34]</sup>	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		7.10 (s. 2H) 7.20 (s. 2H)	77.80	159.70
10d <sup>[34]</sup>	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -			7.00 (s. 4H)	73.60	160.30
10e <sup>[34, 35]</sup>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>		7.80 (s. 4H)	81.70	160.60
10f <sup>[35]</sup>	3-ClC <sub>6</sub> H <sub>4</sub>	3-ClC <sub>6</sub> H <sub>4</sub>		7.98 (s. 4H)	81.30	160.40
10g <sup>[35]</sup>	4-ClC <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>		7.88 (s. 4H)	81.20	160.30
10h <sup>[36]</sup>	CF <sub>3</sub>	CF <sub>3</sub>		8.83 (s. 4H)	77.11	158.27
11a <sup>[34, 37]</sup>	CH <sub>3</sub>	CH <sub>3</sub>		–	73.40	157.40
11b <sup>[34]</sup>	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		–	73.40 75.60	157.60
11c <sup>[34, 37]</sup>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>		–	79.00	158.00
11d <sup>[38]</sup>	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -			–	72.20	158.00
Chemical shift range (Δ)				7.00–8.83	69.80–81.70	157.40–160.60

*C,N-Substituted glycolurils.* In considering particular cases — compounds **12a–k** (Table 9) and **13a–r** (Table 10) with a mixed type of N- and C-substitution the <sup>13</sup>C NMR spectra are the most informative for the analysis of electronic properties and conformational changes in the glycoluril framework. In the presence of an unsubstituted NH group, its signals in the PMR spectra are observed in the region of 5.91–6.19 ppm for **12a–k** and 7.95–8.66 for **13a–r**.

Table 9

**Chemical shifts of 1,5-C-dimethyl-2,6-N-dimethylglycolurils 12a–k**

№	Substituting group		<sup>1</sup> H NMR, ppm, (J/Hz)	<sup>13</sup> C NMR, ppm	
	R <sub>1</sub>	R <sub>2</sub>	NH	CH-CH	C=O
1 <sup>[19]</sup>					
12a <sup>[39]</sup>	H	H	5.91 (s. 1H)	74.70 83.10	161.00
12b <sup>[39]</sup>	CH <sub>3</sub> CO	H	6.00 (s. 1H)	76.40 78.50	153.00 157.20
12c <sup>[40]</sup>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>8</sub> COCH <sub>2</sub> CO	H	6.05 (s. 1H)	76.60 76.71	152.73 157.14
12d <sup>[39]</sup>	CH <sub>3</sub> CH=CHCO	H	6.13 (s. 1H)	76.20 78.20	152.60 157.10
12e <sup>[39]</sup>	CH <sub>3</sub> COCH <sub>2</sub> CO	H	5.95 (s. 1H)	76.60 78.70	152.80 157.10
12f <sup>[39]</sup>	(CH <sub>3</sub> )CCOCH <sub>2</sub> CO	H	6.04 (s. 1H)	78.60 86.60	152.60 157.20

Continuation of Table 9

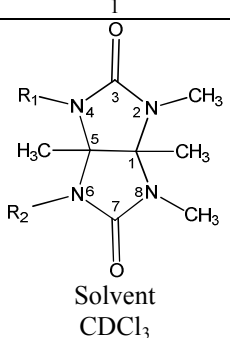
	2	3	4	5	6	7
 Solvent CDCl <sub>3</sub>	12g <sup>[39]</sup>	CH <sub>3</sub> C(OH)CH <sub>2</sub> CO	H	6.19 (s. 1H)	76.70 78.70	152.09 157.10
	12h <sup>[39]</sup>	CH <sub>3</sub> COCH(CH <sub>3</sub> )CO	H	5.94 (s. 1H)	76.90 78.90	153.00 157.20
	12i <sup>[39]</sup>	CH <sub>3</sub> CO	CH <sub>3</sub> CO	-	77.30 80.40	153.10
	12j <sup>[39]</sup>	(CH <sub>3</sub> ) <sub>3</sub> CCO	CH <sub>3</sub> CO	-	78.40 80.50	152.80 153.60
	12k <sup>[39]</sup>	CH <sub>2</sub> =CHCO	CH <sub>3</sub> CO	-	77.90 80.50	153.00
Chemical shift range (Δ)				5.91–6.19	74.70–86.60	152.09–161.00

Table 10

Chemical shifts of 1, 5-C-diphenylglycoluril 13a–r

№	Substituting group			<sup>1</sup> H NMR, ppm, (J/Hz) NH	<sup>13</sup> C NMR, ppm	
	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>		CH-CH	C=O
13a <sup>[41]</sup>	CH <sub>3</sub>	CH <sub>3</sub>	H	8.31 (s. 2H)	83.70	159.00 160.10
13b <sup>[21, 42]</sup>	CH <sub>3</sub>	CH <sub>3</sub>	(CH <sub>2</sub> ) <sub>2</sub> OH	8.54 (s. 1H)	82.64 87.74	158.62 59.86
13c <sup>[21, 42]</sup>	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>2</sub> COOH	8.61 (s. 1H)	82.85 87.05	158.58 159.46
13d <sup>[21, 43]</sup>	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>2</sub> COOCH <sub>3</sub>	8.66 (s. 1H)	83.00 87.98	158.64 158.94
13e <sup>[21]</sup>	CH <sub>3</sub>	CH <sub>3</sub>	(CH <sub>2</sub> ) <sub>2</sub> NH(CO)CH <sub>3</sub>	7.95 (s. 1H)	82.48 87.64	158.42 159.52
13f <sup>[27]</sup>	CH <sub>3</sub>	CH <sub>3</sub>	(CH <sub>2</sub> ) <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	8.49 (s. 1H)	83.00 87.90	158.40 161.00
13g <sup>[21]</sup>	H	CH <sub>2</sub> COOCH <sub>3</sub>	CH <sub>2</sub> COOCH <sub>3</sub>	8.28 (s. 2H)	83.70	158.69
13h <sup>[21]</sup>	CH <sub>2</sub> COOCH <sub>3</sub>	H	CH <sub>2</sub> COOCH <sub>3</sub>	8.29 (s. 2H)	79.95 88.28	159.00
13i <sup>[21]</sup>	(CH <sub>2</sub> ) <sub>2</sub> OH	H	(CH <sub>2</sub> ) <sub>2</sub> OH	8.16 (s. 2H)	79.44 89.79	160.28
13j <sup>[21]</sup>	(CH <sub>2</sub> ) <sub>2</sub> OH	H	CH <sub>3</sub>	8.11 (s. 2H)	79.11 89.05	159.59 160.09
13k <sup>[21]</sup>	(CH <sub>2</sub> ) <sub>2</sub> OH	H	CH <sub>2</sub> COOPr- <i>i</i>	8.12 (s. 1H) 8.26 (s. 1H)	79.85 89.02	159.12 159.92
13l <sup>[21]</sup>	CH <sub>3</sub>	H	n-Bu	7.98 (c. 1H) 8.11 (s. 1H)	79.02 89.04	159.65
13m <sup>[21]</sup>	CH <sub>3</sub>	H	COOPr- <i>i</i>	8.10 (s. 1H)	79.37 88.44	159.10 159.36
13n <sup>[21]</sup>	CH <sub>3</sub>	H	(CH <sub>2</sub> ) <sub>2</sub> NH <sup>+</sup> (CH <sub>3</sub> ) <sub>2</sub> Cl	8.23 (s. 1H) 8.40 (s. 1H)	79.33 89.17	159.52 59.84
13o <sup>[21]</sup>	CH <sub>3</sub>	H	(CH <sub>2</sub> ) <sub>3</sub> COOPr- <i>i</i>	8.04 (s. 1H) 8.14 (s. 1H)	79.03 89.07	159.63
13p <sup>[21]</sup>	CH <sub>3</sub>	H	(CH <sub>2</sub> ) <sub>3</sub> CHCOOHNH <sub>2</sub>	8.08 (s. 1H) 8.12 (s. 1H)	79.00 89.19	158.78 159.68
13q <sup>[21]</sup>	CH <sub>3</sub>	H	COOPr- <i>i</i>	8.26 (s. 1H)	79.37 88.44	159.10 159.36
13r <sup>[27]</sup>	(CH <sub>2</sub> ) <sub>3</sub> COOCH <sub>3</sub>	H	(CH <sub>2</sub> ) <sub>3</sub> COOCH <sub>3</sub>	8.21 (s. 1H)	83.90	159.00
Chemical shift range (Δ)				7.95–8.66	79.00– 89.79	158.40– 161.00

It should be noted that in the analysis of the CS of 1,2,5,6-tetramethylglycolurils **12a–k**, the solvent plays an important role, because the spectra of these compounds were recorded in the CDCl<sub>3</sub> solvent and the proton signals of unsubstituted NH-groups are shifted to the region of high-field (5.9–6.2 ppm) relative to **1**, due to the absence of interactions with the solvent. In this case, the effect of the solvent on the CS of carbon atoms is negligible.

In 1,2,5,6-tetramethylglycolurils **12a–k**, the CH-carbon signals are deshielded due to their «Quaternary», on average, by 10 ppm, and in N-alkylglycoluril **12a** from the N-dimethyl substitution side, up to 22 ppm, relative to the CS of glycoluril **1**. In this case, the positive mesomeric effect of methyl groups [22; 712] «pushes out» an unshared pair of electrons from nitrogen atoms to generalize with the ring, partially hybridizing neighboring C–C atoms to the sp<sup>2</sup> state.

The CS of the C=O groups of compounds **12b–k** (field interval from 152.1 ppm to 157.2 ppm) demonstrate the presence of acceptor acylsubstituents as  $\pi$ -electron groups that create «anisotropy cones» (Fig. 4), due to which shielding occurs of carbonyl carbon relative to **1** and **12a**.

After analyzing the NMR data for compounds **13a–r** (Table 10), it is possible to clearly determine the presence of symmetry in the molecules and its type ( $\sigma^1$  or  $\sigma^2$ ).

The CS of NH-protons of 1,5-C-diphenylglycolurils **13a–r** appear singlet peaks and are shifted to a low-field by 0.8–1.5 ppm relative to **1**, which may be due to the electron-withdrawing effect of phenyl substituents. The effect of the latter is also clearly observed in unsubstituted at nitrogen atoms diphenylglycoluril **10e** (Table 8, (7.80 ppm)).

Carbons of the methine group in substances **13a–r** are deshielded at 14.4–24.6 ppm relative to **1**, where the largest shift of the CS of C5-carbon to the low-field region is observed from the 4, 6-N-substitution side.

### Conclusions

The analysis of CS in the NMR spectra of glycoluril **1** and its derivatives **2–13** (86 compounds in total) makes it possible to accurately identify the spatial symmetry configurations of glycolurils, in the presence of which ( $\sigma^1$  and/or  $\sigma^2$ ) one half of the molecule is a mirror image of the other, where the enantiotopic hydrogen and carbon atoms of the bicyclic framework are manifested by equivalent signals.

In the NMR spectra of asymmetric derivatives of glycolurils, in particular N-monosubstituted **2**, N-trisubstituted **7**, tricyclic derivatives **8** and glycolurils with a mixed type of N-,C,C-substitution **12**, **13**, it is seen that the molecules lose the symmetry planes  $\sigma^1$  or  $\sigma^2$  and the equivalent CS of protons and carbons of glycoluril bicycles manifest as nonequivalent peaks.

Molecules **3** having one plane of symmetry  $\sigma^1$  give equivalent signals of carbonyl carbons and singlet signals of two unsubstituted NH-groups, but protons and carbons of the CH–CH fragment in such symmetric molecules resonate in pairs. Glycolurils with the symmetry plane  $\sigma^2$  (**4**), on the contrary, are identified only by nonequivalent CS of C=O-groups.

The CS of <sup>1</sup>H and <sup>13</sup>C of the glycoluril framework of the symmetric molecules N-anti-**5**, N-tetra-**6**, and C-substituted compounds **10**, **11** are present in the NMR spectra in the form of equivalent singlet signals, which indicates the presence of symmetry planes  $\sigma^1$  and  $\sigma^2$  in the molecules.

In the presence of alkylsubstituents at the nitrogen atoms in the structures of the studied glycolurils **2–13**, the shielding of C=O by 1-3 ppm relative to the signal C=O glycoluril **1** is observed, which can be determined by the effects of steric inhibition of conjugation in the amide fragment with a corresponding decrease in the order of the amide bond [44]. However, in the study of N-alkylglycolurils by the X-ray diffraction method [45], it was determined that nitrogen atoms with their unshared electron pairs participate in conjugation with C=O groups and have a flattened geometry; therefore, N-C(Alk) bonds are almost coplanar to the rings. In the presence of a decrease in the order of the amide bond, the coplanarity of this fragment should probably be violated, as in the case of glycolurils with acceptor substituents [30, 46].

It was shown that for mono- (**2**) and disubstituted glycolurils (**3**, **4**, **5**) at nitrogen atoms, the positions of the signals of unsubstituted NH groups in the NMR spectra are in the range from 7.0 ppm up to 9.9 ppm.

In the presence of electron-donating substituents in the structures of substances **2a–e**, **3a–c**, **4a**, **b**, **d**, **5e–h**, **7a–e**, the shift of the CS of the NH-groups occurs in the range of  $\pm 0.6$  ppm. relative to **1**, which indicates a weak effect of substituents for inhibition of amide conjugation. And in the presence of acceptor substituents in substances **2f**, **g**, **3d**, **4c**, **5e–h**, **7f**, the CS of the NH-group shifts in the low-field region. Moreover, the stronger the inductive effect of the acceptor, the farther the position of the signal in the PMR spectrum (up to 9.9 ppm, (**5g**, **h**), glycoluril **1** (7.14 ppm)). This fact is explained by a violation of the electron density of the amide fragment (Fig. 2), where the substituents reduce the bond multiplicity and the unshared

pair of electrons of the neighboring unsubstituted NH group is isolated from the plane of the imidazolinone ring. Such regularities are also observed for 1, 5-C-substituted glycolurils **10**, **12**, **13**, where electron-donating substituents in substances **10a–d** cause a shift of the CS of NH-groups on average  $\pm 0.5$  ppm, relative to **1**. The negative inductive effect of electron-withdrawing substituents in substances **10e–h**, **13a–r** redistributes the electron density from imidazolinone rings, thereby the nuclei of NH-groups are deshielded by 0.6–1.6 ppm, relative to **1**.

In the  $^{13}\text{C}$  NMR spectra of compounds **2f**, **g**, **3d**, **4c**, **5e–h**, **7f**, **12b–k**, in which substituents with an electron-withdrawing property are present, shielding of the C=O signal to 18 ppm is observed, moreover, the stronger its acceptor character, the signal C=O shifts more to the region of a high-field. There are a number of factors [47; 163] that can affect the shielding constant of the carbonyl fragment in glycolurils **2–13** of which the most significant are the hybridization and resonance effects of substituents with magnetic anisotropy of neighboring groups. In the presence of an electron-withdrawing substituent at nitrogen atoms in the glycoluril framework, more efficient hybridization of carbonyl carbon atoms to the  $\text{sp}^2$  state and in the C–N fragment to the  $\text{sp}^3$  state occurs [48]. An additional effect is exerted by the circulation of electrons of electron-withdrawing substituents with the presence of  $\pi$ -bonds [23; 183], which leads to the appearance of additional fields or «anisotropy cones» (Fig. 4). This circumstance mainly depends on the geometry of the molecule [24].

It should be added that the shielding of carbonyl carbon in the  $^{13}\text{C}$  NMR spectra correlates with the C=O bond length established by X-ray diffraction studies [18, 30, 32]. In compounds **5h** and **6f**, the nuclei of carbonyl carbon atoms show the CS at 149.00 ppm and 151.58 ppm respectively, and the length of C=O bond is on average 1.19 Å, whereas the CS of the carbonyl carbon atoms of glycoluril **1** is 160.30 ppm, and the length of the C=O bond is 1.21 Å. Thus, the results of NMR and X-ray diffraction studies of compounds **5h** and **6f** are consistent with each other and complement each other.

In compounds with electron-donating substituents at nitrogen atoms (in substances **2f**, **g**, **3d**, **4c**, **5e–h**, **7f**, **12b–k**), deshielding of C–C-carbon signals on average by 10–22 ppm is observed, which also can be explained by the general redistribution of electron density in imidazolinone cycles. Thus, the enhanced electron supply by electron-donating groups to nitrogen atoms [22; 712] affects the possibility of pairing its unshared pair of electrons with a five-membered cycle. Therefore, C–C-carbons can partially acquire the properties of  $\text{sp}^2$ -hybridized atoms due to an increase in the electron density, which shifts the CS carbon in the field of «molecular currents» or  $\pi$ -conjugated systems. In this case, a local paramagnetic contribution arises due to the anisotropy of the electron density distribution on C–C carbons for which the CS is measured.

Around the C–C nuclei, an electron circulation occurs, which creates either a secondary magnetic field in the same direction as the superimposed field, or a diamagnetic field that is weaker due to circulation restrictions, which makes a significant contribution to the CS of the CH–CH groups. A similar effect in the case of other nuclei (N, F, O) is observed, in which the ground and excited states are closer in energy [50].

However, anisotropic electron circulation for CH–CH proton atoms in **2f**, **g**, **3d**, **4c**, **5e–h**, **7f**, **12b–k**, substances is not observed, because the excitation energies of empty orbitals of a hydrogen atom with higher energies are very high. The excited state is far removed from the ground one, and this effect can only make an insignificant contribution to most the CS of protons [49; 163].

In a general analysis of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of glycolurils **1–13**, it is clearly seen that for any type of N-,C-substitution, shielding of the carbonyl atom C=O in the imidazolidinone ring is observed.

Thus, in this work, an analysis of the nuclear magnetic resonance for glycoluril derivatives was carried out, where the NMR signals were characterized from the position of molecular symmetry and the nature of the substituents.

The generalization performed makes it possible to distinguish between symmetric and asymmetric molecules, to distinguish impurity signals, which can often accompany the synthesis of bicyclic bisureas. According to NMR spectra, glycolurils with electron-withdrawing N-substituents by shielding the signals of the carbon atom of C=O groups and electron-donating N-substituents by deshielding of CH–CH-carbons can be clearly distinguished.

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### Гликолурил және оның өнімдерін <sup>1</sup>H және <sup>13</sup>C ЯМР спектроскопия әдісімен зерттеу

Гетероциклдық қосылыстар химиясында бициклды зәр қышқылдары, әсіресе 2,4,6,8-тетраазабицикло[3.3.0]октан-3,7-дион 1 (гликолурил) ерекше орынға ие. Гликолурил — молекула құрамында екі реакциялық орталықтың (4 донорлық топ (–NH) және 2 акцепторлы (C=O)) болуымен байланысты құрамындағы карбамидті фрагменті молекуланың қасиетін анықтайтын жартылай функционалды қосылыс. Жұмыста гликолурил және оның өнімдерінің (86 қосылыс) <sup>1</sup>H және <sup>13</sup>C ЯМР спектріндегі химиялық қозғалысқа талдау жасалды. Зерттеу барысында орнын алмастырушылардың донорлық-акцепторлық қасиетінің симметрия және асимметрия позициясынан бициклды қарқастағы электрондық тығыздыққа әсері анықталды. Гликолурилдің <sup>1</sup>H және <sup>13</sup>C ЯМР спектрінің жалпы талдамасы бициклды қарқастың сутегі мен көмірқышқылдың энантиотопты атомдары баламалы сигналдармен белгіленетін молекула симметриясының кеңістіктегі конфигурациясын нақты анықтауға мүмкіндік береді. Сонымен қатар N-алмастырылған гликолурилды қарқастың ЯМР спектріндегі <sup>1</sup>H және <sup>13</sup>C химиялық қозғалыс бойынша C=O-топтың көміртек атомдарын экрандау

бойынша электронды акцепторлы орын басушылары бар гликолурилдерді және СН-СН-көміртектерді экрандамайтын электронды донорлы орын басушылары бар гликолурилдерді айыруға болады. Бұл анизотропия салдарынан электронды тығыздық қайта бөлініп, локальді парамагнитті салымдардың пайда болуына байланысты. Гликолурилдердің  $^1\text{H}$  және  $^{13}\text{C}$  ЯМР спектрінің жалпы талдамасында N-, C-алмастырудың қай түрінде болмасын C=O карбонильді атомның имидазолидинді сақинада экрандалатыны айқын көрінеді.

*Кілт сөздер:* гликолурил, ЯМР, химиялық қозғалыстар, симметрия, энантиотопты атомдар, экрандау, экрандалған, SAR талдау.

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## Исследование гликолурила и его производных методами $^1\text{H}$ и $^{13}\text{C}$ ЯМР спектроскопии

В химии гетероциклических соединений особое место занимают бициклические мочевины, а именно 2,4,6,8-тетраазабицикло[3.3.0.]октан-3,7-дион (гликолурил). Гликолурил — полифункциональное соединение, в котором карбамидный фрагмент определяет свойства молекулы, обусловленные наличием двух реакционных центров в составе молекулы (4 донорные группы (–NH) и 2 акцепторные (C=O)). В данной работе проведен анализ химических сдвигов в спектрах  $^1\text{H}$  и  $^{13}\text{C}$  ЯМР гликолурила и его производных (86 соединений), для выявления влияния донорно-акцепторного характера заместителей на изменения электронной плотности в бициклическом каркасе с позиции симметрии и асимметрии. Общий анализ спектров  $^1\text{H}$  и  $^{13}\text{C}$  ЯМР гликолурилов позволяет точно выявить пространственные конфигурации симметрии молекул, при наличии которой ( $\sigma^1$  и/или  $\sigma^2$ ), энантиотопные атомы водорода и углерода бициклического каркаса проявляются эквивалентными сигналами. Также по химическим сдвигам  $^1\text{H}$  и  $^{13}\text{C}$  в спектрах ЯМР N-замещенного гликолурильного каркаса можно четко различать гликолурилы с электроакцепторными заместителями по экранированию атомов углерода C=O-групп и электронодонорными заместителями по дезэкранированию СН-СН-углеродов, что обусловлено перераспределением электронной плотности и возникновением локальных парамагнитных вкладов вследствие анизотропии. При общем анализе спектров ЯМР  $^1\text{H}$  и  $^{13}\text{C}$  гликолурилов отчетливо видно, что при любом типе N-, C-замещения наблюдается экранирование карбонильного атома C=O в имидазолидиноновом кольце.

*Ключевые слова:* гликолурил, ЯМР, химические сдвиги, симметрия, энантиотопные атомы, экранирование, дезэкранирование, PCA анализ.

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