Structural analogs of tetrapyrrole macrocycles and their biological properties

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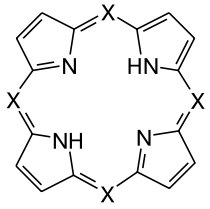
The review summarizes data on the synthesis and properties of analogs of ABBB- and ABAB-type tetrapyrrole macrocycles and their metal complexes. The structural features of these compounds are discussed. Data on aromaticity and biological properties are considered.

Key words: porphyrazine, phthalocyanine, analogs, triazoleporphyrazine, macroheterocyclic compounds, complexes, synthesis, aromaticity, biological properties.

Among a vast diversity of macroheterocyclic compounds, natural tetrapyrrole macrocyclic pigments, such as hemoglobins, chlorophylls, cytochromes, *etc*., are of particular interest. These compounds play a crucial role in vitally important processes of photosynthesis and breathing and are involved in controlling fine metabolic processes in living organisms.

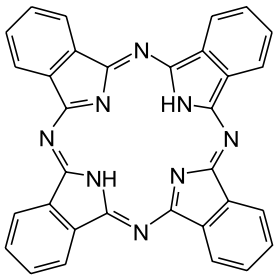
These compounds are based on the aromatic macrocycle consisting of 16 C and N atoms and containing 18 π electrons. Porphine **1a** is the parent compound of this class.

Due to the unique structures, porphyrins and their metal complexes possess numerous interesting properties and have found wide application in science, techniques, and medicine. In particular, these compounds are used as photosensitizers for photodynamic cancer therapy,[1] catalysts,[2] and electrochemical sensors[3] and are promising materials for nanotechnology, nonlinear optics, optoelectronics, liquid-crystalline systems,[4] *etc*.



1a,b

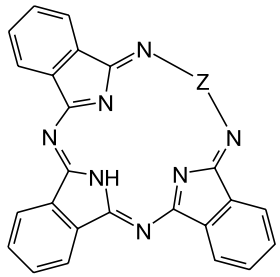
X = CH (**1a**), N (**1b**)



2

Numerous synthetic porphyrin derivatives, for example, tetraazaporphine (porphyrazine) **1b** and tetraazabenzoporphine (phthalocyanine) **2** are known, which are of considerable practical importance. In particular, phthalocyanines serve as pigments and dyes with a deep blue color superior in purity and brightness.[5,6]

Attempts to expand the color range of phthalocyanine dyes led to the discovery of new-generation macroheterocyclic compounds. The latter are structural analogs of phthalocyanine, in which one or two isoindole fragments are replaced by aromatic diamines (compounds **3** and **4**).



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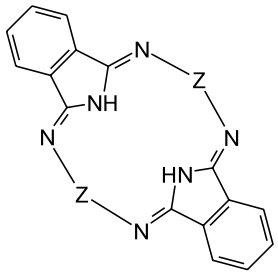

4

An improvement of methods for the synthesis of these compounds with the use of various diamines allows the preparation of macroheterocyclic compounds, which differ in the number and composition of small rings linked to each other to form a single macrocyclic system. This makes it possible to change the size of the coordination cavity and the constituent atoms as desired. This class of compounds is very promising and attractive for designing compounds with properties of practical importance, in particular, with potential biological activity, because the structure of the macrocyclic skeleton can be modified in a wide range, including the involvement of pharmacophore groups, the introduction of substituents at the periphery, and the introduction of metal atoms into the inner coordination cavity.

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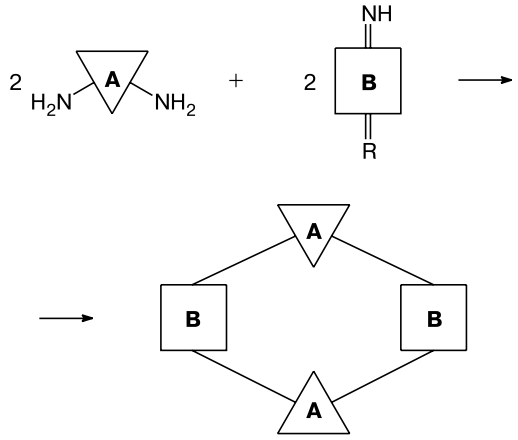
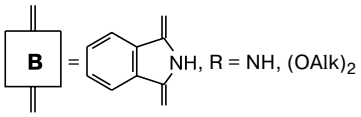
A general method for the synthesis of symmetrical macroheterocyclic compounds **4** is based on the reaction of diamines with phthalonitrile or its functional derivatives, *viz.*, 1,3-diimino- or 1,1-dialkoxy-3-iminoisoindolines (Scheme 1).

Scheme 1

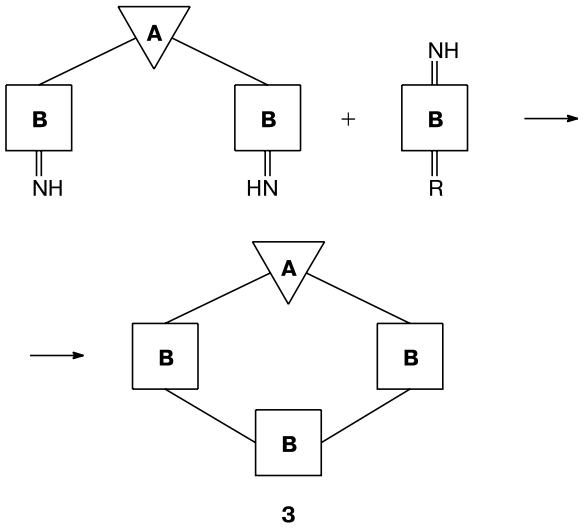


4



The reactions of products **BAB** with functional phthalonitrile derivatives, *viz.*, 1,3-diiminoisoindoline or 1,1-dialkoxy-3-iminoisoindolines, produce derivatives **3** (Scheme 2).

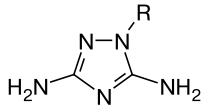
Scheme 2



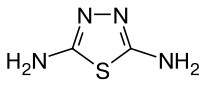
3

Aromatic five- or six-membered carbo- or heterocyclic compounds containing amino groups at positions 1 and 3 are generally used as the starting diamines. The reactions with 1,4-di- and polynuclear diamines afford macrocycles with a larger inner cavity.[7,8]

Being involved in macrosystems, cyclic fragments of diamines can maintain or interrupt conjugation in the macrocycle. In this connection, pyrrole heteroanalogs, for example, diamino derivatives of 1,2,4-triazole **5—8** (see Refs 9—11) and 1,3,4-thiadiazole **9** (see Ref. 12) are of particular interest. The presence of azole fragments allows establishment of a conjugated system in the macrocycle analogous to the porphyrazine system.



5—8

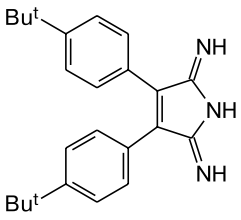


9

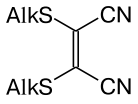
R = H (**5**), Ph (**6**), Nphth (**7**), $C_{12}H_{25}$ (**8**)

Substituted *o*-dinitriles are the key compounds for the synthesis of substituted macroheterocycles.[13] Procedures for the access to substituted phthalonitriles were considered in many reviews (see, for example, Refs 13—16).

Maleonitrile and its derivatives are also of interest for the synthesis of macroheterocycles. However, literature data on the synthesis of such compounds containing pyrrole fragments are scarce. At the same time, even first attempts to use substituted maleonitriles and their functional derivatives led to the discovery of new macroheterocyclic compounds,[17,18] which were synthesized starting from 3,4-bis(4-*tert*-butylphenyl)-2,5-diiminopyrroline[19] (**10**) and di(alkylthio)maleonitriles **11—13**.[20]



10



11—13

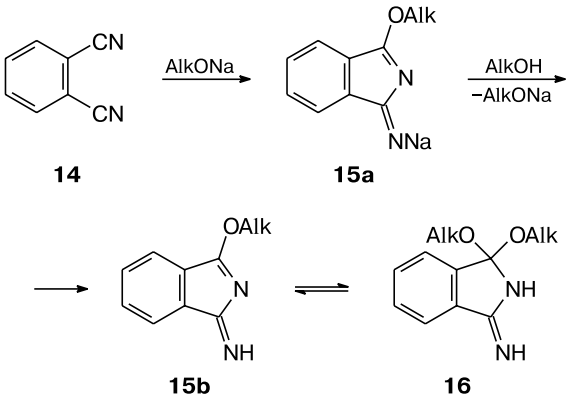
Alk = C_4H_9 (**11**), C_8H_{17} (**12**), $C_{12}H_{25}$ (**13**)

Phthalonitrile and substituted phthalonitriles as such are rarely used for the synthesis of macrocycles. Generally, these compounds are transformed into more reactive alkoxyimino- or diiminoisoindolines, which can be considered as the corresponding benzopyrrolines.

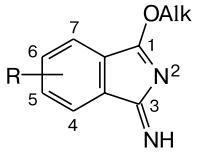
The reactions of phthalonitrile with alkali metal alkoxides in an alcoholic solution (Alk = Me, Et, or Pr) proceed in good yield at room temperature[21] (Scheme 3).

The introduction of substituents into phthalonitrile molecules is accompanied by lowering of the molecular symmetry, which enables the formation of regioisomeric 4- or 7-alkoxy compounds in the case of 3-substituted

Scheme 3



phthalonitriles and 5- or 6-regioisomers in the case of 4-substituted phthalonitriles.



17a,b—20a,b

Compound	R	Compound	R
17a	4-NO_2	**19a**	4-Br
17b	7-NO_2	**19b**	7-Br
18a	4-Cl	**20a**	5-Bu^t
18b	7-Cl	**20b**	6-Bu^t

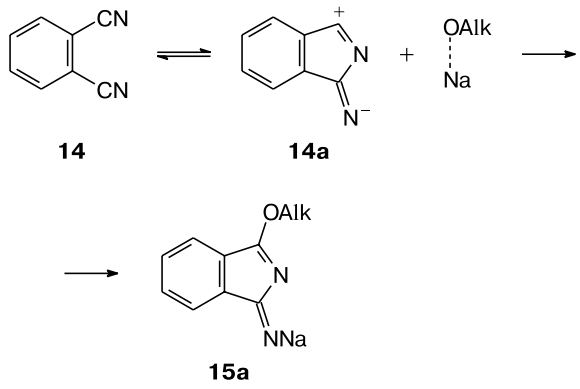
It was found that substituents can affect the reactivity of phthalonitriles. Electron-withdrawing or weak electron-donating substituents at position 3 or 4 do not prevent the formation of the corresponding alkoxy compounds (for example, **17—20**) under standard conditions,[21] whereas 3-amino-, 3,6-dihydroxy-, and 3,6-dimethoxyphthalonitrile do not give alkoxy compounds under these conditions.

Several views on the mechanism of this reaction were published. According to the most popular hypothesis, which was formulated as early as 1956,[21] phthalonitrile **14** is transformed into bipolar ion **14a** in a strongly polar alcoholic medium (Scheme 4). The addition of alkali metal alkoxide to the latter ion affords 1*H*-benzo[*c*]pyrrole derivative **15a**.

It should be emphasized that the formation of bipolar ion **14a** is postulated in this mechanism, and the role of the polarizing effect of the medium remains unclear. No evidence in favor of this mechanism has been presented.

The reaction of phthalonitrile with sodium methoxide in benzene affords the addition product of sodium methoxide to one of the nitrile groups, whereas the reaction in methanol gives the isoindolenine derivative.[22]

Scheme 4

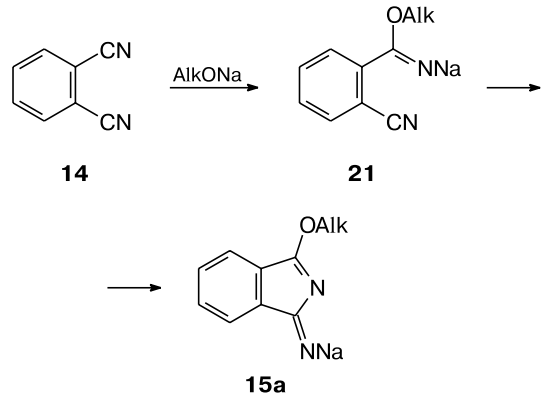


Hence, the reaction apparently does not follow the mechanism presented in Scheme 4.

The formation of the isoindolenine derivative by intramolecular cyclization of the monoaddition product cannot be ruled out as well. The results of kinetic investigations of the reaction of phthalonitrile with phenol are in favor of this mechanism.[23]

Based on the available published data and theoretical investigations (see, for example, Ref. 24), the following mechanism of the isoindolenine ring formation seems to be most probable: the formation of the addition product of an alkali metal alkoxide molecule at one of the nitrile groups of phthalonitrile followed by its intramolecular cyclization (Scheme 5).

Scheme 5



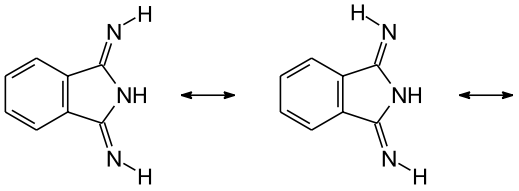
The influence of substituents on the pathway and rate of this reaction were explained in terms of this two-step mechanism.[25]

1,3-Diiminoisoindoline and substituted 1,3-diiminoisoindolines were prepared by the reactions of the corresponding phthalonitriles with ammonia in methanol in the presence of sodium methoxide.[21] Apparently, this compound is formed *via* 3-imino-1-methoxyisoindolenine,

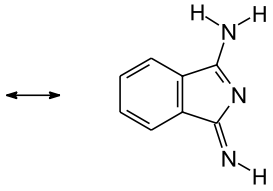
which reacts with ammonia to give the target product. The mechanism of this reaction was studied by the semiempirical AM1 method.[26]

The conformational and tautomeric transformations of 1,3-diiminoisoindoline (Scheme 6) and the influence of substituents and solvents on the energetics of isomeric transformations were investigated.[27]

Scheme 6



22A **22B**

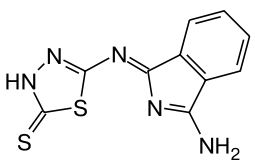


23

An analysis of the critical points on the potential energy surface showed that *cis* form **22A** is the most stable conformation. The energy barrier for the planar inversion (**22A** → **22B**) is rather low (~20 kcal mol^{-1}). For tautomeric transformations (**22B—23**) through intramolecular transfer, the energy barrier is ~70 kcal mol^{-1}. Calculations performed in the supramolecular approximation demonstrated that the prototropic rearrangement in hydroxy-containing solvents (MeOH or H_2O) requires lower energy (by ~17 kcal mol^{-1}). The results of these calculations are in qualitative agreement with the results of *ab initio* calculations (the 6-31G basis set) for the intermolecular proton transfer in formamidine hydrate,[28] which is also accompanied by a decrease in the activation energy by 20.8 kcal mol^{-1} compared to the intramolecular transfer in formamidine.

Condensation products of 1,3-diiminoisoindoline with amines at one of imino groups are of particular interest because they are intermediates in the synthesis of macroheterocycles.

The structure of one of these products, *viz.*, 2-(1-aminoisoindolenin-3-ylideneamino)-5-thioxo-1,3,4-thiadiazol-4-ine (**24**), was established by X-ray diffraction.[29,30]



24

The energy profile for internal rotation of the thiadiazoline (thiadiazole) fragment about the N—C single

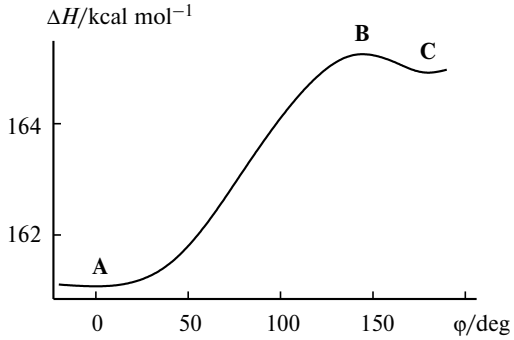
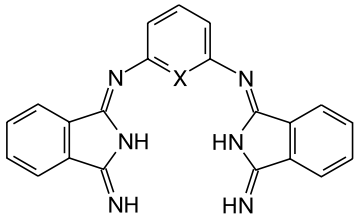


Fig. 1. Energy profiles for internal rotation of tautomer **24**.

bond in molecule **24** was studied by the AM1 semiempirical quantum chemical method. The results of the analysis are presented in Fig. 1.

In the considered configurational space, the internal rotation has a low energy barrier $\Delta\Delta G$ = 4.02 kcal mol^{-1}. Hence, this molecule can be assigned to structurally flexible compounds. Therefore, external rather than internal factors play the decisive role in stabilization of a particular configuration. This is observed in the crystal structure where form **C** (φ = 180°) is stabilized by intermolecular interactions.

Bis(3-iminoisoindolin-1-ylideneamino)arenes and -azoles (BIA) are important intermediates in the synthesis of both symmetrical and nonsymmetrical macroheterocycles.[31—33] Bis(3-iminoisoindolin-1-ylideneamino)arenes **25** and **26** have received most attention.



25, 26

X = CH (**25**), N (**26**)

In spite of the structural similarity, these compounds have different reactivities. For example, compound **25** reacts with 1,3-diiminoisoindoline to form an ABBB-type macrocycle, whereas an attempt to synthesize the analogous product from compound **26** under these conditions failed.[31]

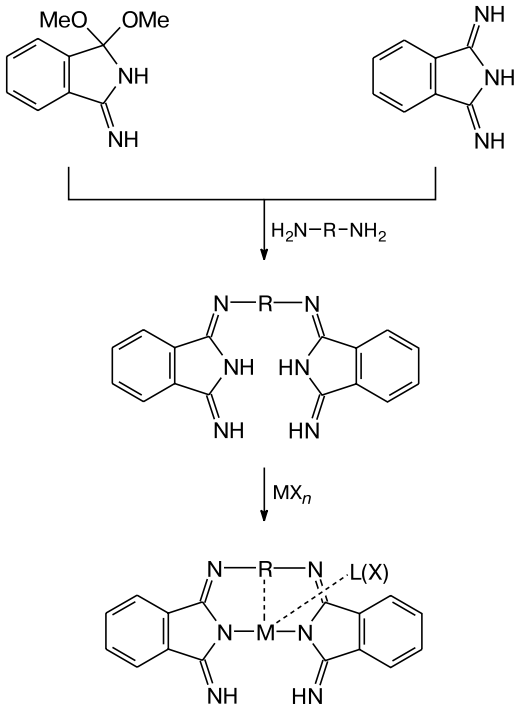
The structures of products **25** and **26** are characterized by the presence of two rather "heavy" benzopyrrole fragments linked to the diamine fragment by aza bridges, which apparently determines the tendency of molecules **25** and **26** to form nonplanar structures due to internal rotation about N—C single bonds.

The planar inversion of the hydrogen atoms of the terminal imino groups, tautomerism, and internal rota-

tion in molecules **25** and **26** were studied by quantum chemical methods.[34] An analysis of the critical points on the potential energy surface showed that the internal rotations have low energy barriers and contribute to structural flexibility of the molecules. It was found that solvation by aprotic solvents, such as DMF, and to an even greater extent, complexation with metals stabilize molecules and have no substantial effect on the electronic structure of the terminal imino groups. In addition, the distance between the nitrogen atoms of these groups is shorter than that in the starting three-membered product. Due to these factors altogether, such metal complexes can be considered as convenient templates for the synthesis of macroheterocycles.

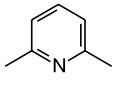
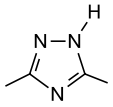
Heating of aromatic diamines with 1,3-diiminoisoindoline or 1,1-dialkoxy-3-iminoisoindoline in methanol[31] (Scheme 7) is most commonly used for the synthesis of BIA.

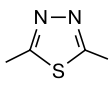
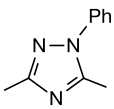
Scheme 7



26a,b, 27a—e, 28a,b,d, 29b

M = Zn (**a**), Al (**b**), Cu (**c**), Co (**d**), Ni (**e**)

R =  (**26**),  (**27**),

 (**28**),  (**29**)

The data on the reaction products of BIA with metal salts are scarce and contradictory. For example, the synthesis of 1 : 1 complexes of 2,6-bis(3-iminoisoindolin-1-ylideneamino)pyridine with Cu, Ni, Co, and Au was documented.[35] At the same time, copper complexes of BIA based on phenylene-1,3-diamine, 3,5-diamino-1,2,4-triazole, and 2,6-diamino-4-chloro-1,3,5-triazine have the composition 2 : 1.[36]

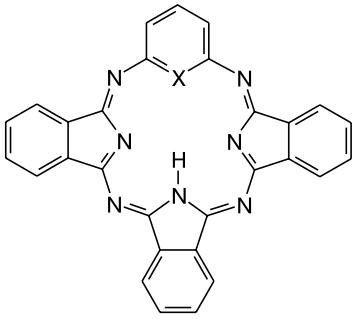
In addition, the synthesis of 1 : 1 metal complexes **28a,b** was documented (see Scheme 7).[37] The latter compounds were used for the template synthesis of **ABBB**-type macrocycles.

ABBB-Type macroheterocyclic compounds

In recent years, noncentrosymmetric analogs of tetrapyrrole compounds have attracted considerable attention.[38—40] These compounds possess properties of practical importance, such as nonlinear optical properties, the ability to form ordered monomolecular Langmuir—Blodgett layers, *etc.*

An elegant approach is based on the replacement of one of the pyrrole or isoindole fragments by an aromatic diamine fragment giving rise to **ABBB**-type structures.

Macrocycle **30a** was the first representative of this class[31] (attempts to extend this approach to the synthesis of macrocycle **30b** were unsuccessful).



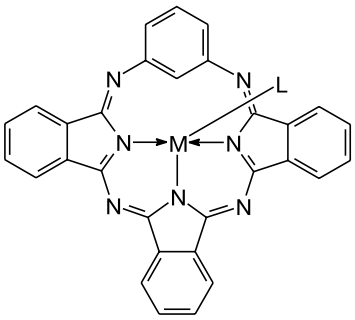
30a,b

X = CH (**a**), N (**b**)

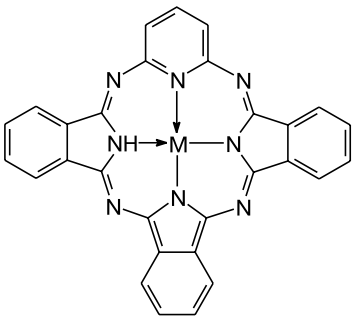
Like phthalocyanine, macrocycle **30a** can form complexes with metals. The corresponding metal complexes **31a—c** and **32a—c** were synthesized for the first time by the reactions of a solution of **30a** with copper(II) or nickel(II) acetate in refluxing pyridine or by the reaction with cobalt(II) acetate in refluxing benzyl alcohol.[31,41] It was noted[41] that the metal complexes are cations but the nature of the counterion (L) was not discussed.

In more recent publications,[42,43] the acetate anion was assumed as the counterion in the cases when metal acetates were used for complexation.

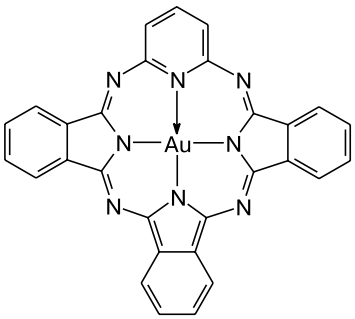
The kinetics of the formation and destruction of nonsymmetrical metal complexes was investigated.[44,45]



31a—c



32a,b



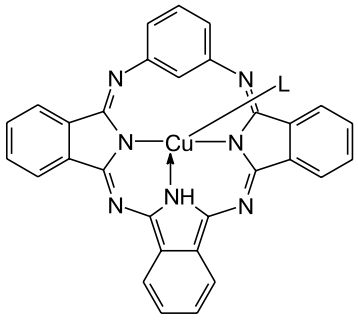
32c

M = Cu (**31a**, **32a**), Ni (**31b**, **32b**), Co (**31c**)
L = OAc, Cl, OH

Metal complexes **31a—c** were demonstrated to be rather stable and have rather high thermal stabilizing activity[46] with respect to polycaproamide. Complex **31a** (L = AcO) has found practical application as a thermo- and light-stabilizer for polymers under the commercial name Stabilin-9.[47]

The discovery of properties of practical importance has stimulated researchers to perform in-depth studies of the structures of nonsymmetrical macroheterocycles. For example, structural formula **31a´** was proposed[48] for the nonsymmetrical copper complex assuming the absence of a counterion. However, complexation with anhydrous copper(II) chloride under conditions excluding exposure to moisture afforded complex **31a** containing the chloride anion as the counterion.[49] Structure **31a** is also confirmed by the results of X-ray electron spectroscopy[50] and X-ray diffraction study.[51]

Bamfield and Mack[35] succeeded in synthesizing complexes of compound **30b** with copper(II), nickel(II), and gold(III) (structures **32a—c**) using 2,6-bis(3-iminoisoindolin-1-ylideneamino)pyridine complexes as templates for cyclization with 1,3-diiminoisoindoline.



31a´

Since these compounds are unstable in light and in alkaline media, further investigations in this field were not performed.

Among **ABBB**-type macroheterocycles, compounds containing azole fragments are of particular interest because these compounds, unlike tetrapyrrole precursors, are noncentrosymmetric, while the inner macrocycle structurally similar to the porphyrazine ring is retained.

Metal complexes of azole-containing macroheterocyclic compounds were synthesized by template condensation of the corresponding metal complexes of BIA with phthalonitrile in a phenol solution[37] (Scheme 8).

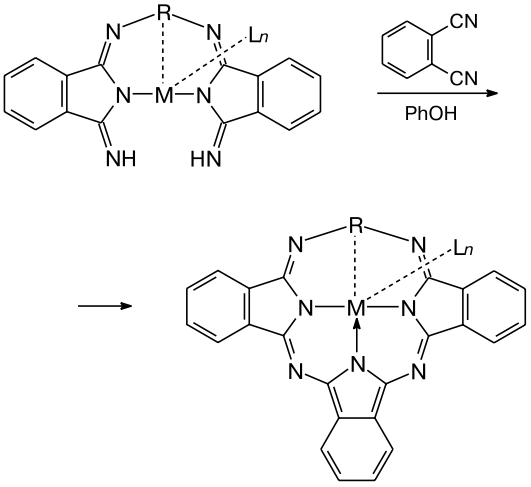
The medium for condensation was chosen taking into account that the starting metal complexes of BIA are readily soluble in phenol. In addition, phthalonitrile is transformed into reactive phenoxy compounds in the reaction with phenol.[52] Besides, phenol slows down side reactions, in particular, the formation of phthalocyanines, which are very difficult to get rid of in the case of formation of poorly soluble reaction products.

The electronic absorption spectra of metal complexes **33a,b—36a,b** are characterized by rather intense absorption bands in the 500—600 nm region, which is indicative of the pronounced aromatic character of the macrocycles.

Since **ABBB**-type compounds containing the triazole ring instead of one of the isoindole fragments are structurally similar to phthalocyanines, these compounds are called triazolephthalocyanines.[53,54]

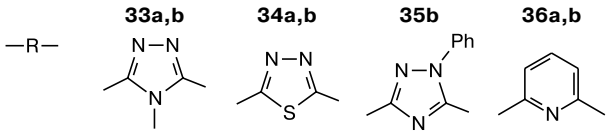
These compounds can also be prepared by random condensation and by the reaction of BIA with the corresponding nitrile or its functional derivatives in the presence of nickel acetate in organic solvents. In the former case, a mixture of substituted 1,3-diiminoisoindoline, 3,5-diamino-1,2,4-triazole, and nickel acetate in a molar ratio of 3 : 1 : 1 is heated in organic solvents (generally, in

Scheme 8

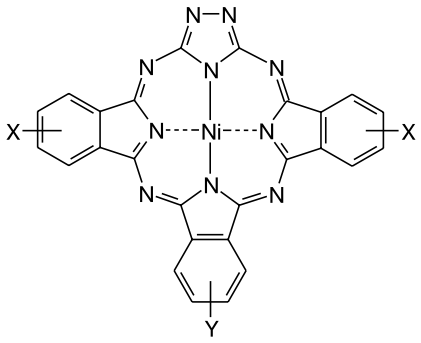


33a,b—36a,b

M = Zn (**a**), Al (**b**)



2-ethoxyethanol, butyronitrile, or butanol) to give macrocycles containing identical substituents in all three isoindole fragments. In the latter case, **ABB´B**-type compounds **37a,b** containing different substituents can be prepared.



37a,b

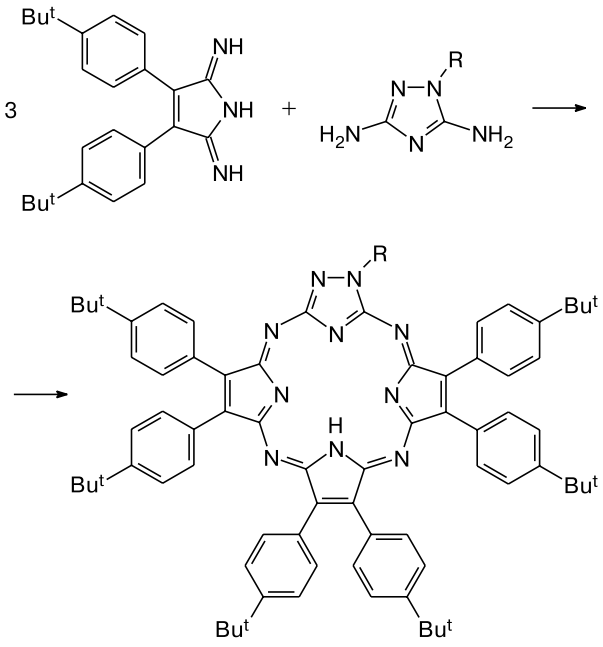
X = OC_8H_{17}; Y = NO_2 (**a**), Bu^t (**b**)

Recently, metal-free triazolephthalocyanine has been synthesized.[55] However, purification of this compound presented great difficulties.

The synthesis of nickel complexes of substituted **ABBB**- and **ABB´B**-type triazolonaphthalocyanines was documented.[56]

Triazolephthalocyanines have an inherent dipole moment, form ordered Langmuir—Blodgett layers[57,58] having semiconducting properties,[59] exhibit nonlinear optical[60,61] and liquid-crystalline properties,[62] and are characterized by high thermal stabilities.[63]

Scheme 9

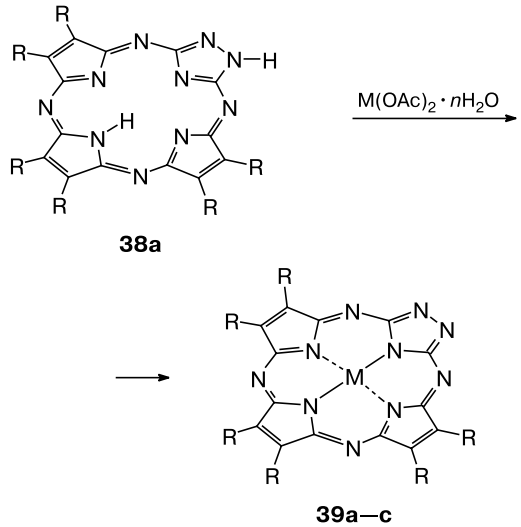


38a,b

R = H (**a**), $C_{12}H_{25}$ (**b**)

The use of substituted maleonitriles and pyrrolines led to the discovery of a new class of non-centrosymmetric **ABBB**-type macroheterocycles, *viz.*, porphyrazine derivatives, called triazoleporphyrazines.[18] For example, the reactions of 3,4-bis(4-*tert*-butylphenyl)-2,5-diimino-

Scheme 10

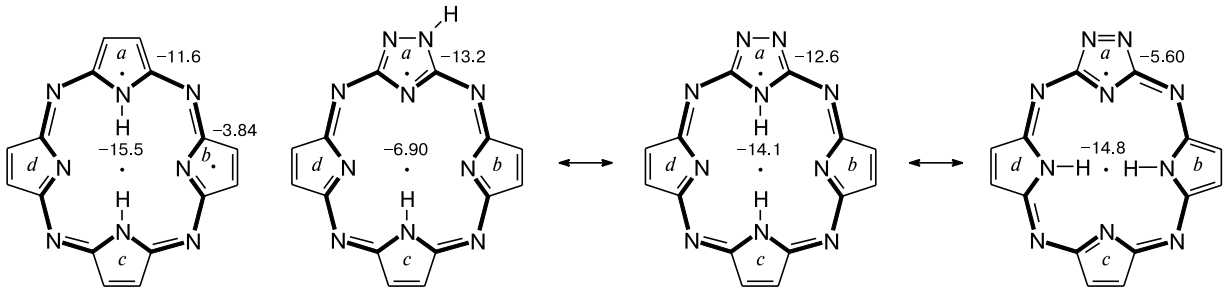


38a

39a—c

R = 4-$Bu^tC_6H_4$; M = Ni (**a**), Cu (**b**), Co (**c**)

Scheme 11



pyrroline with 3,5-diamino-1,2,4-triazole or 1-dodecyl-3,5-diamino-1,2,4-triazole in a molar ratio of 3 : 1 produced hexakis(4-*tert*-butylphenyl)triazoleporphyrazine **38a** and its *N*-dodecyl-substituted analog **38b**, respectively, in good yields (Scheme 9).

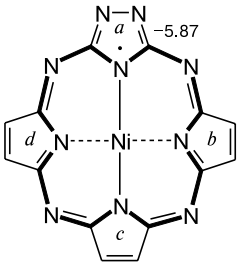
The reactions of triazoleporphyrazine **38a** with nickel, copper, and cobalt acetates in DMF at 100 °C afforded[18] the corresponding complexes **39a—c** (Scheme 10).

The structures of the resulting compounds were established by elemental analysis, NMR, IR, and electronic spectroscopy, and mass spectrometry.

A comparative analysis of the spectral characteristics of compound **38a**, its alkyl analog **38b**, and metal complexes **39a—c** demonstrated that triazoleporphyrazine **38a** exists as a tautomer in which the hydrogen atom is located at position 1 of the triazole ring.

Like porphyrazine **1b**, triazoleporphyrazine **40** has a complex multicontour conjugated system. The structure of **40** can be represented by three tautomeric forms **A—C** (Scheme 11).

The geometric and electronic structures of porphyrazine **1b**, tautomeric forms **40A—C**, and Ni triazoleporphyrazine complex **41** were investigated by the DFT quantum chemical method at the B3LYP/6-31G d,p level.[64] Calculations with full geometry optimization demonstrated that the configurations corresponding to minima on the potential energy surface are planar.



41

The energy difference in the series **40A** > **40B** > **40C** (Table 1) is rather small. Tautomer **40C** is energetically most favorable. The structure of the inner ring of this tautomer is most similar to that of the porphyrazine ring.

In the series **40A**, **40B**, and **40C**, the N—N bond length in the triazole ring decreases and approaches the length of the N=N double bond in structure **40C** (1.287 Å). To the contrary, the N—C bonds between the N—N group and the inner ring are elongated. In **40C**, this bond length is 1.425 Å, which suggests that the N—N fragment in this structure is essentially isolated from the conjugation system of the macrocycle. In complex **41**, this bond length is 1.294 Å and it is intermediate between the corresponding bond lengths in structures **40B** and **40C**.

Table 1. Total ($E_{tot} = E_{RB+HF-LYP}$) and relative (E_{rel}) energies, ionization potentials (IP), and dipole moments (μ) for structures **1b**, **40A—C**, and **41** optimized at the DFT B3LYP/6-31G** level of theory

Structure	E_{tot}/au	E_{rel} /kcal mol^{-1}	IP /eV	μ/D
1b	−1053.72663826	—	5.82	0.00
40A	−1085.75771329	12.54	6.45	2.66
40B	−1085.77012851	4.75	6.48	7.21
40C	−1085.77770003	0.00	6.36	6.13
41	−2592.8681607	—	6.41	6.67

Based on the calculated geometric characteristics, the aromaticity of compounds **1b**, **40A—C**, and **41** was analyzed (see Ref. 64, as well as Table 2 and Scheme 11) using the HOMA (Harmonic Oscillator Model of Aromaticity)[65] and NICS (Nucleus Independent Chemical Shifts) criteria.[66,67]

As can be seen from Table 2, the overall aromaticity increases in the series **40A** < **40B** < **40C** < **41**, which corresponds to the tendency to equalization of the bond lengths in these molecules.

Tautomers **40B** and **40C** are characterized by a higher overall aromaticity and a lower local aromaticity of the triazole ring compared to **40A**. The latter fact is associated with the involvement of a part of the triazole ring, including the N(4) atom and the adjacent carbon atoms, in the conjugation system of the inner macrocycle. This results in isolation of the N—N fragment. In structure **40C**, the N—N bond has a pronounced double bond character, resulting in alternation of single and double bonds in the triazole ring, which is manifested in an increase in the

Table 2. Indices EN*, GEO**, and HOMA for tautomers **40A—C** and Ni complex **41**

Structure	EN	GEO	HOMA
Porphyrazine **1b**	0.115	0.322	0.562
Fragments *a*, *c*	0.211	0.230	0.559
Fragments *b*, *d*	0.265	0.514	0.221
Inner ring	0.022	0.036	0.942
Tautomer **40A**	0.122	0.464	0.414
Ring *a*	0.044	0.034	0.922
Fragment *b*	0.332	0.812	−0.145
Fragment *c*	0.332	0.484	0.184
Fragment *d*	0.316	0.801	−0.117
Inner ring	0.015	0.094	0.892
Tautomer **40B**	0.103	0.322	0.567
Ring *a*	0.081	0.032	0.887
Fragments *b*, *d*	0.280	0.154	0.566
Fragment *c*	0.252	0.325	0.422
Inner ring	0.018	0.039	0.943
Tautomer **40C**	0.098	0.287	0.615
Ring *a*	0.118	0.225	0.657
Fragments *b*, *d*	0.220	0.253	0.527
Fragment *c*	0.289	0.568	0.143
Inner ring	0.016	0.036	0.948
Complex **41**	0.080	0.277	0.643
Ring *a*	0.090	0.074	0.835
Fragments *b*, *d*	0.237	0.356	0.408
Fragment *c*	0.241	0.383	0.376
Inner ring	0.019	0.069	0.913

* EN is the deviation of the average bond length from the optimal value.

** GEO is the deviation of the bond length from the average value.

GEO index from 0.034 in structure **40A** to 0.225 in **40C**. It should be noted that the difference in the HOMA of the overall and local aromaticities of the triazole ring decreases in the series **40A** > **40B** > **40C** (0.508, 0.320, and 0.042, respectively). The aromaticity of the inner ring increases in this series (HOMA = 0.948 for **40C**).

The formation of nickel complex **41** is accompanied by an even more substantial bond-length equalization and an increase in HOMA for the whole molecule to 0.643. The bonds at the bridging nitrogen atoms are shortened and equalized with a simultaneous elongation of the C—N bonds with the nitrogen atoms directly interacting with nickel. These changes result in a decrease in the aromaticity of the inner macrocycle (HOMA, 0.913) compared to the analogous characteristics of metal-free structures **40B** and **40C**.

The magnetic criterion NICS (see Scheme 11) confirms the changes in aromaticity in the series **1b**, **40A—C**, and **41** that have been revealed based on the HOMA criterion.

For example, tautomer **40A** is the least aromatic compound (NICS −6.90 ppm), whereas **40C** is the most aromatic of all the tautomers (NICS −14.8 ppm). It is also very interesting that the NICS criteria for this series of tautomers show a decrease in aromaticity of the triazole ring, which is consistent with the data obtained with the use of the HOMA criteria. Therefore, for the efficient involvement in the formation of an aromatic macrocycle, the constituent heterocycles should partially lose aromaticity, which should be compensated by a decrease in the energy due to conjugation in the macrosystem.

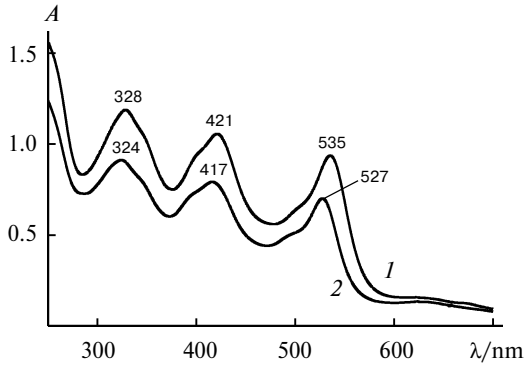


Fig. 2. Electronic absorption spectra (in $CHCl_3$) of compounds **38a** ($c = 2.16 \cdot 10^{-5}$ mol L^{-1}) (*1*) and **38b** ($c = 1.71 \cdot 10^{-5}$ mol L^{-1}) (*2*).

The spectrum of compound **38a** shown in Fig. 2 is characterized by the presence of four intense absorption bands. The intensity of the bands decreases toward longer wavelengths. The most intense band is observed at 244 nm. This band is apparently attributed to electron transitions in the phenyl rings of the substituents. By analogy with tetraazaporphine, the band at 324 nm can be interpreted as the Soret band. The bands observed in the visible spectral region are associated with electron transitions involving the highest occupied and lowest unoccupied molecular orbitals. The intense band at 417 nm (this band is weak in the spectrum of substituted porphyrazine[68] and is observed at 450 nm) is apparently attributed to violation of the molecular symmetry due to substitution of the triazole group for the pyrrole fragment.

The long-wavelength band at 527 nm in the spectrum of substituted triazoleporphyrazine **2** is hypsochromically shifted by 139 nm compared to the band of the corresponding porphyrazine.[68]

The spectral pattern of **38a** is virtually identical with that of dodecyl-substituted compound **38b** (see Fig. 2), which suggests the similarity of their chromophore systems. It should be noted that the 1*H*-triazole fragment in compound **38b** is fixed by the alkyl substituent at position 1. This fact confirms the presence of the hydrogen atom at position 1 of the triazole ring in triazoleporphyrazine **38a**. In the spectrum of **38b**, the absorption bands are slightly shifted to longer wavelengths as a consequence of the weak +I effect of the substituent.

In the electronic absorption spectra of complexes **39a—c** (Fig. 3), there are three groups of bands: the long-

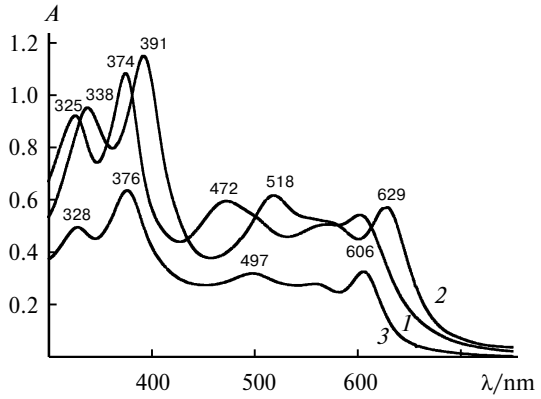


Fig. 3. Electronic absorption spectra of compounds **39a** (CH_2Cl_2, $c = 1.71 \cdot 10^{-5}$ mol L^{-1}) (*1*), **39b** ($CHCl_3$, $c = 2.05 \cdot 10^{-5}$ mol L^{-1}) (*2*), and **39c** ($CHCl_3$, $c = 1.03 \cdot 10^{-5}$ mol L^{-1}) (*3*).

wavelength absorption band at 602—629 nm and a broadened band at 570 nm, which is observed in the spectra of compounds **39a** and **39b** as an inflection, a broad band in the middle of the spectrum at 472—518 nm, and two bands in the UV region at 325—391 nm. The position and a rather high intensity of the long-wavelength absorption band suggest the aromatic character of metal complexes. It was found that the nature of metal affects the positions of the absorption bands. The bathochromic shift of the long-wavelength absorption band increases in the series Ni < Co < Cu.

The acid-base reaction involving porphyrazines has a complex character.[69,70] Unlike porphyrazines, triazoleporphyrazines contain two additional nucleophilic centers in the triazole ring, which can be considered as potential protonation sites. In addition, the proximity of these atoms to the inner macrocycle suggests a substantial influence of protonation on the properties of triazoleporphyrazines, in particular, on the spectroscopic properties.

The state and stability of 1*H*-hexakis(4-*tert*-butylphenyl)triazoleporphyrazine **38a** in a benzene—100% AcOH solution were studied by spectrophotometry[71,72] (H_0 for this system were taken from the publication[73]).

The addition of a small amount of acetic acid (0.4 mol L^{-1}, $H_0 = 7.5$) to a benzene solution of triazoleporphyrazine was demonstrated to cause a hypsochromic shift of the Q band in the electronic absorption spectrum (Fig. 4). The formation of the acidic form is completed in an AcOH—H_2SO_4—antipyrine medium ($H_0 = 3.95$), which is accompanied by a hypsochromic shift of the absorption maximum of the Q band by 473 cm^{-1}.

The stability constant of acidic form **38a** estimated by the Hammett equation is 4.48±0.18. The number of donor centers involved in the acid-base interaction can be determined from the $\log I/H_0$ plot and is 0.97 (Fig. 5).

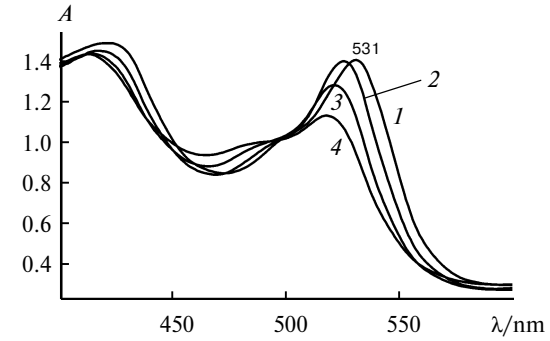


Fig. 4. Changes in the electronic absorption spectrum of triazoleporphyrazine **38a** in benzene (*1*) and in benzene—AcOH mixtures (*2—4*): $H_0 = 6.08$ (*2*), 5.33 (*3*), 4.5 (*4*).

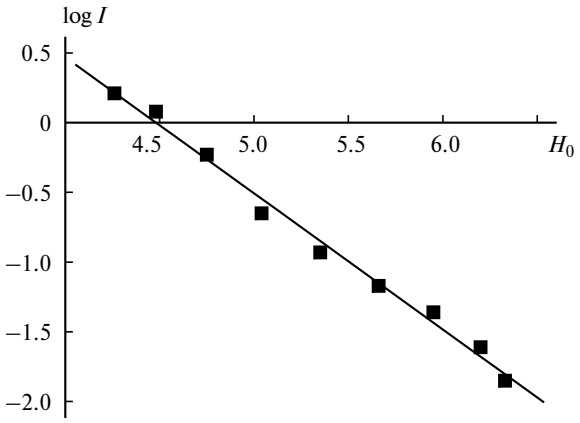


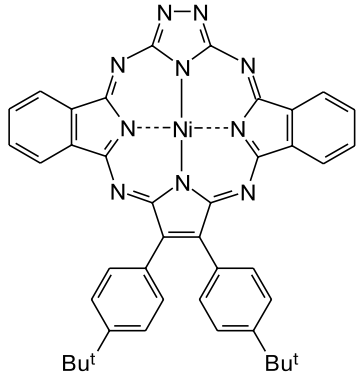
Fig. 5. Plot of $\log I$ *vs.* H_0 for the acid-base interaction of triazoleporphyrazine **38a** in a benzene—AcOH mixture.

Taking into account that the acid-base reactions of triazoleporphyrazines proceed in a medium with poor ionizing ability, it can be concluded that these reactions produce ion-ion associates.

A comparison of pK_s for triazoleporphyrazine **38a** (4.48), tetraazaporphine (1.0), and octaphenyltetraazaporphine (−1.33) shows that the replacement of the pyrrole ring by the triazole fragment leads to an increase in the basicity of the macrocycle. In addition, the first step of the acid-base interaction of porphyrazines occurs at one of four *meso*-nitrogen atoms and is accompanied by a bathochromic shift of the Q band in the electronic absorption spectrum.[70] The high basicity of **38a** and the hypsochromic shift of the Q band suggest that the nitrogen atom of the triazole ring at position 4 serves as the protonation site. This assumption was confirmed by quantum chemical investigations of the electronic and spatial structures of the protonated forms of triazoleporphyrazine at the DFT level of theory. Protonation was demonstrated to result in a substantial decrease in the aromaticity of the macrocycle.

Triazoleporphyrazine **38a** appeared to be less stable than porphyrazines in proton-donor solvents. Compound **38a** decomposes[72] in solutions of AcOH in benzene at H_0 = 5.32, 5.17, 4.87, 4.80, and 4.60 in the temperature range of 313—333 K. Apparently, decomposition of triazoleporphyrazine in a benzene—AcOH solution is acidoproteolytic and occurs according to the following scheme. The first step involves protonation of the nitrogen atom at position 4 of the triazole ring. Then the reaction with two AcOH molecules leads to protonation of the *meso*-nitrogen atom followed by the attack of the acetate ion on the α-carbon atom of the pyrrole fragment and the C—N bond cleavage in the macrocycle. The proposed mechanism was confirmed by AM1 quantum chemical calculations.[72]

The acid-base reactions of the 1*H*-hexakis(4-*tert*-butylphenyl)triazoleporphyrazine complexes with nickel(II) (**39a**) and copper(II) (**39b**) and the nickel(II) complexes with 3′,4′-bis(4-*tert*-butylphenyl)dibenzotriazoleporphyrazine (**42**) and [4′-(4-triphenylmethylphenoxy)]-7,8:12,13:17,18-tribenzotriazoleporphyrazine (**43**) in benzene—AcOH and dichloromethane—AcOH solutions were studied.[71,74]



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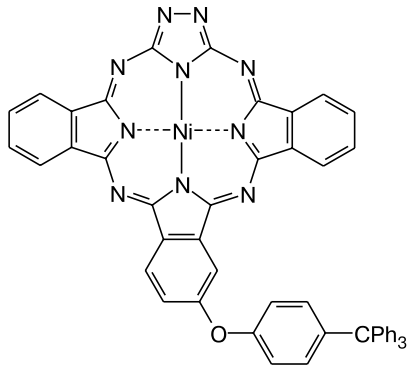


43

The stability constants of the acidic forms of triazoleporphyrazines in the first protonation step are given in Table 3.

Table 3. Stability constants (pK_s at 298 K) of the acidic forms of triazoleporphyrazines

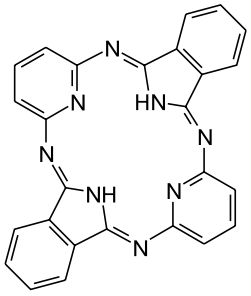
Compound	Medium	pK_s
38a	Benzene—AcOH	4.48±0.18
39a	Benzene—AcOH	6.22±0.03
39b	Benzene—AcOH	6.50±0.04
42	Benzene—AcOH	6.45±0.05
	Dichloromethane—AcOH	0.43±0.04
43	Dichloromethane—AcOH	0.27±0.07

The introduction of metals into the coordination cavity of the triazoleporphyrazine macrocycle was found to enhance the basic properties of these compounds. The acid-base reactions of triazoleporphyrazines involve one donor center. High basicity of triazoleporphyrazine complexes and the hypsochromic shift of the Q band in the electronic absorption spectra suggest that the nitrogen atom at position 1 of the triazole ring serves as the protonation site.

Experimental data show that nickel and copper complexes are more basic than the ligand, the copper complex being more basic than the nickel complex. The presence of the triphenylmethylphenoxy substituent in triazoleporphyrazine **43** leads to a decrease in the basicity of the macrocycle.

ABAB-Type macroheterocyclic compounds

Symmetrical pyridine macrocycle[75,76] **44** called hemiporphyrazine was the first representative of this vast class of **ABAB**-type macrocycles **4**.[76] Later, this term was extended to the whole class of macrocycles **4**. In this case, the name of the residue R is added as a prefix to the stem "hemiporphyrazine".[33] For example, compound **44** can be called pyridinohemiporphyrazine.



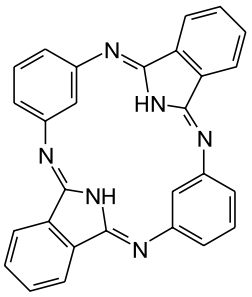
44

The structure of compound **44** and its complexes with Ni, Cu, Co, Mn, Zn, and Ge were established by X-ray diffraction.[77—81]

In the solid state, symmetrical macroheterocyclic compound **44** composed of isoindole and pyridine fragments can adopt both planar and nonplanar conformations depending on the nature of the complex-forming metal, as well as on the presence or absence of solvated solvent molecules.

An X-ray diffraction study of symmetrical macroheterocyclic compound **45** demonstrated[82] that, in the

crystalline state, the macrocycle exists as a solvate containing ethanol and water molecules and is nonplanar.



45

Studies of the symmetrical *tert*-butyl derivative by ^{1}H NMR spectroscopy demonstrated[83] that this compound form stable complexes with a solvent, in particular, with DMF. However, the structures of these complexes have remained unknown. To solve this problem, complexes of **45** with DMF were studied by X-ray diffraction.[84] Compound **45** was demonstrated to form 1 : 1 and 1 : 2 complexes with DMF in which the macrocycle adopts a saddle-like conformation (Fig. 6).

In the 1 : 1 complexes, the exocyclic N(2), N(3), N(5), and N(6) atoms lie in a single plane within 0.04 Å.

The benzene rings and isoindole fragments deviate from the mean plane of the molecule in the opposite directions. This conformation of the macrocycle is apparently determined by shortened intramolecular contacts: H(1N)...C(28), 2.72 Å (the sum of the van der Waals radii[30] is 2.87 Å); H(1N)...C(10), 2.75 Å; H(1N)...C(9), 2.77 Å; H(1N)...C(27), 2.77 Å; H(4N)...C(10), 2.68 Å; H(4N)...C(11), 2.74 Å; H(4N)...C(23), 2.79 Å; H(4N)...C(28), 2.69 Å.

The macrocycle forms an inner oval cavity, whose sizes are determined by the H(10)...H(28) (3.33 Å) and H(1N)...H(4N) (2.64 Å) distances. The DMF molecule is located above the macrocycle and forms three-center hydrogen bonds N(1)—H(1N)...O(1S) (2.14 Å; the N—H...O angle is 160°) and N(4)—H(4N)...O(1S) (2.17 Å; the N—H...O angle is 152°).

The addition of the second DMF molecule (the 1 : 2 complex) is accompanied by a substantial change in the conformation of the macrocycle. The exocyclic atoms do not lie in a single plane. The angle between the N(2)...N(6) and N(3)...N(5) lines is 5.8°. In compound **45**·2DMF, one DMF molecule occupies the position analogous to that observed in the 1 : 1 complex and forms three-center hydrogen bonds N(1)—H(1N)...O(1S) (1.98 Å; the N—H...O angle is 172°) and N(4)—H(4N)...O(1S) (2.12 Å; the N—H...O angle is 166°).

The second solvent molecule is located on the opposite side of the macrocycle and is linked to the latter by a weak intermolecular hydrogen bond C(10)—H(10)...O(2S) (2.24 Å; the C—H...O angle is 158°).

In the crystalline state, intermolecular interactions strongly influence the structure of the macromolecules and disturb the internal effects. The structures of the compounds in the isolated state can be determined by quantum chemical methods.

We performed a theoretical study of the structure of macrocycle **45** by the semiempirical AM1 method for planar configuration **45PL** (D_{2h}), nonplanar configurations **45A** (C_{2v}) and **45B** (C_{2h}), the crystal solvate **45**·DMF, and transition state **45TS** between configurations **45A—45B**.

The molecular models and the calculated heats of formation of planar configuration **45PL** (D_{2h}), nonplanar configuration **45A,B**, and the solvate **45**·DMF are presented in Fig. 7.

In planar configuration **45PL** (D_{2h}), the hydrogen atoms in the inner coordination sphere are in spatial proximity. In particular, the distance between the hydrogen atoms of the benzene rings is 2.17 Å, and the distance between the hydrogen atoms of the imino groups is 2.59 Å. The spatial proximity of the atoms in the inner sphere results in their strong mutual repulsions. The molecule is stabilized as a result of deviations of the benzene and isoindole fragments from the plane.

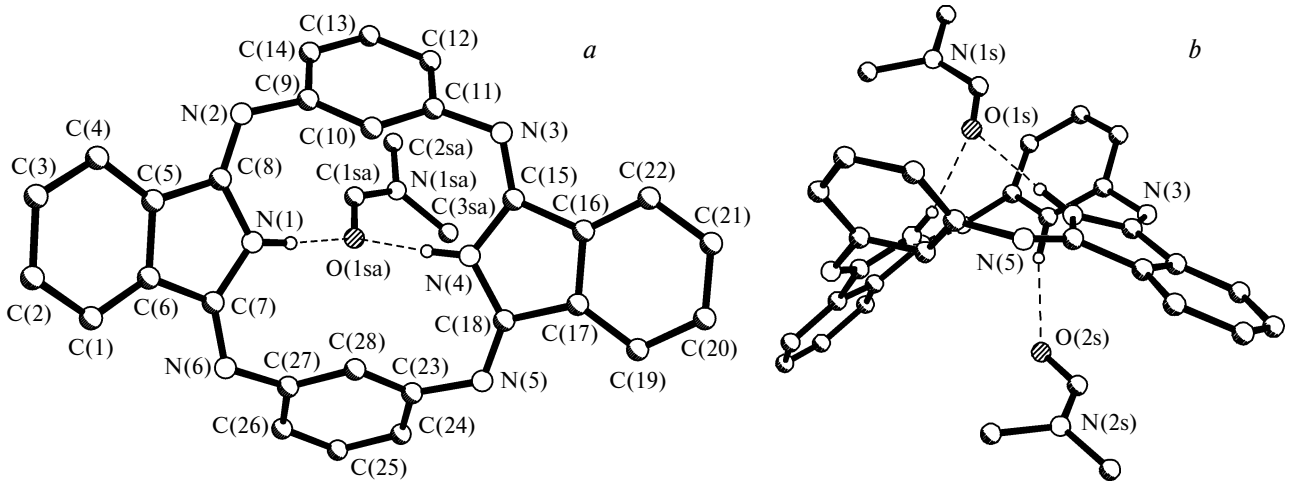


Fig. 6. X-ray diffraction structures of complexes **45**·DMF (*a*) and **45**·2 DMF (*b*) (hydrogens at carbon atoms are omitted).

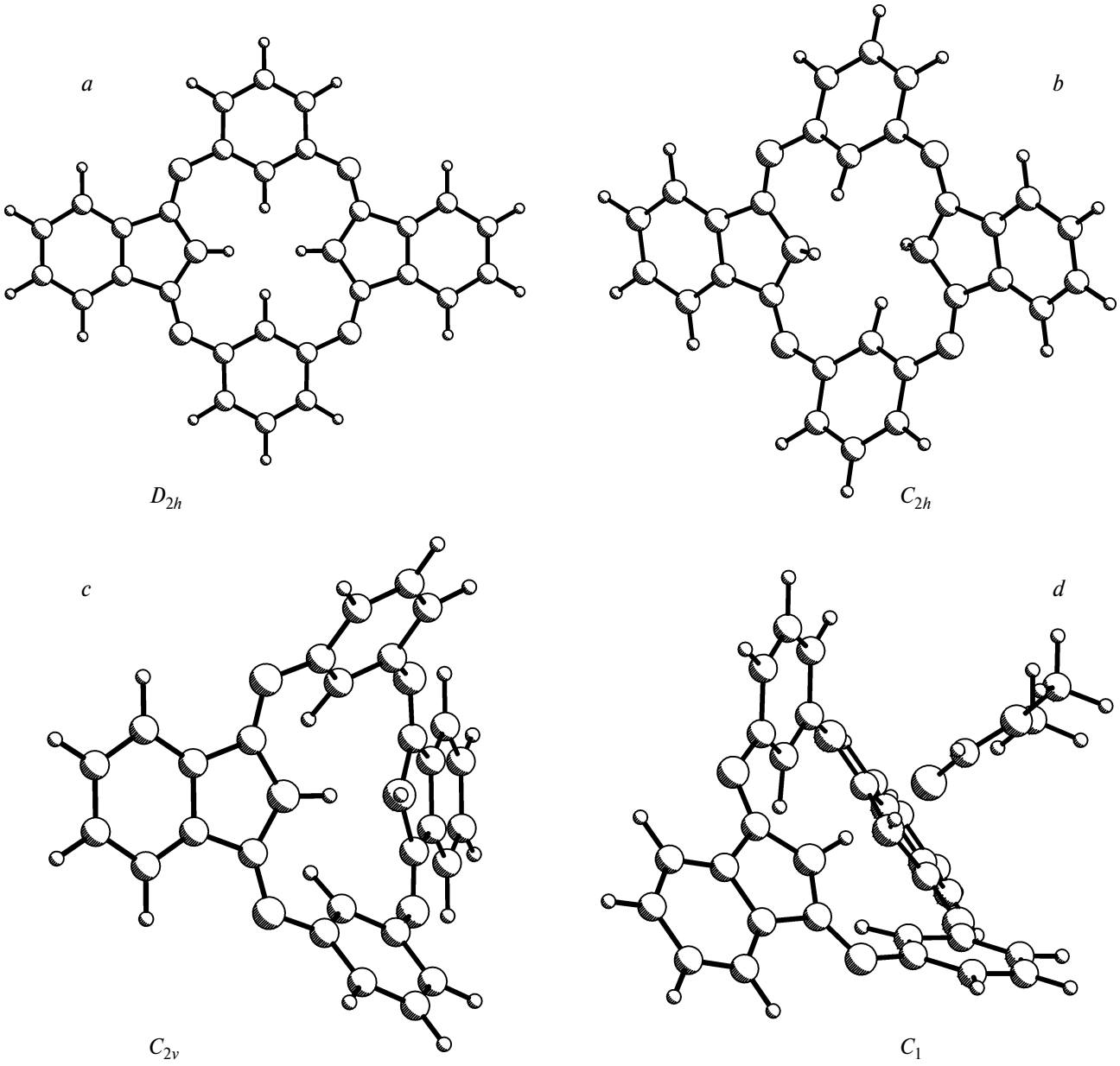


Fig. 7. Three-dimensional structures of compounds **45PL** (*a*), **45A** (*b*), **45B** (*c*), and **45** · DMF (*d*) calculated by the AM1 quantum chemical method; ΔH_f/kcal mol^{-1}: 259.8 (**45PL**), 250.4 (**45A**), 242.5 (**45B**), 200.0 (**45** · DMF).

Two stereoisomers corresponding to minima on the potential energy surface were found. These stereoisomers adopt a chair **45A** (C_{2h}) and saddle-like conformations **45B** (C_{2v}) and are energetically more favorable than planar configuration **45PL** with the symmetry D_{2h} by 9.4 and 17.3 kcal mol^{-1}, respectively.

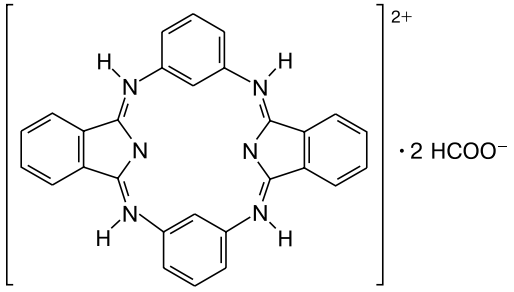
Therefore, isomer **45B** having a saddle-like configuration is energetically most favorable. In this configuration, the benzene rings deviate from the plane through the exocyclic nitrogen atoms by 42.8°. The isoindole fragments deviate in the opposite direction by −21.2°. This configuration is also fixed in solvate **45** · DMF, which is in agreement with X-ray diffraction data.

The calculated energy barrier between conformers **45A** and **45B** is 0.6 kcal mol^{-1}; for the inverse transition, this barrier is 8.5 kcal mol^{-1}. Such small energies of the conformational transitions comparable to the hydrogen bond energy suggest that analogous transformations can occur in solutions. Depending on the nature of the solvent, a particular conformation can be stabilized. Recently, this conclusion has been confirmed in the study,[85] in which the influence of the solvents was examined by ^{1}H NMR

spectroscopy for the *tert*-butyl-substituted macroheterocycle.

Therefore, symmetrical compounds are structurally flexible and can exist as different conformers separated by low activation barriers. The predominance of a particular form in the crystalline state and in solution depends on the character of intermolecular interactions, among which specific solvation plays a considerable role.

Recently, an X-ray diffraction study has demonstrated that dicationic form **45C** of this compound is planar.[86]



45C

It should be noted that unsubstituted macrocycles are poorly soluble in organic solvents. However, their solubility can be substantially increased by introducing bulky substituents, for example, *tert*-butyl groups.

Compounds **46—50** were synthesized by the reaction of 4-*tert*-butylphthalonitrile or the corresponding alkoxy or three-unit compounds with aromatic diamines in ethylene glycol or butanol (Scheme 12).[12] It is most convenient to synthesize compounds **46—50** from 4-*tert*-butylphthalonitrile *via* the corresponding alkoxy compounds without isolation of the latter from the reaction mixture (see Scheme 12).

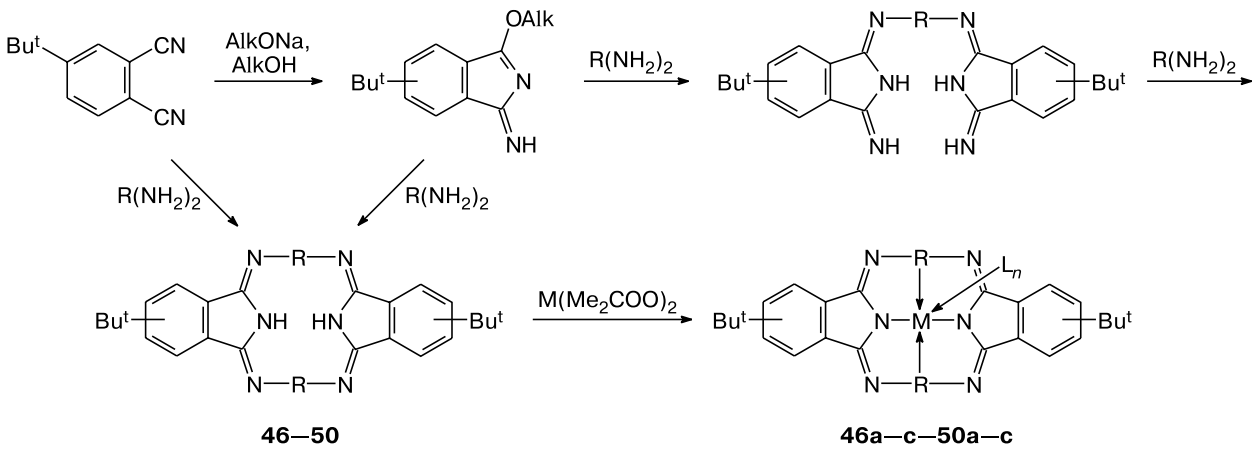
The introduction of *tert*-butyl groups has virtually no effect on the electronic spectra. Generally, a slight shift of absorption bands to longer wavelengths is observed, the absorption in the 300—450 nm region remaining unchanged.

This is consistent with the experimental values determined by NMR spectroscopy. The signals for the protons of the imino groups are observed at δ 10.2—12.6. The presence of signals for endocyclic protons at low field is experimental evidence for the absence of the common macrocyclic conjugation system in compounds **46—50**.

The conclusion about the absence of the common aromatic system in the macrocycles is in agreement with the results of ^{1}H NMR spectroscopic study of the germanium complex with the symmetrical pyridine macroheterocycle.[87] More recently,[88] signals for endocyclic protons have been observed at low field (δ 15.7 and 15.2) in the ^{1}H NMR spectrum ($CDCl_3$) of the symmetrical *tert*-butyl-substituted macroheterocycle with 1-dodecyl-1,2,4-triazole fragments containing two nitrile groups in one of the isoindole fragments.

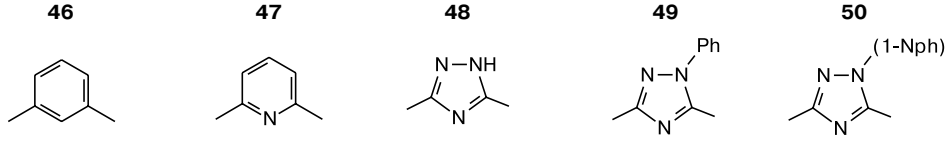
The reactions of compounds **46—50** with an excess of anhydrous metal acetates in butanol produced the corresponding metal complexes[89] (see Scheme 12). Thermal stability of compounds increases upon complexation. The copper complex of macroheterocyclic compound **49a** containing 1-phenyl-1,2,4-triazole fragments appeared to be

Scheme 12



46—50 **46a—c—50a—c**

M = Cu (**a**), Co (**b**), Ni (**c**)



most thermally stable.[89] For this compound, the maximum exo effect (the weight loss was 86%) in air was observed at 602 °C.

The introduction of *tert*-butyl groups leads to a decrease in stability of the macrocycles in proton-donor solvents.[90] Apparently, this is attributed to the fact that the introduction of two *tert*-butyl groups having a pronounced +I effect is accompanied by an increase in the electron density on the exocyclic nitrogen atoms, thus facilitating protonation and subsequent decomposition of the molecules.

Upon complexation, the stability of *tert*-butyl-substituted compounds increases by approximately an order of magnitude. The effective rate constant of decomposition of compound **49** is $0.11 \cdot 10^{-3}$ s^{-1}, whereas this constant for its complex with copper[90] is $0.47 \cdot 10^{-4}$ s^{-1}.

Complexation is accompanied by a decrease in solubility of *tert*-butyl derivatives in organic solvents.

Macroheterocyclic compounds and their complexes with metals have a spectrum of properties of practical importance. Investigations of these properties are far from being completed.

At the moment of the discovery of macroheterocyclic compounds,[75,76] phthalocyanines have been already rather well studied and have found wide application as pigments and dyes.[5] Hence, first investigations concerned primarily with their coloring properties.[91,92] It is not difficult to note that the compounds were tested primarily for the presence of the properties of practical importance, which were revealed for phthalocyanines. Although, in most cases, the presence of these properties was confirmed, these compounds proved to be less efficient than phthalocyanines.[93—98]

The discovery of the ability of macroheterocycles to trap and deactivate free radicals has been a qualitative breakthrough in the estimation of properties of these compounds. Metal-containing macrocycles were found[46] to have pronounced thermo- and light-stabilizing activities.[46,47] Apparently, this property provides the basis for stabilization of siloxane rubbers[99] and for retardation of polyorganosiloxane polymer combustion[100] by metal complex macrocycles.

The development of new approaches to the synthesis made it possible to perform structural modifications of these compounds, resulting in the discovery of new properties of practical importance, in particular, liquid-crystalline[62] and nonlinear optical properties[61,101] and the ability to form ordered Langmuir—Blodgett layers.[57]

Investigations of biological properties of macroheterocycles are of particular interest.

The antimicrobial activity was estimated based on germination of test cultures and the lysis zone diameter. It was found that *tert*-butyl-substituted macrocycles and their copper complexes containing 1,2,4-triazole fragments show moderate antimicrobial activity against *Escherichia coli* sp. 676.0 and *Staphylococcus aureus*.[102]

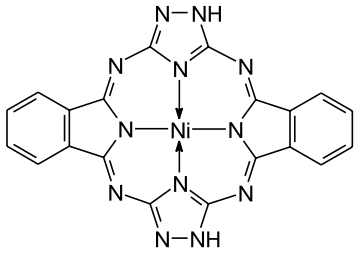
Types of biological activity of several macroheterocyclic compounds, their metal complexes, and the starting compounds for their synthesis were predicted using the PASS program.[103] All the tested compounds would be expected to exhibit antitumor activity.

Hence, the activity of these compounds was experimentally tested using a model of the L-1210 tumor reinoculated in mice.[104]

Initially, the maximum tolerated doses (MTD) were determined for each compound, and then the daily therapeutic doses were chosen based on MTD. The MTD allowed the assignment of all tested compounds to toxicity class IV (low-toxicity compounds).[105]

Experimental investigations of antitumor activity were performed using intraperitoneal administration. None of compounds of the 1,3,4-thiadiazole series exhibit antitumor activity, and BIA containing the 1,3,4-thiadiazole fragment **28** even can substantially initiate the disease development. 2,5-Diamino-1,3,4-thiadiazole itself exhibits weak activity against leukemia L-1210, which is consistent with the literature data.[106]

3,5-Diamino-1,2,4-triazole and the nickel complex of a symmetrical macroheterocyclic compound containing 3,5-diamino-1,2,4-triazole fragments (**51**) exhibit moderate antitumor activity against lymphoid leukemia L-1210.



51

Thus, antitumor activity of triazole derivatives depends both on the structure of the organic part of the molecule and the nature of the complex-forming metal. The introduction of a metal into the macrocycle improves the overall effect, thus weakening the adverse effect of descriptors that are present in the macrocyclic molecule. Nickel complex **51** proved to be the most efficient compound in the series of all macrocycles and their complexes under study, whereas the cobalt and copper complexes do not exhibit activity against leukemia L-1210.

These results gave impetus to further investigations aimed at estimating antitumor and antimetastatic activities of 3,5-diamino-1,2,4-triazole and compound **51** against solid LLC tumor. However, these compounds did not exhibit specific activity against the LLC tumor.

Thus, of all the tested compounds, only 3,5-diamino-1,2,4-triazole and nickel complex **51** exhibit moderate antitumor activity against a model of lymphoid leukemia L-1210. This provides a basis for the synthesis and a search for more active compounds among their analogs (1,2,4-triazole derivatives), which are required for subsequent studies aimed at designing potential antitumor agents.

Recently, **ABABAB**-type compounds have been synthesized based on 1,3,4-thiadiazole, and these compounds exhibit radioprotective properties.[107]

In conclusion, let us note that the accumulated evidence is still insufficient for revealing particular structure—property relationships. However, the available data allow the conclusion that macroheterocycles hold promise for the design of compounds with interesting biological properties.

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