Uncharged water-soluble amide derivatives of pillar[5]arene: synthesis and supramolecular self-assembly with tetrazole-containing polymers*

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New uncharged water-soluble pillar[5]arene derivatives bearing 2-hydroxyethylamide and 2-hydroxypropylamide moieties have been for the first time synthesized *via* aminolysis. A detailed analysis performed for the spectral data (UV, IR; and ^{1}H, ^{13}C, NOESY, and HSQC NMR) allowed us to determine the spatial structure of the synthesized macrocycles. Aggregation properties of the obtained compounds with water-soluble tetrazole-containing polymers, *viz.* poly-5-vinyltetrazole (PVT) and polyvinyl(tetrazolyl)ethyl ether (PVTE), were evaluated. Pillar[5]-arene containing 2-hydroxyethylamide moieties formed monodisperse nanoscale aggregates with an average hydrodynamic diameter of 117 nm in the presence of PVTE in aqueous solution. The morphology of resulting particles was determined by scanning electron microscopy.

Key words: water-soluble synthetic receptors, pillar[5]arene, self-organization, supramolecular chemistry, macrocycles, self-assembly.

Recent advances in the pharmaceutical chemistry are associated with the development of new drugs bearing a tetrazole ring as the structural moiety.[1,2] Tetrazoles have not been found in the nature. With minor exceptions, these compounds do not exhibit any significant biological activity, but at the same time, they are resistant to a biodegradation.[3] This particular property allows tetrazoles to be used as convenient pH-dependent functional moieties for the design of new drugs and for the development of drug delivery systems based on them.[1—4]

Carbon nanotubes, liposomes, polymers, dendrimers, macrocyclic capsule molecules, and magnetic nanoparticles are currently being intensively investigated as the drug delivery systems.[5—8] Polymer nanoparticles are of particular interest due to their stability, bio- and functional compatibility.[6] At this end, polymer compositions based on polyvinyltetrazoles (PVT) are considered as promising carriers for the development of targeted drug delivery systems.[9] PVT-based polymers exhibit a pronounced antiinflammatory activity, promote blood coagulation, and accelerate wound healing.[9] However, it should be noted that the PVT-based polymer compositions do not form stable nanoscale aggregates in aqueous solutions.[10] To obtain the nanosized particles with the given shape and size,[10] the polymer compositions containing polyfunctional macrocyclic compounds[11,12] are employed. These macrocyclic compounds possess a number of attractive characteristics such as preorganized spatial structure, the macrocyclic cavity capable of containing the guest molecule, and functional groups that regulate receptor properties of the macrocyclic system.[13,14] To date, the most promising macrocyclic compounds are pillar[*n*]arenes, representatives of the new class of *para*-cyclophanes.[15] In contrast to relative classes of macrocycles (calix[*n*]-arenes, cyclodextrins, and cucurbit[*n*]urils), pillar[*n*]-arenes are synthetically available and can be easily functionalized thus providing the opportunity to work under the conditions that are not suitable for other macrocycles (pH, aqueous and buffer systems).[16—18]

In the present work, we describe the first example of application of uncharged water-soluble pillar[5]arene derivatives bearing 2-amidoethanol and 3-amidopropanol moieties for the preparation of nanosized associates with poly-5-vinyltetrazole (PVT) and polyvinyl(tetrazol-5-yl)ethyl ether (PVTE) *via* supramolecular self-assembly.

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Results and Discussion

Pillar[5]arenes bearing various hydrophilic groups (carboxyl, ammonium, amide, and amino groups) are the most studied homologues of pillar[*n*]arenes. These compounds are highly soluble in water and exhibit a high complexing ability.[15]

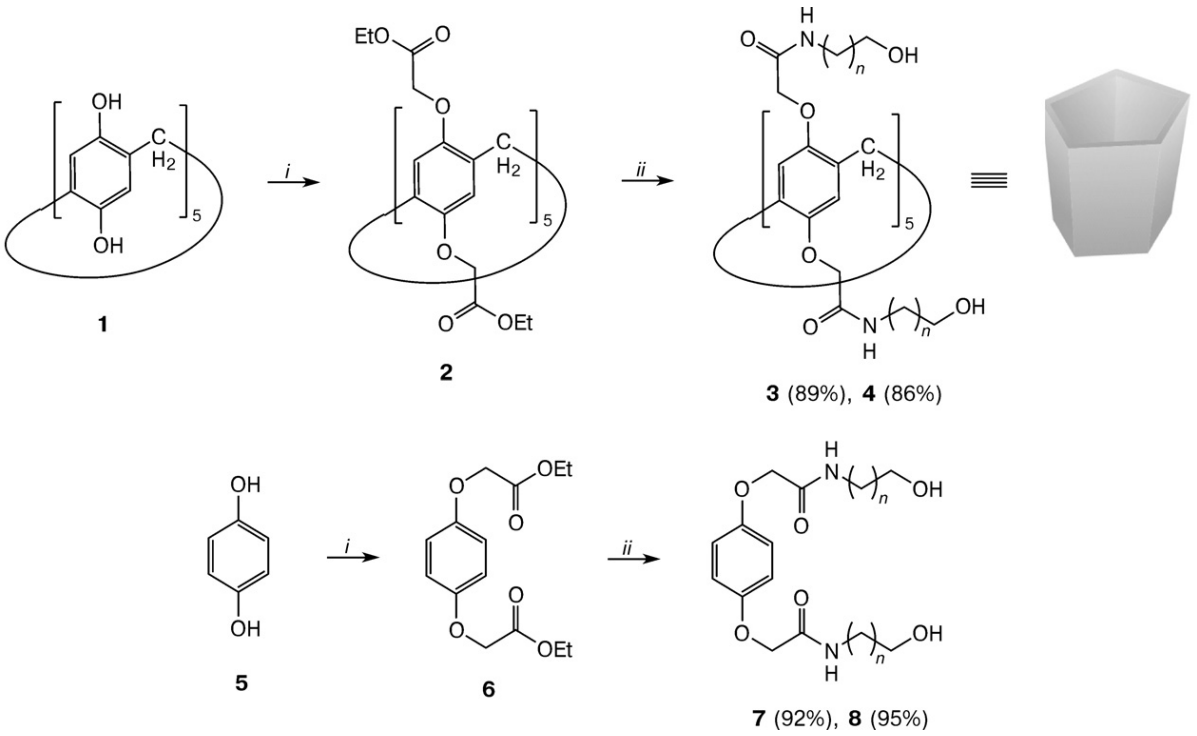
We have previously developed[19] the procedure for introducing amide groups into a pillar[5]arene framework. Diamines containing the both primary and tertiary amino groups were used as the amidating agents. In the present work, we have selected commercially available 2-aminoethanol and 3-aminopropanol as the amidating agents. Starting macrocycles **1** and **2** were synthesized according to the known procedure.[20] Subsequent aminolysis of decaester **2** with 2-aminoethanol or 3-aminopropanol in methanol afforded macrocycles **3** and **4** in the yields of 89 and 86%, respectively (Scheme 1).

Model compounds **7** and **8** were prepared in order to evaluate an effect of the macrocyclic platform of pillar[5]arene on its aggregation properties with poly-5-vinyltetrazole and polyvinyl(tetrazol-5-yl)ethyl ether. For this purpose, diester **6** was obtained by alkylation of *p*-hydroquinone **5** according to the procedure reported previously,[21] aminolysis of which with 2-aminoethanol and 3-aminopropanol in methanol afforded desired amides **7** and **8** in the yields of 92 and 95%, respectively.

Structures of all the obtained products were confirmed by a set of physicochemical methods: 1D and 2D NMR spectroscopy, IR spectroscopy, and their compositions were confirmed by elemental analysis and mass spectrometry. Thus, the ^{1}H NMR spectrum of macrocycle **4** (Fig. 1) contains a signal from the protons of amide group as a broadened singlet at δ 7.71. Signals from H(1) and H(3) aromatic protons of the macrocycle were observed as a singlet (δ 6.81), which is typical of decasubstituted derivatives of the pillar[5]arene.[18,19] Proton signals from the OC(4)H_2C(O) groups were observed as an AB spin system (δ 4.39 and 4.40) with $^2J_{H,H}$ = 12.9 Hz. Protons of the hydroxy groups resonate as a multiplet in the range of δ 4.10—4.15. A singlet at δ 3.76 corresponds to signals from the H(2) protons of methylene bridges. The H(5), H(6), and H(7) protons of propylidene moieties resonate as multiplets in the range δ 1.35—3.39. The chemical shifts, ratio of integral intensities, and multiplicity of the proton signals in the ^{1}H NMR spectrum of pillar[5]arene **4** are in a good agreement with the proposed structure.

It has been previously observed[22] that an introduction of the bulky substituents into the structure of pillar[5]arene inhibits the oxygen-through-the-annulus rotation of its aro-

Схема 1



n = 1 (**3**, **7**), 2 (**4**, **8**)

Reagents and conditions: *i*. $BrCH_2COOH$, K_2CO_3, KI, MeCN; *ii*. $H_2N(CH_2)_{n+1}OH$, MeOH.

matic units. However, the rotation speed increases upon increasing the temperature of system.[22] It should be noted that in macrocycle **4**, spin-spin coupling constants for the AB spin systems of $OC(4)H_2C(O)$ groups are ~13 Hz, and the H(5) protons of methylene moieties of the amide group (see Fig. 1) form two four-spin non-first-order systems that were not analyzed. The proton nonequivalence is most likely caused by an inhibition of the rotation of aryl moieties by long substituents at the aryl moieties, by planar chirality of pillar[5]arene **4**, and also by formation of cyclic hydrogen bonds between the amide moieties. Thus, the assignment of signals from each proton and carbon atom of the 3-amidopropanol moiety of macrocycle **4** was carried out by the analysis of cross-peaks in the 2D $^1H—^{13}C$ HSQC NMR spectrum (see Fig. 1). One can see from the spectrum that signals from the two non-equivalent H(5) protons correspond to the signal from the C(5) carbon atom at the amide group, while signals from the equivalent H(6) and H(7) protons correspond to the signals from the C(6) and C(7) carbon atoms, which is in a good agreement with the integral intensity of signals in the ^1H NMR spectrum. This fact indicates an absence of the dynamic processes caused by rotation of the aryl moieties.[23] In the case of macrocycle **3**, a different ^1H NMR pattern was observed. For compound **3**, signals of the methylene protons at the amide group (δ 3.35) and the protons of the $OCH_2C(O)$ groups (δ 4.37) are observed as the broadened multiplets, which indicates the absence of the cyclic amide hydrogen bond and rotation of the aromatic moieties in pillar[5]arene **3**.

To confirm the hypothesis about the presence of the cyclic hydrogen bond inhibiting the rotation of the aromatic moieties in macrocycle **4**, IR spectra of compounds **3**, **4**, **7**, and **8** were investigated. Table 1 shows characteristic bands of the stretching vibrations of pillar[5]arenes **3**, **4** and model compounds **7**, **8**. In the IR spectra, the stretching vibrations bands of amide moieties of macrocycles **3** and **4** are different. Thus, intense ν(C=O) (amide I) at 1681.6 cm^{-1} and less intense δ(NH) (amide II) at 1654.2 cm^{-1} bands indicate the presence of free amide groups in the structure of macrocycle **3**. For macrocycle **4**, intense ν(C=O) (amide I) at 1643.3 cm^{-1} and less intense δ(NH) (amide II) at 1640.5 cm^{-1} bands are observed, which corresponds to the associated amide group. In model compounds **7** and **8**, the both characteristic bands of

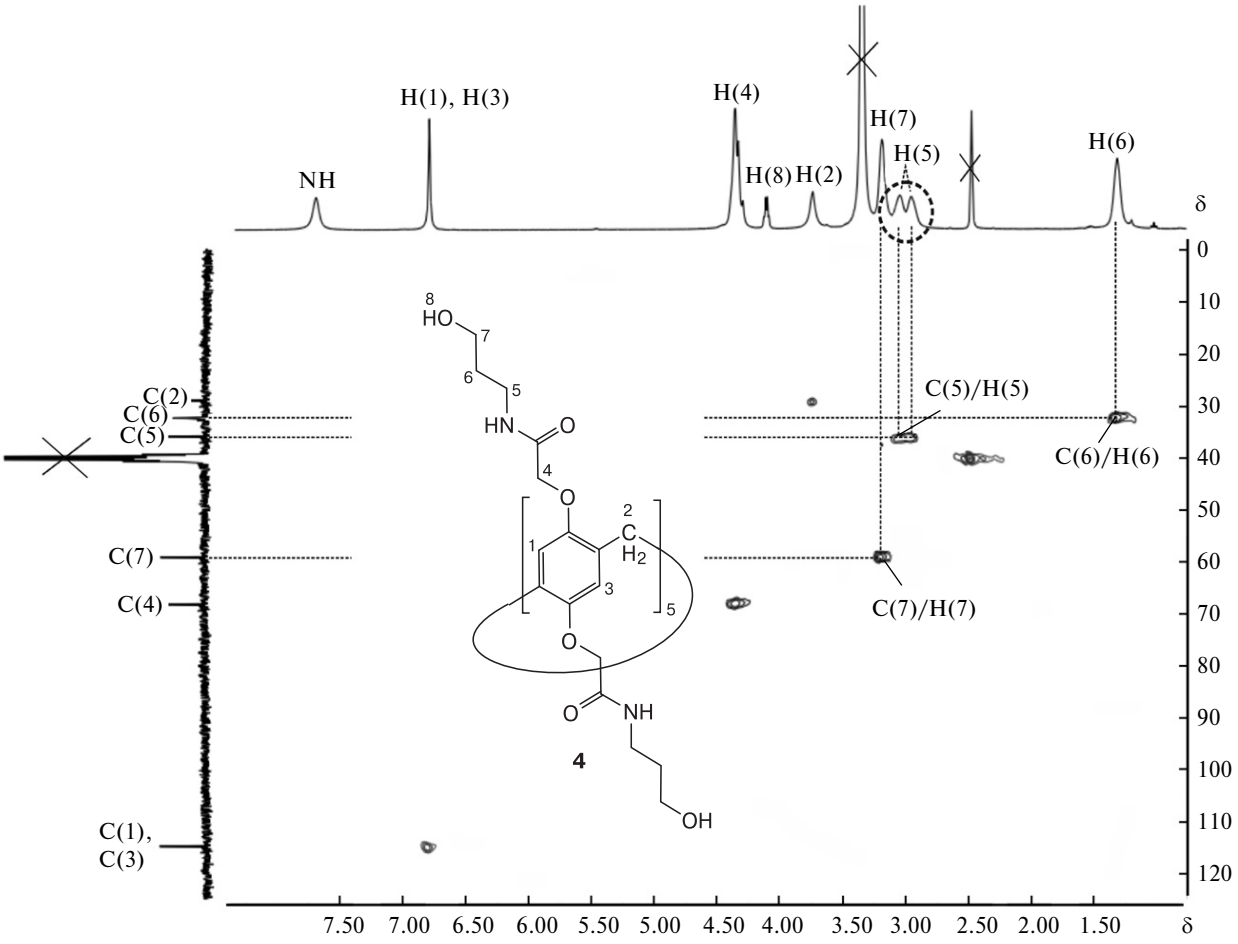


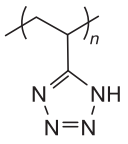
Fig. 1. $^1H—^{13}C$ HSQC spectrum of compound **4** (DMSO-d_6, 25 °C, Bruker Avance-400). The numbering of atoms in compound **4** does not correspond to the IUPAC nomenclature and was used for the interpretation of NMR spectra.

Table 1. Characteristic bands in the IR spectra (cm^{-1}) of compounds **3**, **4**, **7** and **8**

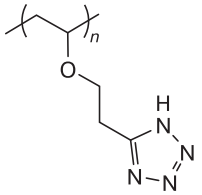
Compound	OH	C(O)NH		C_{Ar}—O—CH_2
		ν(C=O)	δ(NH)	
3	3289.4	1681.6	1654.2	1250.7
4	3289.5	1643.3	1640.5	1251.1
7	3337.1	1679.9	1657.2	1216.1
8	3360.3	1673.3	1661.2	1232.5

stretching vibrations of the amide moieties correspond to the free amide groups. Therefore, the acquired experimental data indicate that in contrast to macrocycle **3**, the formation of inter- and intramolecular hydrogen bonds is characteristic of macrocycle **4**.

Investigation of the supramolecular self-assembly with tetrazole-containing polymers. The next step of this work was the study of self-assembly and association of the synthesized macrocycles **3** and **4** in the presence of tetrazole-containing polymers: poly-5-vinyltetrazole and polyvinyl(tetrazol-5-yl)ethyl ether. The starting PVT and PVTE are insoluble in water in non-ionized state,[24,25] since the tetrazole moieties present in the polymer chains are prone to the formation of multiple intra- and intermolecular hydrogen bonds.[26] At this end, PVT and PVTE were converted into water-soluble polyammonium salts according to the known procedures.[27,28]



PVT



PVTE

Consequently, the self-association of the obtained compounds **3**, **4**, **7**, and **8** and their supramolecular self-assembly in water with the prepared salts of PVT and PVTE were investigated. The study of self-association of compounds **3**, **4**, **7**, and **8** in water was carried out using the dynamic light scattering (DLS). It was shown that macrocycles **3** and **4** and model compounds **7** and **8** do not form any stable self-associates in water in the studied concentration range (10^{-3}—10^{-5} mol L^{-1}).

The interaction of pillar[5]arenes **3** and **4** with PVT and PVTE was investigated by DLS, UV spectroscopy, ^1H and ^{13}C NMR spectroscopy, and 2D NMR spectroscopy. The UV spectroscopy showed no shifts in the absorption maxima upon the addition of excess of PVT and PVTE (they do not absorb in the UV range) to macrocycles **3** and **4**, but in the case of macrocycle **3** (10^{-5} mol L^{-1}) and PVTE (10^{-4} mol L^{-1}), there was a "rise" of the baseline (Fig. 2). In the case of compound **4**, the rise of baseline upon the addition

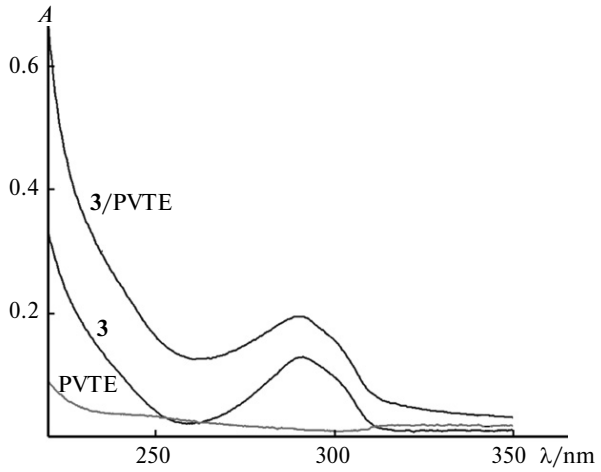


Fig. 2. UV spectra of PVTE (10^{-4} mol L^{-1}), pillar[5]arene **3** (10^{-5} mol L^{-1}), and **3** (10^{-5} mol L^{-1})/PVTE (10^{-4} mol L^{-1}) system in water.

of excess of PVT and PVTE was not observed in the UV spectra. Apparently, the elevated baseline in the UV spectra of pillar[5]arene **3** is due to its aggregation with PVTE.

The next step was DLS studies of the macrocycle/polymer systems at the component ratios of 10 : 1, 5 : 1, 1 : 1, 1 : 5, 1 : 10, and 1 : 15 in the concentration range of 10^{-3}—10^{-5} mol L^{-1}. It is interesting that only in the case of macrocycle **3** (10^{-4} mol L^{-1}) in the presence of PVTE (10^{-5} mol L^{-1}) monodisperse (PDI = 0.21) stable **3**/PVTE associates with an average hydrodynamic diameter of 118 nm were formed (Table 2, Fig. 3). An increase in the ζ potential for **3** : PVTE = 10 : 1 system (Δζ = 9.1 mV) with time (see Table 2) has additionally confirmed the formation of a supramolecular system that stabilizes over time. This is apparently explained by the presence of free, unassociated amide and hydroxy groups in macrocycle **3**, which can form multiple intermolecular macrocycle/polymer hydrogen bonds in contrast to macrocycle **4**.

According to scanning electron microscopy (SEM) data, associates **3** (10^{-3} mol L^{-1})/PVTE (10^{-4} mol L^{-1}) are spherical particles with an average diameter of 117 nm

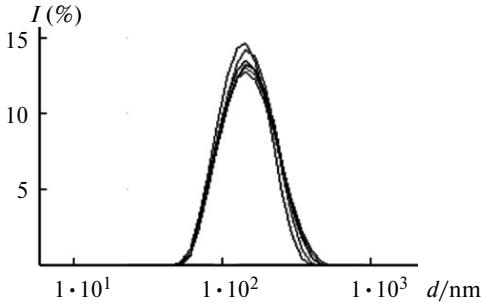


Fig. 3. Size distribution for **3** (10^{-4} mol L^{-1})/PVTE (10^{-4} mol L^{-1}) associates formed in water. Particle polydispersity index (PDI) is 0.21.

Table 2. Characteristics of light scattering for associates of macrocycle **3** (10^{-4} mol L^{-1}) with PVT (10^{-5} mol L^{-1}) and PVTE (10^{-5} mol L^{-1}) in water immediately after preparation (I) and 24 h after preparation (II)

Parameter	**3**/PVTE		**3**/PVT	
	I	II	I	II
d/nm	290±31	118±2	150±20	156±31
PDI	0.24±0.03	0.21±0.01	0.41±0.10	0.45±0.16
ζ/mV	−8.5±0.7	−17.6±1.6	—*	—*

Note: *d* is the average hydrodynamic diameter of associates, PDI is the polydispersity index, and ζ is the electrokinetic potential.
* ζ-Potential was not measured due to the polydispersity of system.

(Fig. 4, *a* and *b*). It should be noted that according to the SEM data, pure macrocycle **3** (10^{-3} mol L^{-1}) formed submicron aggregates (Fig. 4, *c* and *d*), while micron-sized dendritic aggregates were observed for PVTE (10^{-4} mol L^{-1}) (Fig. 4, *e* and *f*).

To estimate an effect of the macrocyclic platform of pillar[5]arene on the formation of nanoscale associates with PVT and PVTE, the behavior of model compounds **7** and **8** in the presence of PVT and PVTE was studied at the compound : polymer ratios of 10 : 1, 5 : 1, 1 : 1, 1 : 5, 1 : 10, and 1 : 15 in the concentration range of 10^{-3}—10^{-5} mol L^{-1} by DLS. It emerged that model compounds **7** and **8** do not form any stable nanoscale associates with PVT and PVTE in the studied concentration range. Therefore, the acquired experimental data suggest that

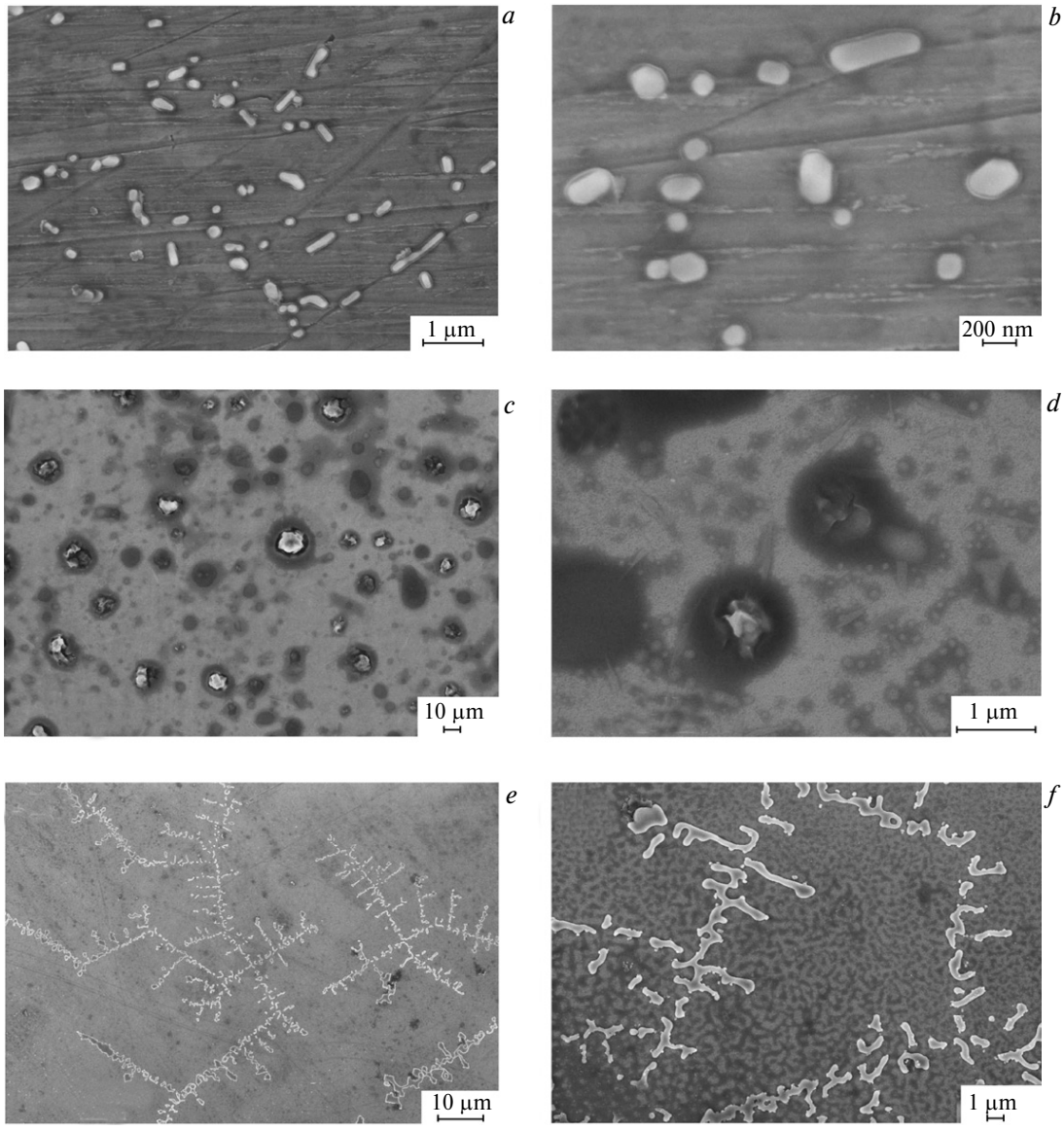


Fig. 4. SEM images of pillar[5]arene **3** (10^{-3} mol L^{-1})/PVTE (10^{-4} mol L^{-1}) associates (*a*, *b*), aggregates of macrocycle **3** (10^{-3} mol L^{-1}) (*c*, *d*), and PVTE (10^{-4} mol L^{-1}) (*e*, *f*) in water.

during association an important role is played not only by the possibility of formation of multiple hydrogen bonds, but also by the macrocyclic platform of pillar[5]arene **3**.

To verify this hypothesis, the interaction of macrocycle **3** with PVTE was investigated by ^{1}H NMR spectroscopy. Unfortunately, the only changes observed in the ^{1}H NMR spectra of **3**/PVTE system were broadening of the signals from the macrocycle and polymer, which indirectly indicates aggregation and formation of **3**/PVTE associates.[16] Thus, 2D ^{1}H—^{1}H NOESY and DOSY NMR spectroscopy were used to confirm the formation of associates. In the case of macrocycle **3**, the ^{1}H—^{1}H NOESY NMR spectrum contained cross-peaks between the protons of the methylene groups of propylene bridge and the protons of moieties of the (CH_2) polymer chain of PVTE, cross-peaks between the protons of the aryl moieties (ArH) of pillar[5]-arene **3** and the protons of tetrazolylethoxyl (CH_2CH_2O) moieties of PVTE (Fig. 5, *a*). The presence of these cross-peaks indicates a spatial proximity of the tetrazole moieties of PVTE polymer and aromatic moieties of pillar[5]arene **3**. There were no similar cross-peaks observed in the ^{1}H—^{1}H NOESY NMR spectrum of **4**/PVTE mixture.

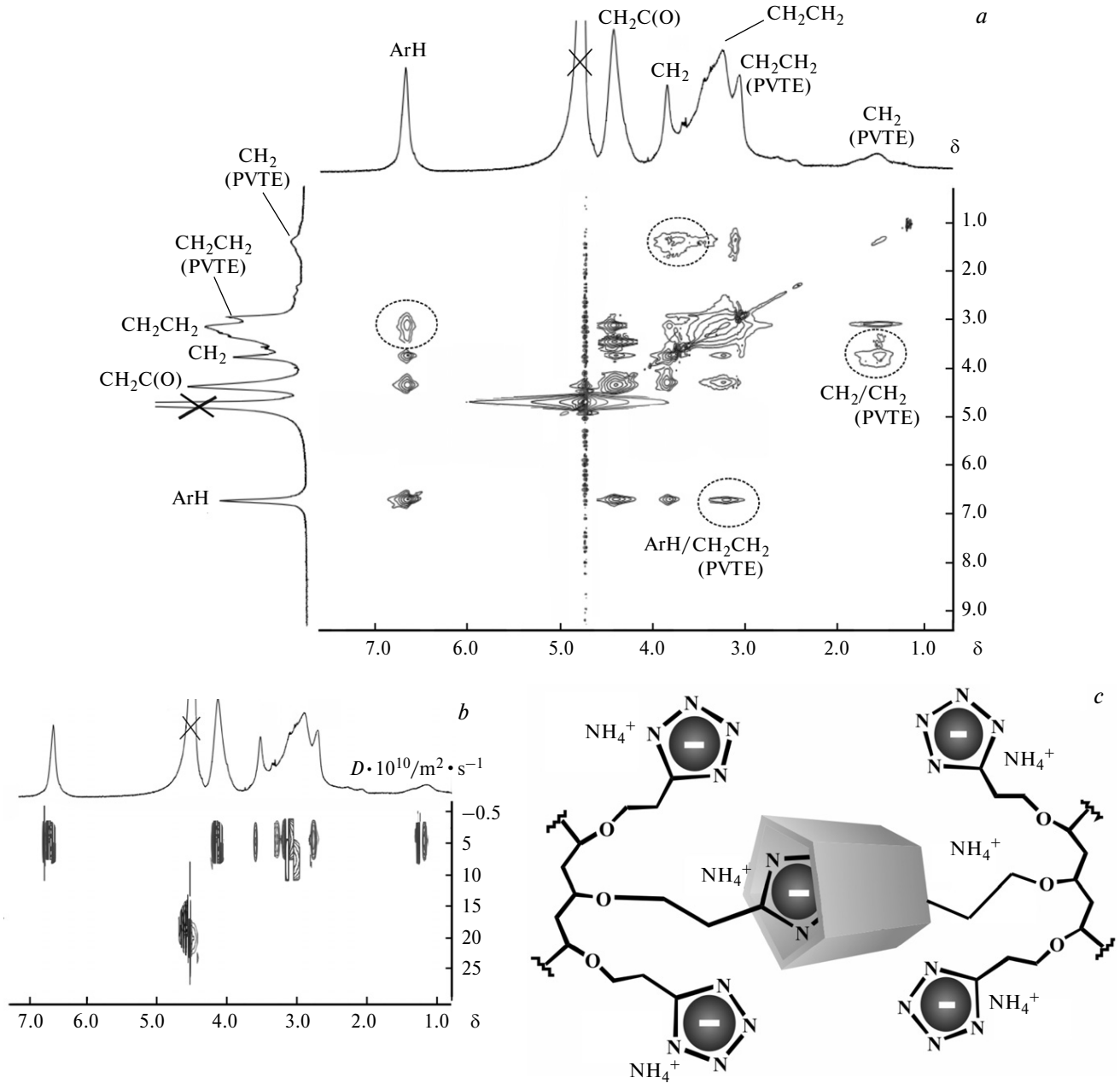


Fig. 5. ^{1}H—^{1}H NOESY (*a*) and DOSY (*b*) spectra (D_2O, 25 °C, Bruker Avance-400) for **3** (10^{-2} mol L^{-1})/PVTE (10^{-3} mol L^{-1}) associates, and the proposed structure of **3**/PVTE complex (*c*).

The formation of **3**/PVTE associates was additionally confirmed by the 2D DOSY spectroscopy (Fig. 5, *b*). Diffusion coefficients were determined at 298 K for pillar[5]-arene **3** (10^{-2} mol L^{-1}), PVTE (10^{-3} mol L^{-1}), and **3** (10^{-2} mol L^{-1})/PVTE (10^{-3} mol L^{-1}) associates. In the DOSY spectrum of **3**/PVTE associates, there is only the one type of the signals lying along a straight line with one diffusion coefficient ($D = 2.11 \cdot 10^{-10}$ m^2 s^{-1}), which is much smaller than the self-diffusion coefficient of macrocycle **3** ($D = 5.53 \cdot 10^{-10}$ m^2 s^{-1}) under the same conditions. An analysis of the data acquired using the 2D NMR spectroscopy allowed us to conclude that association of macrocycle **3** with PVTE results in host-guest complexes, in which the tetrazole moieties are incapsulated within the cavity of pillar[5]arene **3** (Fig. 5, *c*) and several chains are associated into one. The formation of additional intermolecular macrocycle—polymer hydrogen bonds leads to a compaction of the polymer into nanoscale associates.

In conclusion, the present work is the first report on the synthesis of uncharged water-soluble derivatives of pillar[5]-arenes **3** and **4** bearing 2-amidoethanol and 3-amidopropanol fragments. The structures of the obtained products were fully confirmed by a set of physicochemical methods. The DLS method revealed that pillar[5]arenes **3** and **4** do not form stable self-associates in an aqueous solution. The DLS, UV spectroscopy, ^{1}H and ^{13}C NMR spectroscopy, and 2D NMR spectroscopy data confirmed the association of macrocycle **3** with polyvinyl(tetrazol-5-yl)ethyl ether (PVTE). The association of macrocycle **3** with PVTE at the molar ratio of 10 : 1 results in the formation of **3** (10^{-4} mol L^{-1})/PVTE (10^{-5} mol L^{-1}) monodisperse nano-sized particles, whose polydispersity index is 0.21. According to the SEM data, **3**/PVTE associates possess a spherical shape and an average hydrodynamic diameter of 117 nm. It was shown using 2D NOESY and DOSY NMR spectroscopy that pillar[5]arene **3** host-guest complexes with tetrazole moieties of PVTE were formed. Supramolecular self-assembly of nanoscale PVT and PVTE associates with uncharged water-soluble derivatives of pillar[5]arene bearing 2-amidoethanol and 3-amidopropanol moieties provides additional opportunities to employ high molecular weight derivatives of tetrazoles and their supramolecular associates of the given morphology in the personalized medicine and high-tech health care for the design of new targeted therapeutic agents.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer (operating frequencies of 400.0 and 100.0 MHz, respectively). Chemical shifts in the ^{13}C NMR spectra are reported relative to the Me_4Si standard, and chemical shifts in the ^{1}H NMR spectra are given relative to the residual proton signals of deuterated solvent: HDO (δ 4.79) and DMSO-d_5 (δ 2.50). The concentration of analyzed solutions was 3—5 wt.%. Diffusion ordered spectroscopy (DOSY) was performed in D_2O using a Bruker Avance 400 spectrometer with an STE pulse sequence of the bipolar pulse gradient (stebpgp1s). The 16 scans and 16000 data points were recorded. The maximum gradient force obtained along the *z* axis was 5.35 G mm^{-1}. The duration of magnetic field pulse gradients (δ) was optimized for the each diffusion time (Δ) in order to obtain a 2% residual signal with the maximum gradient strength. The values of δ and Δ were 1.800 μs and 100 ms, respectively. The pulse gradients were increased from 2 to 95% of the maximum gradient strength in a linear ramp.[29] IR spectra were recorded on a Spectrum 400 (Perkin Elmer) Fourier spectrometer equipped with an ATR imaging accessory in the wavenumber range of 400—4000 cm^{-1}: resolution of 1 cm^{-1}, acquisition of 64 scans, and recording time of 16 s. Particle sizes in the solution were determined by dynamic light scattering (DLS) using a Zetasizer Nano ZS (Malvern) nanoparticle size analyzer equipped with a He—Ne laser (4 mW) operating at the wavelength of 633 nm, scattered light detection angle of 173°, and with an automatic determination of the measurement position inside the cell. To prepare solutions of macrocycles **3**, **4** and ammonium salts of the PVT and PVTE polymers, deionized water with the specific resistance of 18.0 MΩ cm at 25 °C obtained in the Millipore-Q purification system was used. Solutions of individual macrocycles (**3** and **4**) and polymers (PVT and PVTE) were mixed during the experiment at the macrocycle : polymer ratios of 10 : 1, 5 : 1, 1 : 1, 1 : 5, 1 : 10, and 1 : 15 in the concentration range of 10^{-3}—10^{-5} mol L^{-1}. The solutions were kept for 1 h, and the size of the resulting particles was then measured. The measurements were repeated after 3 and 5 h under the similar conditions in order to assess the kinetic stability of systems. Electronic absorption spectra were recorded on a Shimadzu UV-3600 spectrometer, the thickness of transmission layer was 1 cm. The purity of compounds was monitored by ^{1}H NMR spectroscopy. The purity of compounds was additionally controlled by TLC on Silica 200 μm, UV 254 plates (Sorbtech); and spots of the substances were visualized under UV light (λ = 254 nm). Scanning electron microscopy (SEM) was performed using a Carl Zeiss Auriga Cross Beam microscope on a silicon support. The samples were diluted with water to the final concentration of $1 \cdot 10^{-4}$ g mL^{-1}, poured onto the silicon support, and dried in a vacuum desiccator for 1 h. Elemental analysis of the crystalline samples was carried out on a Perkin Elmer 2400 Series II analyzer. Melting points were determined on a Boetius heating stage. MALDI-TOF spectra were recorded on an Ultraflex III mass spectrometer; *p*-nitroaniline was used as the matrix.

Compounds **1**, **2**, and **6** were synthesized according to the known procedures.[20,21] Poly-5-vinyltetrazole and polyvinyl(tetrazol-5-yl)ethyl ether were obtained according to the known procedures.[24,25]

Synthesis of macrocycles 3 and 4 (general procedure). Compound **2** (0.3 g, 0.2 mmol) in methanol (30 mL) and 2-aminoethanol (or 3-aminopropanol) (6.1 mmol) were placed in a round-bottomed flask equipped with a magnetic stirrer and a reflux condenser. The mixture was refluxed for 72 h, and the solvent was evaporated under a reduced pressure. The residue was dissolved in dichloromethane (20 mL) and washed with distilled water (2×30 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and the solvent was evaporated under a reduced pressure. The products were isolated by recrystallization from propan-2-ol as light yellow powders.

4,8,14,18,23,26,28,31,32,35-Deca[(*N*-2-hydroxyethyl)carbamoylmethoxy]pillar[5]arene (3). The yield was 0.29 g (89%), m.p. 115 °C. IR, ν/cm^{-1}: 3289 (OH), 3088 (N—H), 1682 (C=O),

1654 (C(O)—NH), 1251 (C—O—C). ^{1}H NMR (DMSO-d_6), δ: 3.08—3.12 (m, 20 H, CH_2); 3.33—3.37 (m, 20 H, CH_2); 3.77 (s, 10 H, CH_2); 4.37 (br.s, 20 H, $CH_2C(O)$); 4.52—4.56 (m, 10 H, OH); 6.85 (s, 10 H, ArH); 7.76 (br.s, 10 H, NH). ^{13}C NMR (DMSO-d_6), δ: 29.35, 41.51, 60.06, 68.17, 115.30, 128.46, 149.50, 168.61. MS (MALDI-TOF), *m/z*: 1644 $[M + Na]^+$. Found (%): C, 54.86; H, 6.79; N, 7.94. $C_{75}H_{100}N_{10}O_{30}$. Calculated (%): C, 55.55; H, 6.22; N, 8.64.

4,8,14,18,23,26,28,31,32,35-Deca[(*N*-3-hydroxypropyl)-carbamoylmethoxy]pillar[5]arene (4). The yield was 0.30 g (86%), m.p. 118 °C. IR, ν/cm^{-1}: 3289 (O—H), 3088.64 (N—H), 1643 (C=O), 1640 (C(O)—NH), 1251 (C—O—C). ^{1}H NMR (DMSO-d_6), δ: 1.32—1.36 (m, 20 H, H(6)); 3.04—3.28 (m, 20 H, H(5)); 3.30—3.39 (m, 20 H, H(7)); 3.76 (s, 10 H, H(2)); 4.12—4.14 (m, 10 H, H(8)); 4.39 (AB system, 10 H, H(4), $^2J_{H,H}$ = 12.9 Hz); 4.40 (AB system, 10 H, H(4), $^2J_{H,H}$ = 12.9 Hz); 6.81 (s, 10 H, H(1), H(3)); 7.71 (br.s, 10 H, NH). ^{13}C NMR (DMSO-d_6), δ: 28.89, 31.91, 35.94, 58.70, 67.70, 114.66, 127.91, 148.85, 168.18. MS (MALDI-TOF), *m/z*: 1784 $[M + Na]^+$. Found (%): C, 56.92; H, 6.58; N, 7.67. $C_{85}H_{120}N_{10}O_{30}$. Calculated (%): C, 57.94; H, 6.87; N, 7.95.

Synthesis of macrocycles 7 and 8 (general procedure). Compound **6** (1g, 3.5 mmol) in methanol (20 mL) and 2-aminoethanol (or 3-aminopropanol) (2.1 mmol)) were placed in a round-bottomed flask equipped with a magnetic stirrer and a reflux condenser. The mixture was refluxed for 72 h, and the solvent was evaporated under a reduced pressure. The products were isolated by recrystallization from a propan-2-ol—hexane mixture (1 : 4) as white powders.

1,4-Bis[(*N*-2-hydroxyethyl)carbamoylmethoxy]benzene (7). The yield was 1.00 g (92%), m.p. 109 °C. IR, ν/cm^{-1}: 3337 (O—H), 1648 (C=O), 1657 (C(O)—NH), 1216 (C—O—C). ^{1}H NMR (DMSO-d_6), δ: 3.13—3.23 (m, 4 H, CH_2); 3.40—3.44 (m, 6 H, CH_2); 4.39 (s, 4 H, CH_2); 4.71—4.73 (m, 2 H, OH); 6.90 (s, 4 H, ArH); 7.98—7.99 (m, 2 H, NH). ^{13}C NMR (DMSO-d_6), δ: 41.16, 59.66, 67.61, 115.70, 152.36, 167.96. MS (MALDI-TOF), *m/z*: 335 $[M + Na]^+$. Found (%): C, 52.67; H, 6.15; N, 7.99. $C_{14}H_{20}N_2O_6$. Calculated (%): C, 53.84; H, 6.45; N, 8.97.

1,4-Bis[(*N*-(3-hydroxypropyl)carbamoylmethoxy]benzene (8). The yield was 1.13 g (95%), m.p. 111 °C. IR, ν/cm^{-1}: 3360 (O—H), 1673 (C=O), 1661 (C(O)—NH), 1232 (C—O—C). ^{1}H NMR (DMSO-d_6), δ: 1.54—1.56 (m, 4 H, CH_2); 3.17—3.19 (m, 4 H, CH_2); 3.36—3.40 (m, 6 H, CH_2); 4.39 (s, 4 H, CH_2); 4.46—4.48 (m, 2 H, OH); 6.90 (s, 4 H, ArH); 8.04—8.06 (m, 2 H, NH). ^{13}C NMR (DMSO-d_6), δ: 32.28, 35.84, 58.62, 67.67, 115.69, 152.28, 167.75. MS (MALDI-TOF), *m/z*: 363 $[M + Na]^+$. Found (%): C, 55.83; H, 7.15; N, 8.02. $C_{16}H_{24}N_2O_6$. Calculated (%): C, 56.46; H, 7.11; N, 8.23.

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