

Structure and Properties of Macrocyclic Compounds Containing a Pyrimidine Fragment

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Abstract—The structure of a series of macrocyclic compounds consisting of a pyrimidine or 1,3,5-triazine ring and an aza- or thiapolymethylene bridge connecting the N¹ and N³ atoms of the heteroring is discussed. Some macroheterocycles undergo methylation at the sulfur atom by the action of methyl *p*-toluenesulfonate. The length of the polymethylene bridge determines conformation of the macroring. Compounds with a shorter bridge both in crystal and in solution are characterized by closely located structural fragments, while extension of the polymethylene chain gives rise to an unfolded structure. Conformational changes in solution are promoted by protonation of the bridging nitrogen atom, and deprotonation restores the initial structure of the macroring. The basicity of the bridging nitrogen atom depends on the geometric parameters of the macroring.

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Macrocyclic compounds containing pyrimidine fragments, specifically those typical of nucleic acid bases, attract interest as biologically active substances [1] and complexing agents toward neutral molecules [2] and metal cations [3]. In addition, such macrocycles (pyrimidinophanes) can be used as model structures simulating interactions between nucleic acid fragments, as well as between nucleic acid bases and proteins [4].

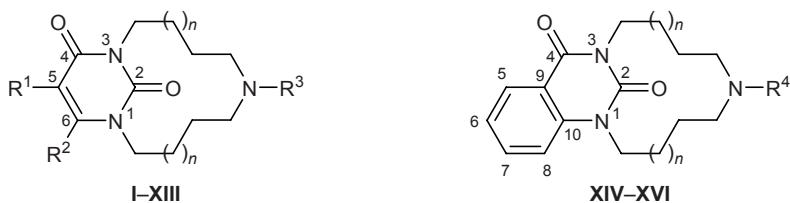
By analogy with cyclophanes, pyrimidinophanes containing one pyrimidine ring may be referred to as pyrimidinocyclophanes [5]. We previously synthesized a series of pyrimidinocyclophanes **I–XVII** (Scheme 1) in which the hydrocarbon bridge connecting the N¹ and N³ atoms of 1,2,3,4-tetrahydropyrimidine-2,4-dione (uracil) or its substituted analog includes a nitrogen atom [6–8]. Macrocyclic compounds **I–XVII** have azapolymethylene bridges of different lengths and different substituents at the C⁵ and C⁶ atoms of the pyrimidine ring and at the bridging nitrogen atom; some derivatives contained a 1,2,3,4-tetrahydroquinazoline-2,4-dione (compounds **XIV–XVI**) or 1,3,5-triazine fragment (**XVII**) instead of uracil. Compounds **I–XVII** were synthesized according to a general procedure based on reactions of 1,3-bis(ω-bromopentyl- or -hex-

yl)-substituted uracils, 1,2,3,4-tetrahydroquinazoline-2,4-dione, and 5-methylhexahydro-1,3,5-triazine-2,4,6-trione with aliphatic amines and amines containing an aromatic fragment. The reactions were carried out at a reactant ratio of 1:1 to 1:3 in butan-1-ol in the presence of potassium carbonate and a catalytic amount of tetrabutylammonium hydrogen sulfate. Quaternization of the bridging nitrogen atom in compounds **III** and **I** with decyl bromide or methyl *p*-toluenesulfonate (**XVIII**), respectively, gave amphiphilic pyrimidinocyclophanes **XIX** and **XX** [8].

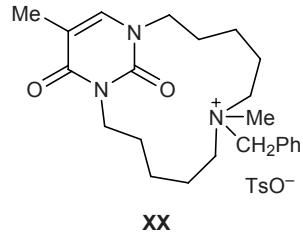
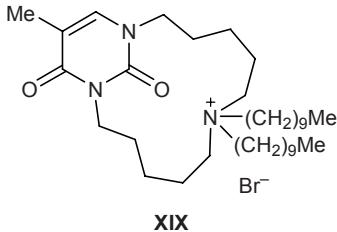
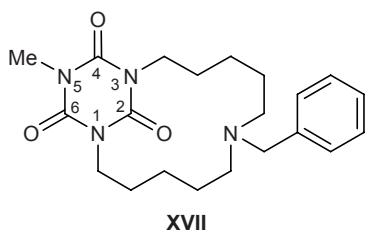
In the preceding communications [6, 7] we considered the structure of first representatives of pyrimidinocyclophanes **I**, **III**, and **V** in crystal and in solution, their conformational behavior, and aggregation in the presence of acids. The present article discusses structural specificities of a wide series of macrocyclic compounds having one heterocyclic fragment in crystal and in solution, their basic properties, and factors determining structural differences.

With a view to elucidate the effect of the nature of bridging heteroatom on the structure of macrocyclic compounds we synthesized pyrimidinocyclophanes **XXI** and **XXII** containing a sulfur atom in the polymethylene bridge. As in the synthesis of nitrogen-

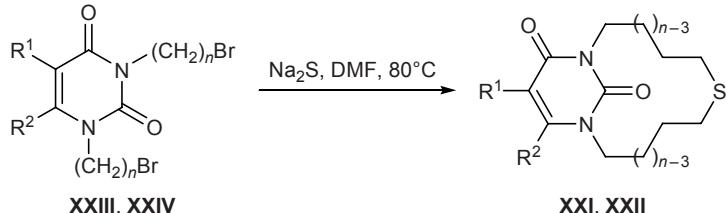
Scheme 1.



I–XII, XIV, XV, n = 2; XIII, XVI, n = 3; I–IV, XIII, XVI, R¹ = Me, R² = H; V, VI, R¹ = H, R² = Me; VII–XI, R¹ = R² = H; XII, XIV, XV, R¹ = NO₂, R² = H; I, V, XII, XIII, R³ = PhCH₂; II, R³ = 4-MeOC₆H₄CH₂; III, R³ = Bu; IV, R³ = Ph(CH₂)₃; VI, R³ = PhCH(Me); VII, R³ = 4-MeOC₆H₄; VIII, R³ = 3-MeOC₆H₄CH₂; IX, R³ = 1-naphthylmethyl; X, R³ = 4-ClC₆H₄CH₂; XI, R³ = 2-ClC₆H₄CH₂; XIV–XVI, R⁴ = PhCH₂.



Scheme 2.



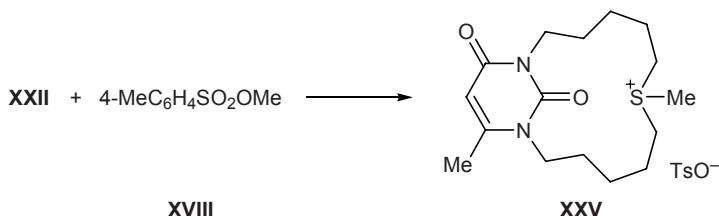
XXI, XXIII, n = 4, R¹ = Me, R² = H; XXII, XXIV, n = 5, R¹ = H, R² = Me.

bridged analogs, the starting compounds were 1,3-bis-(ω -bromoalkyl)uracils **XXIII** and **XXIV** which were treated with sodium sulfide in dimethylformamide at 80°C (Scheme 2). The yields of pyrimidinocyclophanes **XXI** and **XXII** (40%) were considerably higher than the yields of their nitrogen-containing analogs. We also tried to synthesize amphiphilic compounds via alkylation of the bridging sulfur atom with alkyl halides. However, our attempts were unsuccessful despite variation of the reaction conditions. We succeeded in methylating the bridging sulfur atom in **XXII** only under severe conditions using methyl *p*-toluenesulfonate (**XVIII**) as both alkylating agent and solvent.

We thus obtained pyrimidinocyclophane **XXV** (yield 63%) having a sulfonium group in the bridging fragment (Scheme 3).

Azapolymethylene-bridged compounds **I**, **III**, and **V** ($n = 2$) were studied previously by X-ray diffraction (in crystal) and NMR spectroscopy (in solution) [6, 7]. Molecules **I** and **V** in crystal are characterized by orthogonal orientation of the benzene and pyrimidine rings with the shortest distances between protons of these fragments ranging from 2.7 to 4.1 Å. The conformation of the macroring may be regarded as C-shaped (folded) with spatially close benzene and uracil fragments. Analogous conformations were found

Scheme 3.



to exist in solution in both polar and nonpolar solvents. This followed from the results of NOE experiments. The spectra of pyrimidinocyclophanes contained “unusual” cross peaks between protons in the benzene ring or butyl group and protons in the uracil fragment. Conformational rigidity of molecules **I**, **III**, and **V**, i.e., slow (on the NMR time scale) inversion of the macrocyclic ring between two or more symmetric forms, on the one hand, and magnetically anisotropic properties of the pyrimidine ring, on the other, determined magnetic nonequivalence of protons in each of the methylene groups attached to N^1 and N^3 of the pyrimidine ring. The corresponding signals were located in the ^1H NMR spectra in the range from δ 4.5 to 3.5 ppm and were distant from each other by 0.2–0.4 ppm. Just nonequivalence of the geminal methylene protons at N^1 and N^3 is a distinct indication of the above structural specificities of pyrimidinocyclophanes in solution.

The same applies to other cyclophanes **II**, **IV**, **VI**–**XII**, **XIV**, **XV**, and **XVII** having a $(\text{CH}_2)_5\text{N}(\text{R})(\text{CH}_2)_5$ linker with different heterocyclic fragments and different substituents R in solution and probably in crystal. Figure 1 shows the structure of pyrimidinocyclophane **VI** molecule having a 1-phenylethyl substituent on the nitrogen; the chiral carbon atom in that substituent retains configuration intrinsic to initial (R) - $(+)$ -1-phenylethylamine. The macrocyclic ring adopts a folded conformation where the shortest distance between the benzene and uracil fragments is 3.2 Å. It should be noted that 1,3,5-triazine analog **XVII** is characterized by a similar conformation with the distance ~3.3 Å between the benzene and triazine fragments (Fig. 2).

The ^1H NMR spectra of solutions of **II**, **IV**, **VI**–**XII**, **XIV**, **XV**, and **XVII** in CDCl_3 showed nonequivalence of protons in each of the methylene groups on N^1 and N^3 ; in the spectrum of **XVII** signals from the N^1CH_2 and N^3CH_2 protons appear as a triplet due to symmetric structure of the triazine fragment. Protons in the phenyl or naphthyl substituent at the bridging nitrogen atom and methylene protons in the bridge displayed NOE with protons in the heterocyclic fragment or protons in the methyl group attached thereto. For example, in the 1D ROESY spectrum of **II** in CDCl_3 we observed NOEs between 6-H in the pyrimidine ring and protons in the benzene ring, as well as in the NCH_2Ph , N^1CH_2 , N^1CCH_2 , N^3CH_2 , N^3CCH_2 , and OCH_3 groups, and between protons in the 5-CH_3 group and those in the benzene ring and OCH_3 group. Pyrimidinocyclophane **IX** showed in the 1D ROESY spectrum interactions between 5-H and protons in the naphthyl substituent and between 6-H and 1-CH₂. These

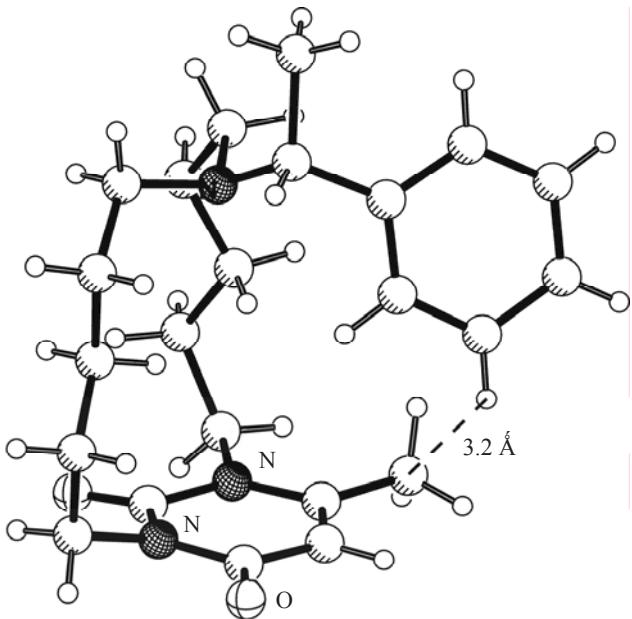


Fig. 1. Structure of the molecule of macrocyclic compound **VI** in crystal according to the X-ray diffraction data. The dashed line corresponds to the shortest distance between the benzene and uracil fragments.

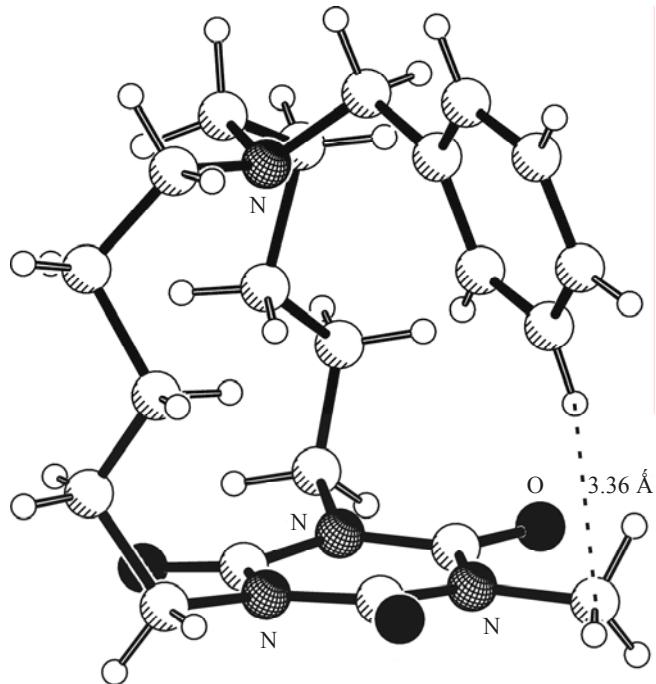


Fig. 2. Structure of the molecule of macrocyclic compound **XVII** in crystal according to the X-ray diffraction data. The dashed line corresponds to the shortest distance between the benzene and 1,3,5-triazine fragments.

findings suggest that the macrocyclic compounds having $(\text{CH}_2)_5\text{N}(\text{R})(\text{CH}_2)_5$ bridges in crystal and in solution exist in a conformation characterized by spatially

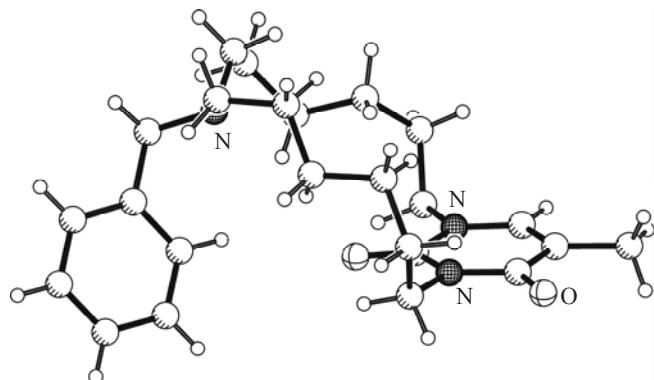


Fig. 3. Structure of the molecule of macrocyclic compound **XIII** in crystal according to the X-ray diffraction data.

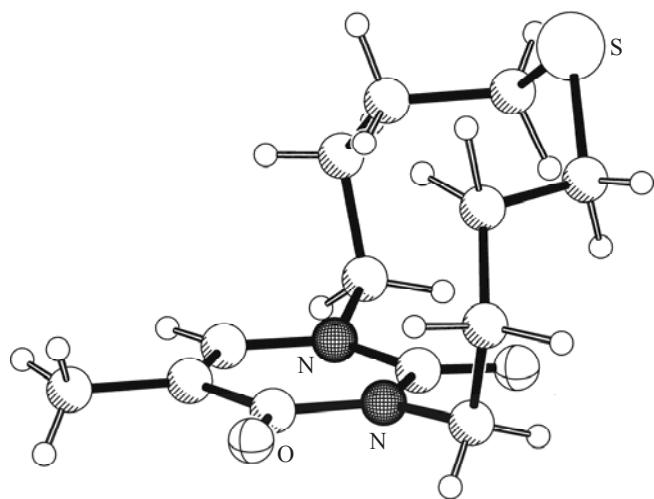


Fig. 4. Structure of the molecule of macrocyclic compound **XXI** in crystal according to the X-ray diffraction data.

close location of the heterocyclic fragment and substituent on the bridging nitrogen atom.

The mobility (i.e., the rate of inversion) of pyrimidinocyclophanes increases with extension of the polymethylene chain. Compounds **XIII** and **XVI** having a 13-membered linker showed no nonequivalence of the geminal methylene protons on N^1 and N^3 in the ^1H NMR spectra. Furthermore, no appreciable nuclear Overhauser effects were observed at 303 K, indicating that these compounds in solution have an unfolded conformation where the pyrimidine and benzyl fragments are distant from each other. Like cyclophanes having a $(\text{CH}_2)_5\text{N}(\text{R})(\text{CH}_2)_5$ bridge, the structure of compounds **XIII** and **XVI** in crystal (according to the X-ray diffraction data) correlates with their structure in solution (according to the NMR data). The structure of molecule **XIII** in crystal is characterized by torsion angles in the polymethylene chain approaching 180°

and by remoteness of the benzene and pyrimidine fragments from each other (Fig. 3).

Pyrimidinocyclophanes having a thiopolymethylene bridge retain structural specificity of their nitrogen-containing analogs. On the whole, the molecular geometry of $(\text{CH}_2)_4\text{S}(\text{CH}_2)_4$ -bridged compound **XXI** in crystal (Fig. 4) is similar to that found for pyrimidinocyclophanes with a longer linker, $(\text{CH}_2)_5\text{N}(\text{R})(\text{CH}_2)_5$. Like the latter, compound **XXI** displayed in the ^1H NMR spectrum nonequivalence of geminal protons in the N^1CH_2 and N^3CH_2 groups. Their signals appeared as resolved multiplets even at 298 K (Fig. 5a); by contrast, the corresponding signals in the spectra of pyrimidinocyclophanes with a bridging nitrogen atom were not resolved even at reduced temperature [6, 7]. This means that the rate of conformational transformations of sulfur-containing pyrimidinocyclophanes is lower, i.e., the macroring therein is more conformationally rigid than in nitrogen-containing analogs. Extension of the polymethylene chain in going from compound **XXI** to **XXII** (Fig. 5b) is accompanied by the same variations in the ^1H NMR spectra as those observed for $(\text{CH}_2)_n\text{N}(\text{R})(\text{CH}_2)_n$ -bridged derivatives ($n = 5, 6$): signals from the geminal methylene protons at N^1 and N^3 coalesce.

We previously studied in detail conformational behavior of pyrimidinocyclophane **I** upon protonation of the bridging nitrogen atom with trifluoroacetic or hydrochloric acid and subsequent deprotonation with triethylamine or sodium hydroxide [7]. Addition of less than 0.5 equiv of an acid to a solution of **I** in a polar or nonpolar solvent enhances mobility of the $(\text{CH}_2)_5\text{N}(\text{R})(\text{CH}_2)_5$ bridge, and the conformation of the macroring changes from folded to unfolded where the benzyl group on the bridging nitrogen atom is distant from the thymine fragment. This follows from broadening (and coalescence in the presence of a larger amount of acid) of signals from the geminal methylene protons at N^1 and N^3 (fast exchange on the NMR time scale) and the absence of NOE between protons in the benzyl group and in the thymine fragment. Signals from the methylene protons neighboring to the bridging nitrogen atom are displaced appreciably downfield ($\delta\Delta = 0.6\text{--}0.8$ ppm). Protonation of macrocycle **I** is reversible. The ^1H NMR spectrum restores its original pattern after addition of triethylamine (which is a stronger base than **I**) or sodium hydroxide to a solution of **I** in CDCl_3 or aqueous methanol, respectively, containing trifluoroacetic or hydrochloric acid. Thus the system macrocycle **I**–acid– NEt_3 (NaOH) may be

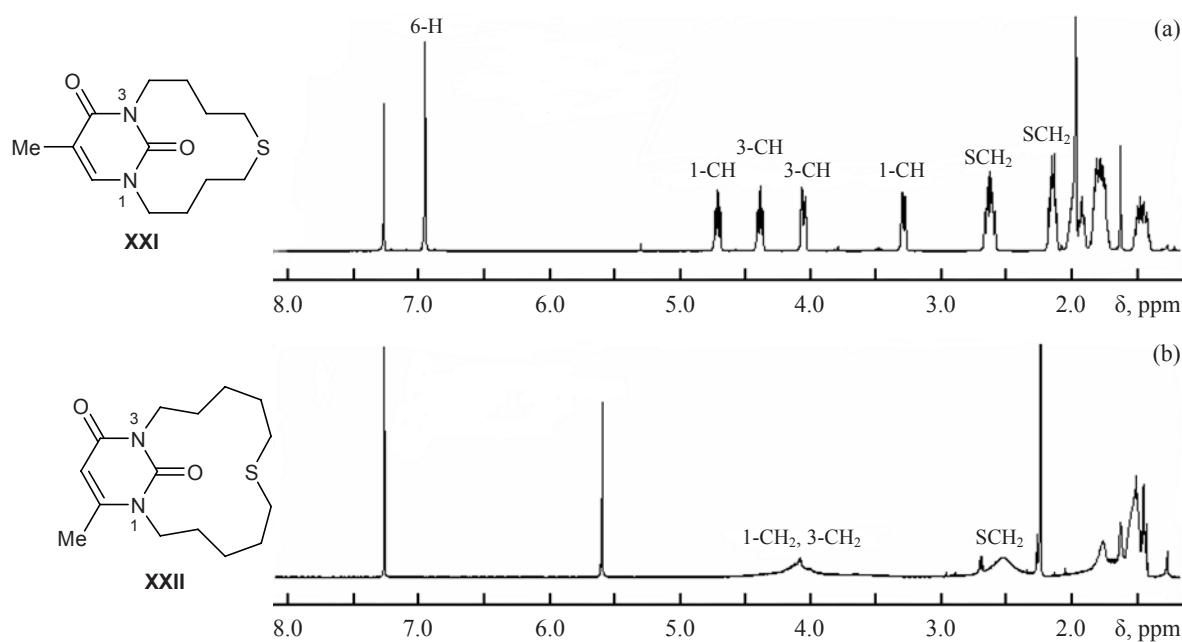


Fig. 5. ¹H NMR spectra of compounds (a) XXI and (b) XXII in CDCl₃.

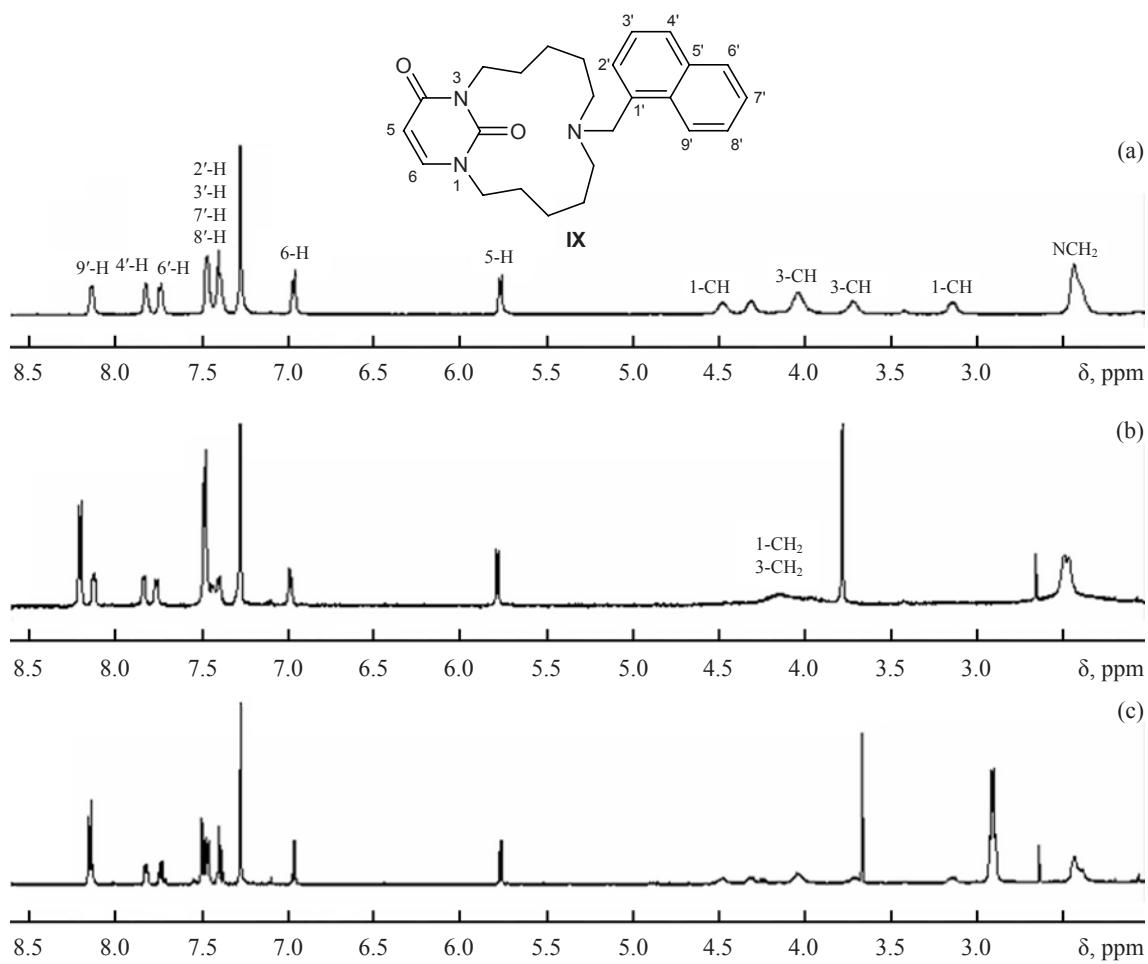


Fig. 6. ¹H NMR spectra of compound IX in CDCl₃ (a) before addition of *p*-nitrophenylacetic acid, (b) after addition of 1 equiv of *p*-nitrophenylacetic acid, and (c) after addition of 1.5 equiv of triethylamine to a 1:1 mixture of IX with *p*-nitrophenylacetic acid.

Basicity constants pK_a of couples of pyrimidinocyclophanes having identical structural fragments but different numbers of methylene groups in the $(\text{CH}_2)_n\text{N}(\text{CH}_2\text{Ph})(\text{CH}_2)_n$ bridge

Base	n	pK_a
I	5	5.90 ± 0.08
XIII	6	7.07 ± 0.02
XIV	5	6.25 ± 0.02
XVI	6	7.33 ± 0.03
NEt_3	—	8.61 ± 0.03

regarded as a molecular machine activated by a proton donor [9].

Analogous structural variations are typical of all other cyclophanes having a $(\text{CH}_2)_5\text{N}(\text{R})(\text{CH}_2)_5$ bridge upon addition of trifluoroacetic acid and subsequent deprotonation with NEt_3 . The same effect is produced by other organic acids, e.g., benzoic or phenylacetic. Figure 6 shows the ^1H NMR spectra of pyrimidinocyclophane **IX** and its mixtures with *p*-nitrophenylacetic acid (protonation) and with *p*-nitrophenylacetic acid and triethylamine (deprotonation). It is seen that after addition of triethylamine to a mixture of compound **I** with *p*-nitrophenylacetic acid the spectrum becomes almost identical to the spectrum of unprotonated pyrimidinocyclophane **IX** (Fig. 6a, c).

We can conclude that macrocyclic compounds containing a pyrimidine or 1,3,5-triazine fragment and

a $(\text{CH}_2)_5\text{N}(\text{R})(\text{CH}_2)_5$ linker are systems structurally sensitive to proton donors, organic or inorganic acids. Neutralization of the acid restores the original state of the system.

Quaternization of the nitrogen atom in the $(\text{CH}_2)_5\text{N}(\text{R})(\text{CH}_2)_5$ bridge of pyrimidinocyclophanes with alkyl or benzyl halides induces the same conformational variations as those observed upon protonation with acids. In the ^1H NMR spectra of compounds **XIX** and **XX**, signals from the methylene protons at N^1 and N^3 appear as two multiplets, and signals from the methylene groups on the bridging nitrogen atom are displaced downfield. Obviously, like protonation, quaternization is accompanied by transformation of the rigid folded structure into conformationally labile unfolded structure.

Pyrimidinocyclophanes **XIII** and **XVI** having a 13-membered bridging fragment exist in unfolded conformation, and addition of an acid to their solutions does not induce structural transitions like those described above. Nevertheless, the ^1H NMR spectra of compounds **XIII** and **XVI** in CDCl_3 containing trifluoroacetic acid differ from the spectra of solutions of the pure substrates. Presumably, the observed differences are related to other processes, in particular association of pyrimidinocyclophanes in acid medium.

We also made an attempt to elucidate how conformation of pyrimidinocyclophanes with different

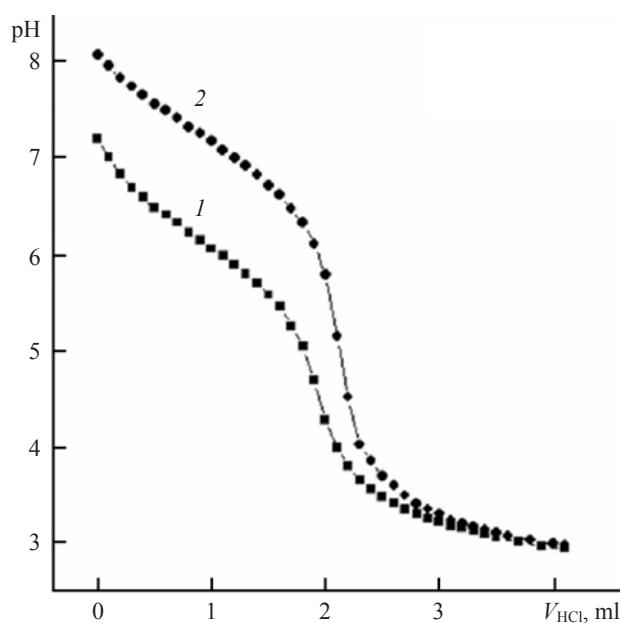
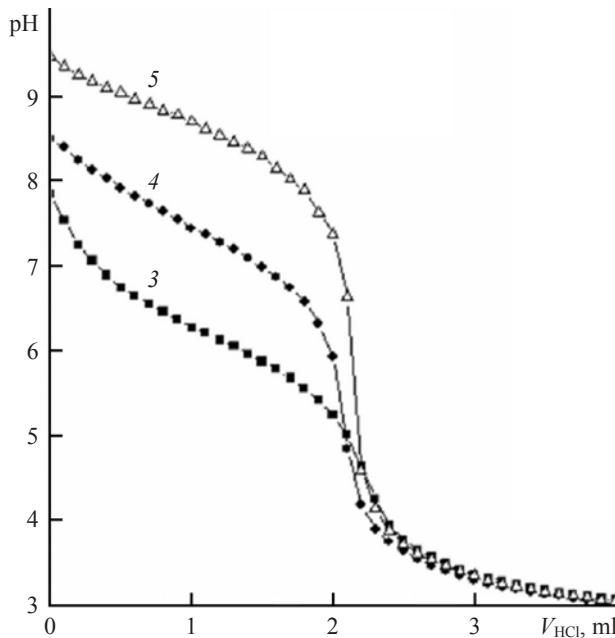


Fig. 7. Titration curves of aqueous-ethanolic solutions of macrocyclic compounds (1) **I**, (2) **XIII**, (3) **XIV**, and (4) **XVI** and (5) of triethylamine with hydrochloric acid.



numbers of methylene units in the bridging fragment affects the basicity of the bridging nitrogen atom. For this purpose, we performed pH-metric titration of solutions of compounds **I**, **XIII**, **XIV**, and **XVI** ($n = 2, 3$) in aqueous ethanol (20:80 by volume) with hydrochloric acid. As follows from the titration curves (Fig. 7a, b), only one nitrogen atom undergoes protonation; obviously, it is the bridging nitrogen atom. The corresponding pK_a values are given in table; in addition, the pK_a value of triethylamine was determined under the same conditions (Fig. 7b). The results showed that extension of the polymethylene bridge is accompanied by increase in the basicity of the bridging nitrogen atom and that compounds **I**, **XIII**, **XIV**, and **XVI** remain weaker bases than triethylamine. Therefore, the latter is capable of acting as deprotonating agent toward conjugate acids of pyrimidinocyclophanes.

Apart from pK_a values, different conformations of pyrimidinocyclophanes having $(\text{CH}_2)_5\text{N}(\text{R})(\text{CH}_2)_5$ and $(\text{CH}_2)_6\text{N}(\text{R})(\text{CH}_2)_6$ bridges are also responsible for differences in their extractability, specifically in the transfer of picric acid from an aqueous solution to a solution of pyrimidinocyclophane in chloroform. Figure 8 shows the plots of the amount of picric acid extracted from aqueous solution to solutions of **XIV** and **XVI** in CHCl_3 versus pH. It is seen that compound **XVI** with a longer bridging fragment is a more effective extractant toward picric acid and that it is capable of acting at higher pH values. Obviously, the lone electron pairs on the bridging nitrogen atoms in **XIV** and **XVI** are characterized by different accessibilities.

The bridging sulfur atom in pyrimidinocyclophanes **XXI** and **XXII** turned out to be inactive toward proton donors. Addition of an acid to a solution of **XXI** or **XXII** in CDCl_3 induced no appreciable variations in the ^1H NMR spectra even on heating. Methylation of the bridging sulfur atom changes the conformation. Unlike compound **XXII**, the geminal methylene protons at N^1 and N^3 in sulfonium salt **XXV** are magnetically nonequivalent, and the ^1H NMR spectrum of **XXV** is analogous to those of pyrimidinocyclophanes having a $(\text{CH}_2)_5\text{N}(\text{R})(\text{CH}_2)_5$ bridging group.

As concerns factors determining conformations of pyrimidinocyclophane molecules in solution and in crystal, we can state that noncovalent interactions between spatially close fragments in pyrimidinocyclophanes with a $(\text{CH}_2)_5\text{N}(\text{R})(\text{CH}_2)_5$ linker were not found. Their ^1H NMR spectra do not change in going from nonpolar solvents to polar (CD_3OD , $\text{DMSO-}d_6$, CD_3CN), indicating the absence of hydrogen bonds

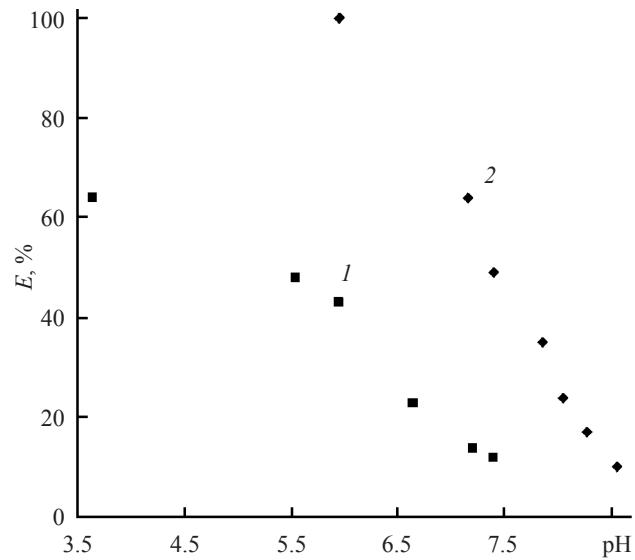


Fig. 8. Plots of the amount of picric acid ($E, \%$) extracted from aqueous phase to a chloroform solution of pyrimidinocyclophane (1) **XIV** and (2) **XVI** versus pH of the aqueous phase.

between molecular fragments [7]. Moreover, taking into account that nuclear Overhauser effects are observed for pyrimidinocyclophanes having both alkyl and phenyl group on the bridging nitrogen atom, $\pi-\pi$ interactions (face-to-face or edge-to-face) cannot be regarded as a factor stabilizing conformation of the macrocyclic. Neither H-bonding nor $\pi-\pi$ interaction between molecular fragments was revealed in the crystalline structure of pyrimidinocyclophanes as well [6].

Presumably, mutual orientation of molecular fragments in $(\text{CH}_2)_5\text{N}(\text{R})(\text{CH}_2)_5$ -bridged pyrimidinocyclophanes is determined by steric conditions for closure of the pentamethylene chains. Conformational lability of these chains depends on their length. The chain consisting of 10 methylene units is sufficiently long to form a $(\text{CH}_2)_5\text{N}(\text{R})(\text{CH}_2)_5$ bridge between the pyrimidine nitrogen atoms, but its length is insufficient to ensure conformational lability of the bridge, at least on the NMR time scale. This clearly follows from the X-ray diffraction and NMR data for pyrimidinocyclophanes **XXI** and **XXII** having a bridging sulfur atom. Insofar as the radius of the sulfur atom is larger than that of nitrogen atom, the length of tetramethylene chains in molecule **XXIII** is sufficient for ring closure via reaction of the terminal bromine atoms with Na_2S (Scheme 2), whereas cyclization with benzylamine failed [8]. The $(\text{CH}_2)_6\text{N}(\text{R})(\text{CH}_2)_6$ and $(\text{CH}_2)_5\text{S}(\text{CH}_2)_5$ bridging fragments are conformationally labile.

Different basicities of the nitrogen atoms in $(\text{CH}_2)_5\text{N}(\text{R})(\text{CH}_2)_5$ and $(\text{CH}_2)_6\text{N}(\text{R})(\text{CH}_2)_6$ bridges may

be interpreted by comparing pyrimidinocyclophanes with bicyclic amines and diamines, such as [4.4.4]diamine and [1.1.1]cryptand [10], as well as with structurally rigid cavitands containing bridgehead nitrogen atoms [11]. Bicyclic amines and diamines are characterized by low pK_a values due to energy loss related to inversion of the lone electron pair (LEP) orbital of the nitrogen atom upon protonation: the inward orientation of the LEP changes to outward [10]. According to calculations, the latter conformation is energetically unfavorable, so that the nitrogen atom tends to lose proton in order to turn back to the inward conformation. Presumably, just this factor is responsible for the higher (by more than an order of magnitude) basicity of **I** relative to **XIII** and of **XIV** relative to **XVI**. Folded conformation of pyrimidinocyclophanes **I** and **XIV** could constrain the nitrogen LEP orbital to be oriented inward. We believe that analogous effect in considerably more flexible pyrimidinocyclophanes (as compared to strained bicyclic diamines, cryptands, and cavitands) undoubtedly attracts interest. Presumably, the same applies to some extent to pyrimidinocyclophanes having 12 methylene groups in the bridge. The above considerations are likely to rationalize different conformations of amphiphilic macrocycle **XXV** and its precursor **XXII**. The positively charged sulfur atom in **XXV** has one lone electron pair whose orbital is oriented inward, thus restricting the mobility of the $(\text{CH}_2)_5\text{S}(\text{CH}_2)_5$ bridge.

Thus we have synthesized a series of cyclophanes consisting of a pyrimidine or 1,3,5-triazine ring and an aza(thia)polymethylene bridge connecting the N^1 and N^3 atoms in the heteroring. The structure of these compounds in crystal and in solution is determined by the length of the $(\text{CH}_2)_n\text{N}(\text{R})(\text{CH}_2)_n$ ($n = 5, 6$) or $(\text{CH}_2)_n\text{S}(\text{CH}_2)_n$ bridge ($n = 4, 5$). Pyrimidinophanes having a short bridge exist in a conformation where the substituent on the bridging nitrogen atom approaches the pyrimidine fragment. Extension of the bridging moiety enhances its conformational mobility, and the macrocyclic has an unfolded structure with distant molecular fragments. As a result, the basicity constants of pyrimidinocyclophanes with shorter bridges are higher by an order of magnitude than those of their analogs with longer bridges. Protonation of the nitrogen atom in the $(\text{CH}_2)_5\text{N}(\text{R})(\text{CH}_2)_5$ bridge with organic and inorganic acids promotes reversible transformation of folded conformation into unfolded, which makes such compounds promising from the viewpoint of design of molecular machines.

EXPERIMENTAL

The NMR spectra were recorded on a Bruker Avance-600 spectrometer (600 MHz for ^1H) at 30°C from solutions in CDCl_3 using the solvent as reference (CHCl_3 , δ 7.26 ppm; CDCl_3 , δ_{C} 77.0 ppm). The structure of the isolated macrocyclic compounds was determined using a number of one- and two-dimensional correlation techniques (DEPT, ^1H - ^1H COSY, ^1H - ^{13}C HSQC, ^1H - ^{13}C HMBC) [12–14]. The mass spectra (electron impact, 70 eV) were obtained on a Finnigan MAT-212 mass spectrometer at a resolution of 1000 with direct sample admission into the ion source; vaporizer temperature 20–300°C; electron emission current 1.0 mA; MSS MASPEC II³² data processing system.

X-Ray analysis of a single crystal of compound **XIII** was performed on a Nonius Kappa CCD diffractometer at –75°C, and the X-ray diffraction data for compounds **VI**, **XVII**, and **XXI** were acquired at 20°C using an Enraf–Nonius CAD-4 diffractometer. Single crystals of **VI**, **XIII**, **XVII**, and **XXI** were obtained by crystallization from solutions in DMSO. The structures were solved by the direct method using MolEN [15] and SIR software [16] and were refined using SHELXL97 [17] and WinGX [18].

X-Ray diffraction data. Compound **VI**. $\text{C}_{23}\text{H}_{33}\text{N}_3\text{O}_2$, *M* 383.52. Rhombic crystals, space group $P2_12_12_1$ (no. 19); $a = 9.117(2)$, $b = 13.39(1)$, $c = 35.18(1)$ Å; $V = 4296(4)$ Å³. MoK_{α} irradiation, $\lambda = 0.71073$ nm. Compound **XIII**. $\text{C}_{24}\text{H}_{35}\text{N}_3\text{O}_2$, *M* 397.55. Triclinic crystals, space group *P*-1 (no. 2); $a = 9.576(2)$, $b = 12.859(1)$, $c = 18.713(3)$ Å; $\alpha = 78.27(1)$, $\beta = 84.24(1)$, $\gamma = 89.34(1)$ °; $V = 2244.7(6)$ Å³. MoK_{α} irradiation, $\lambda = 0.71073$ nm. Compound **XVII**. $\text{C}_{21}\text{H}_{30}\text{N}_4\text{O}_3$. *M* 386.49. Monoclinic crystals, space group $P2_1/a$ (no. 14); $a = 8.983(2)$, $b = 24.742(4)$, $c = 19.176(2)$ Å; $V = 4176.6(1)$ Å³. CuK_{α} irradiation, $\lambda = 1.54184$. Compound **XXI**. $\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$, *M* 268.37. Rhombic crystals, space group $P_{bc}\bar{a}$ (no. 61); $a = 9.333(2)$, $b = 13.119(3)$, $c = 21.998(3)$ Å; $V = 2693.4(9)$ Å³. CuK_{α} irradiation, $\lambda = 1.54184$ nm.

pH-Metric titration was performed on an I-130 instrument at 20 ± 1 °C using a 6 mM solution of HCl in an H_2O –EtOH mixture (80 vol %) with an accuracy of ± 0.05 log units. The acidities were determined according to the procedure described in [19, 20]. The concentration of **I**, **XIII**, **XIV**, and **XVI** was 2 mM, and the initial volume was 6.41 ml. The experimental data were processed using CPESSP program [20].

Extraction of picric acid from its aqueous solution (2 ml, $c = 0.25$ mM) into of a solution of pyrimidinocyclophane **XIV** or **XVI** in CHCl_3 (2 ml, $c = 1$ mM) was performed by stirring the two-phase system over a period of 1 h. The concentration of picric acid in the aqueous phase was determined before and after extraction by spectrophotometry at λ 355 nm (picrate ion); pH was varied using a TRIS/ HNO_3 buffer.

Compounds **XXIII** [8] and **XXIV** [21] were synthesized previously.

Pyrimidinocyclophanes XXI and XXII (general procedure). 1,3-Bis(4-bromobutyl)thymine or 1,3-bis(5-bromopentyl)-6-methyluracil, 1 equiv, was dissolved in DMF, the solution was heated to 60°C, a catalytic amount of tetrabutylammonium hydrogen sulfonate and a suspension of 1.3 equiv of anhydrous sodium sulfide in DMF were added, and the mixture was stirred at 100–110°C, the progress of the reaction being monitored by TLC. When the reaction was complete, the mixture was cooled, the solvent was distilled off, the residue was treated with 150 ml of chloroform, the mixture was filtered, and the filtrate was concentrated to a volume of 10–20 ml and subjected to column chromatography on silica gel.

13-Methyl-6-thia-1,11-diazabicyclo[9.3.1]pentadec-13-ene-12,15-dione (XXI) was obtained from 3.00 g (7.58 mmol) of compound **XXIII** and 0.77 g (9.87 mmol) of Na_2S in 150 ml of DMF. The column was eluted in succession with petroleum ether and diethyl ether–petroleum ether (3:1). From the second fraction we isolated 0.30 g (15%) of compound **XXI**, mp 151–152°C. ^1H NMR spectrum, δ , ppm: 6.96 s (1H, 14-H), 4.70 m (1H, 1- CH_2), 4.38 m (1H, 11- CH_2), 4.04 m (1H, 11- CH_2), 3.28 m (1H, 1- CH_2), 2.61 m (2H, SCH_2), 2.12 m (2H, SCH_2), 1.96 s (3H, CH_3), 1.92 m (2H, NCH_2CH_2), 1.77 m (4H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1.46 m (2H, $\text{NCH}_2\text{CH}_2\text{CH}_2$). Mass spectrum, m/z (I_{rel} , %): 269 (15) $[M + 1]^+$, 268 (100) $[M]^+$, 235 (21), 214 (17), 195 (28), 183 (60), 181 (42), 180 (10), 167 (14), 166 (23), 155 (11), 127 (48), 126 (14), 110 (12). Found, %: C 58.27; H 7.59; N 10.31; S 12.03. $[M]^+$ 268.1210. $\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$. Calculated, %: C 58.18; H 7.51; N 10.44; S 11.95. M 268.1245.

16-Methyl-7-thia-1,13-diazabicyclo[11.3.1]heptadec-15-ene-14,17-dione (XXII) was obtained from 2.50 g (5.90 mmol) of compound **XXIV** and 0.60 g (7.69 mmol) of Na_2S in 150 ml of DMF. The column was eluted in succession with petroleum ether and ethyl acetate–petroleum ether (1.2:1). From the second fraction we isolated 0.54 g (31%) of compound **XXII**, mp 119.5–121.5°C. ^1H NMR spectrum, δ , ppm: 5.59 s

(1H, 17-H), 4.29–3.90 m (4H, NCH_2), 2.60–2.40 m (4H, SCH_2), 2.23 s (3H, CH_3), 1.80–1.70 m (4H, NCH_2CH_2), 1.65–1.40 m (8H, $\text{SCH}_2\text{CH}_2\text{CH}_2$). Mass spectrum, m/z (I_{rel} , %): 297 (18) $[M + 1]^+$, 296 (100) $[M]^+$, 281 (18) $[M - 15]^+$, 229 (23), 227 (12), 197 (33), 195 (40), 181 (18), 153 (13), 141 (19), 140 (21), 127 (61), 110 (11), 101 (26), 100 (16), 96 (25). Found, %: C 60.69; H 8.19; N 9.37; S 10.89. $[M]^+$ 296.1556. $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}_2\text{S}$. Calculated, %: C 60.78; H 8.16; N 9.45; S 10.82. M 296.1558.

7,15-Dimethyl-16,17-dioxo-7-thonia-1,13-diazabicyclo[11.3.1]heptadec-14-ene 4-toluenesulfonate (XXV). A mixture of 0.07 g (0.23 mmol) of pyrimidinocyclophane **XXII** and 4 g of methyl *p*-toluenesulfonate (**XVIII**) was stirred for 6 h at 80°C. The mixture was cooled and diluted with 30 ml of diethyl ether, and the precipitate was separated by decanting, washed with several portions of diethyl ether (the product was separated each time by decanting), and dried under reduced pressure. Yield 0.07 g (63%). ^1H NMR spectrum, δ , ppm: 7.74–7.72 m (2H, H_{arom}), 7.16–7.14 m (2H, H_{arom}), 5.60 s (1H, 14-H), 4.28 m (1H, NCH_2), 4.14 m (1H, NCH_2), 3.97 m (1H, NCH_2), 3.84 m (1H, NCH_2), 3.53 m (4H, CH_2S), 3.18 s (3H, SCH_3), 2.35 s (3H, $\text{C}_6\text{H}_4\text{CH}_3$), 2.23 s (3H, 15- CH_3), 2.00–1.40 m [12H, $\text{NCH}_2(\text{CH}_2)_3$]. Found, %: C 57.35; H 7.19; N 5.69; S 13.11. $\text{C}_{23}\text{H}_{34}\text{N}_2\text{O}_5\text{S}_2$. Calculated, %: C 57.23; H 7.10; N 5.80; S 13.29.

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