Binuclear and polynuclear transition metal complexes with macrocyclic ligands

7.* Directed step-by-step synthesis of novel unsymmetric macrocyclic ligands**

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Novel asymmetric macrocyclic Schiff bases were synthesized by the condensation of *N*,*N*′-bis(2-aminophenyl)-3,4-diphenylthiophene-2,5-dicarboxamide (**1**) with diformyl derivatives of phenol, furan, difurans, pyridine, pyrrole, and dipyrroles. The reaction proceeds in high yields and without by-products in methanol in the presence of inorganic and organic acids (proton-template condensation). In the case of monocyclic diformyl derivatives and di(5-formylfuran-2-yl) sulfide, the reaction occurs in 1,4-dioxane (templateless synthesis). The synthesized macrocycles were characterized by elemental analysis data and NMR and mass spectra.

Key words: macrocyclic ligands, Schiff bases, step-by-step synthesis.

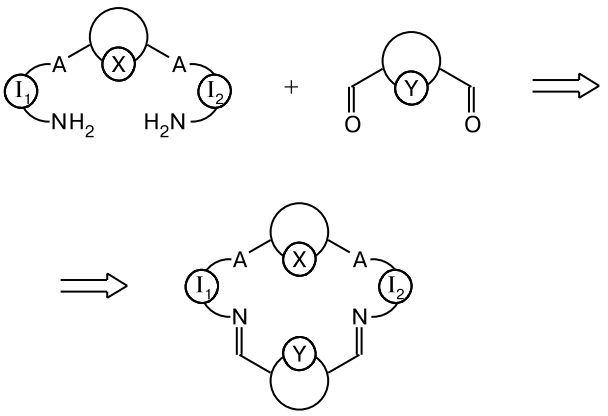
Unsymmetric polydentate macrocyclic and acyclic Schiff bases and related hybrid systems with donor centers different in nature are of great interest as ligands for syntheses of mono- and polynuclear transition metal complexes,[2,3] lanthanides or actinides,[4,5] and as artificial receptors for selective anion binding.[6,7] The modern approaches to the preparation of such systems are mainly based on step-by-step syntheses[8] from enlarged precursor blocks (Scheme 1).

The Schiff condensation with macrocycle closure is usually template. Metal ions[8] or anions of protic acids (proton-template condensation) can be used as template agents. The latter was proposed for the first time by the Sessler research group[9] and used for the synthesis of several pyrrole-containing macrocycles.[6,10]

Continuing the series of studies on the synthesis of symmetric and unsymmetric macrocycles based on diamines and dicarbonyl compounds, we prepared compound **1**, which simultaneously contains groups capable of binding both anionic and cationic substrates (Scheme 2).

The reactions of diamine **1** with dicarbonyl compounds of different structure in 1,4-dioxane occur readily already at room temperature and afford the corresponding macrocycles **3—7** in rather high yields and without admixtures of oligomeric products (Scheme 3).

Scheme 1



Dimethylbis(5-formylpyrrol-2-yl)methane, 5,5′-diformyl-3,3′-dimethyl-4,4′-dipropyl-2,2′-dipyrrole, and 5,5′-diformyl-2,2′-difuran react with compound **1** less easily. The reactions do not occur at room temperature, and only trace amounts of the macrocycles are formed upon prolong reflux. However, the reaction in methanol in the presence of protic acids occurs at room temperature to give macrocycles **8—10** in high yields. Macrocycles **3—6** can also be obtained by this method in rather high yields, while macrocycle **7** is not formed under these conditions. The reactions in the presence of protic acids are performed, depending on the nature of the starting

* For Part 6, see Ref. 1.

** Dedicated to Academician N. S. Zefirov on the occasion of his 70th birthday.

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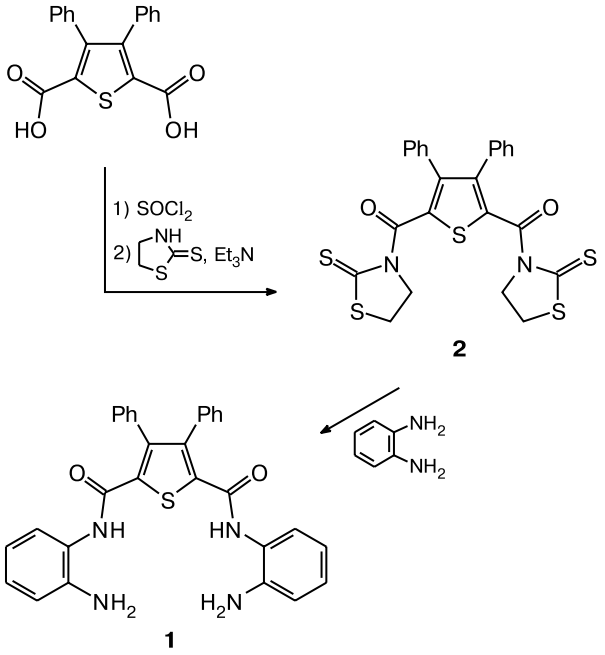
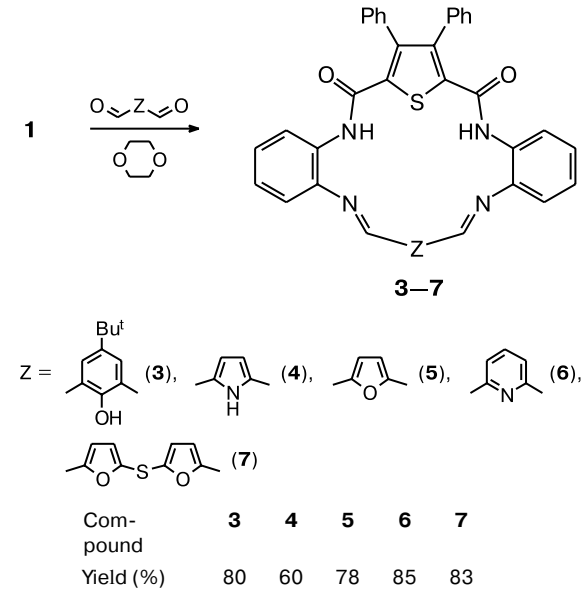
Scheme 2



Scheme 3

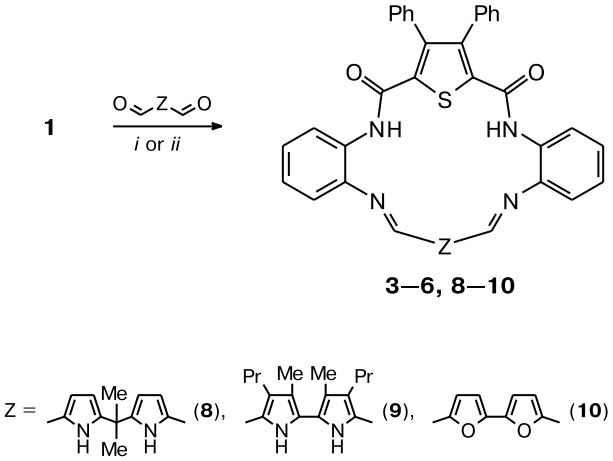


Compound	3	4	5	6	7
Yield (%)	80	60	78	85	83

dicarbonyl compounds and acid, to form either free ligands **4—6** and **10** or protonated macrocycles. In the last case, free ligands **3**, **8**, and **9** can easily be isolated by the treatment with triethylamine (Scheme 4).

Thus, in this work we obtained the series of novel macrocyclic Schiff bases. Presently, we are studying their properties concerning the ability to form complexes with metal ions and bind anions.

Scheme 4



Reaction conditions: *i*. (for **4—6**, **10**) HA (conc.), MeOH; *ii*. (for **3**, **8**, **9**) 1) HA (conc.), MeOH, 2) Et_3N, CH_2Cl_2. HA is protic acid.

Compound	HA	Yield (%)	Compound	HA	Yield (%)
3	HCl	88	**8**	H_2SO_4	95
4	HCl	73	**9**	HCl	83
5	HCl	73	**10**	H_3PO_4	85
6	HCl	42		CF_3CO_2H	70

Experimental

NMR spectra were recorded on an AVANCE-400 instrument (400 MHz for ^1H and 100 MHz for ^{13}C) at 24 °C. Mass spectra MALDI-TOF were obtained on a Reflex 3 instrument (Bruker) in the positive ion mode. Mass spectra ESI(+) (electrospray ionization) were recorded on a Finigan-MAT LCQ instrument. High-resolution mass spectra (HRMS) were measured on a VG ZAB-3E instrument with chemical ionization (CI). 2,6-Diformylpyridine,[11] 2,5-diformylfuran,[12] and 2,5-diformylpyrrole[13] were synthesized and purified according to published procedures. 5,5′-Diformyl-2,2′-difuran,[14] dimethylbis(5-formylpyrrol-2-yl)methane,[15] and di(5-formylfuran-2-yl) sulfide[16] were prepared and purified according to described procedures. 5,5′-Diformyl-3,3′-dimethyl-4,4′-dipropyl-2,2′-dipyrrole was synthesized similarly.[17] Thiazolidine-2-thione (Acros) was used without additional purification.

3,4-Diphenyl-2,5-bis(2-thioxo-1,3-thiazolidin-3-ylcarbonyl)thiophene (2). Freshly distilled thionyl chloride (35 mL) and several droplets of dimethylformamide were added to 3,4-diphenylthiophene-2,5-dicarboxylic acid[18] (9.0 g, 27.7 mmol). After reflux for 1 h, the solvent was distilled off under reduced pressure, and the resulting oily dichloride was dried *in vacuo* using a roughing pump at 100 °C. The obtained crystalline substance was dissolved in anhydrous THF (130 mL), and the solution was added dropwise with stirring at 50 °C for 2 h to a solution of thiazolidine-2-thione (6.6 g, 55.4 mmol) and triethylamine (20 mL) in anhydrous THF (330 mL). The reaction mixture was stirred for 2 h at 50 °C and for 16 h at room temperature, and a precipitate was filtered off and washed with

Table 1. Physicochemical characteristics of compounds **3—10**

Compound	M.p. /°C	Found / Calculated (%)			Molecular formula
		C	H	N	
3	>350	74.78 74.76	5.08 5.08	8.28 8.30	$C_{42}H_{34}N_4O_3S$
4	>350	73.08 73.08	4.21 4.26	11.71 11.84	$C_{36}H_{25}N_5O_2S$
5	>350	72.87 72.96	4.08 4.08	9.43 9.45	$C_{36}H_{24}N_4O_3S$
6	>350	72.61 72.32	4.57 4.51	10.74 10.87	$C_{37}H_{25}N_5O_2S\cdot 0.5C_4H_8O_2$[b]
7	234—236 (decomp.)	68.30 68.65	3.82 4.11	7.68 7.62	$C_{40}H_{26}N_4O_4S_2\cdot 0.5C_4H_8O_2$[b]
8	180—182[a]	72.93 72.99	5.16 5.33	11.37 11.10	$C_{43}H_{34}N_6O_2S\cdot C_3H_6O$[c]
9	244—246 (decomp.)	71.29 71.58	5.61 5.63	10.37 10.43	$C_{48}H_{44}N_6O_2S\cdot HCl$
10	>350	72.91 72.93	4.04 3.98	8.53 8.51	$C_{40}H_{26}N_4O_4S$

[a] For $C_{40}H_{26}N_4O_4S_2\cdot C_3H_6O$.
[b] $C_4H_8O_2$ is dioxane.
[c] C_3H_6O is acetone.

THF (2×30 mL). Combined filtrates were concentrated to dryness on a rotary evaporator. The residue was mixed with ethyl acetate (30 mL), and a yellow powder (10.8 g, 74%) was filtered off, m.p. 254—256 °C (from 1,2-dichloroethane). Found (%): C, 54.73; H, 3.44; N, 5.32. $C_{24}H_{18}N_2O_2S_5$. Calculated (%): C, 54.98; H, 3.23; N, 5.36. ^{1}H NMR ($CDCl_3$), δ: 2.72 (t, 4 H, CH_2S, J = 7 Hz); 4.21 (t, 4 H, CH_2N, J = 7 Hz); 7.05 (m, 4 H, H_{arom}); 7.22 (m, 6 H, H_{arom}). ^{13}C NMR ($CDCl_3$), δ: 29.61, 55.80, 127.90, 127.99, 129.60, 134.21, 136.08, 144.34, 164.16, 200.37. Mass spectrum (ESI+), m/z: 548.9 $[M + Na]^+$, 1074.3 $[2 M + Na]^+$, 1601.8 $[3 M + Na]^+$.

***N,N´*-Bis(2-aminophenyl)-3,4-diphenylthiophene-2,5-dicarboxamide (1).** Compound **2** (5.0 g, 9.45 mmol) was added with stirring to a solution of 1,2-diaminobenzene (3.1 g, 28.4 mmol) in anhydrous CH_2Cl_2 (125 mL). The reaction mixture was stirred for 2 days at ~20 °C. The precipitate was filtered off, and compound **1** was obtained in 78% yield (3.7 g), m.p. 228—230 °C (MeCN). Found (%): C, 71.40; H, 4.77; N, 11.45. $C_{30}H_{24}N_4O_2S$. Calculated (%): C, 71.41; H, 4.79; N, 11.10. ^{1}H NMR (DMSO-d_6), δ: 4.50 (s, 4 H, NH_2); 6.53 (t, 2 H, H_{arom}, J = 7.0 Hz); 6.68 (d, 2 H, H_{arom}, J = 7.0 Hz); 6.90 (t, 2 H, H_{arom}, J = 7.0 Hz); 7.02 (d, 2 H, H_{arom}, J = 7.0 Hz); 7.17 (m, 4 H, H_{arom}); 7.25 (m, 6 H, H_{arom}); 8.76 (s, 2 H, CH=N). ^{13}C NMR (DMSO-d_6), δ: 127.48, 127.90, 133.71, 136.90, 138.13, 139.58, 139.37, 141.32, 145.59, 147.12, 153.39, 153.48, 171.99. Mass spectrum (ESI+), m/z: 527.1 $[M + Na]^+$, 1030.9 $[2 M + Na]^+$, 1535.8 $[3 M + Na]^+$.

14-*tert*-Butyl-31-hydroxy-2,26-dioxo-28,29-diphenyl-3,10,18,25-tetraaza-30-thiapentacyclo[25,2,1,$1^{12,16}$,$0^{4,9}$,$0^{19,24}$]hentriaconta-5,7,9(4),10,12(31),13,15,17,19,21,23,27,29-tridecaene (3), 27,28-diphenyl-2,25-dioxa-3,10,17,24,30-pentaaza-29-thiapentacyclo[24,2,1,$1^{12,15}$,$0^{4,9}$,$0^{18,23}$]triaconta-5,7,9(4),10,12,14,16,18,20,22,26,28-dodecaene (4), 2,25-dioxo-27,28-diphenyl-3,10,17,24-tetraaza-30-oxa-29-thiapentacyclo[24,2,1,$1^{12,15}$,$0^{4,9}$,$0^{18,23}$]triaconta-5,7,9(4),10,12,14,16,18,20,22,26,28-dodecaene (5), 2,26-dioxo-28,29-diphenyl-3,10,18,25,31-pentaaza-30-thiapentacyclo[25,2,1,$1^{12,16}$,$0^{4,9}$,$0^{19,24}$]hentriaconta-5,7,9(4),10,12(31),13,15,17,19,21,23,27,29-tridecaene (6), and 2,30-dioxo-32,33-diphenyl-3,10,22,29-tetraza-35,36-dioxa-16,34-dithiahexacyclo[29,2,1,$1^{12,15}$,$1^{17,20}$,$0^{4,9}$,$0^{23,28}$]hexatriaconta-5,7,9(4),10,12,14,17,19,21,23,25,27,31,33-tetradecaene (7) (general procedure). A mixture of diamide **1** (204 mg, 0.4 mmol) and the corresponding diformyl derivative (0.4 mmol) in a minimum

Table 2. Spectral characteristics of compounds **3—10**

Compound	MALDI-TOF mass spectrum, m/z	^{1}H NMR, δ, J/Hz*	^{13}C NMR, δ*
3	675.09 $[M + H]^+$	1.39 (s, 9 H, Bu^t); 7.14—7.29 (m, 16 H, H_{arom}); 7.69 (d, 2 H, H_{arom}, J = 8); 7.99 (s, 2 H, H_{arom}); 8.22 (d, 2 H, H_{arom}, J = 8); 9.16 (s, 2 H, CH=N); 10.39 (s, 2 H, NH); 14.42 (br.s, 1 H, OH)	31.51 (3 CH_3), 33.88 (C—Bu^t), 66.77, 117.12, 120.45, 121.81, 125.00, 127.82, 127.89, 128.13, 130.47, 133.15, 133.76, 134.66, 135.24, 138.11, 141.58, 145.40, 158.96, 159.09 (C=N), 161.43 (C=O)
4	592.0 $[M + H]^+$	6.94 (d, 2 H, H_{arom}, J = 2); 7.13—7.22 (m, 14 H, H_{arom}); 7.63 (d, 2 H, H_{arom}, J = 8); 8.25 (d, 2 H, H_{arom}, J = 8); 8.80 (s, 2 H, CH=N); 10.49 (s, 2 H, NH); 11.89 (s, 1 H, NH of pyrrole)	115.60, 118.53, 118.58, 123.86, 127.06, 127.10, 127.32, 129.84, 132.31, 134.00, 134.05, 134.83, 136.52, 145.22, 147.14 (C=N), 157.92 (C=O)
5	593.10 $[M + H]^+$	7.05—7.24 (m, 16 H, H_{arom}); 7.36 (d, 2 H, H_{arom}, J = 8); 8.50 (d, 2 H, H_{arom}, J = 8); 8.52 (s, 2 H, CH=N); 10.38 (s, 2 H, NH)	114.67, 119.41, 120.56, 123.68, 127.37, 127.54, 129.43, 130.12, 132.25, 134.41, 135.43, 135.82, 142.66, 148.52, 154.21 (C=N), 157.99 (C=O)
6	602.35 $[M - H]^-$	7.15 (m, 10 H, H_{arom}); 7.22 (d, 2 H, H_{arom}, J = 7); 7.31 (d, 2 H, H_{arom}, J = 7); 7.35 (d, 2 H, H_{arom}, J = 7); 7.55 (d, 2 H, H_{arom}, J = 7); 8.18 (m, 3 H, H_{arom}); 10.05 (s, 2 H, CH=N); 10.19 (s, 2 H, NH)	124.80, 126.00, 126.10, 127.10, 127.20, 127.70, 127.90, 128.70, 130.20, 131.30, 134.20, 134.30, 143.40, 161.50 (C=N), 192.90 (C=O)

(*to be continued*)

Table 2. Spectral characteristics of compounds **3—10**

Compound	MALDI-TOF mass spectrum, *m/z*	^{1}H NMR, δ, *J*/Hz*	^{13}C NMR, δ*
7	691.02 $[M + H]^+$	7.10 (t, 2 H, H_{arom}, $J = 7$); 7.20—7.38 (m, 14 H, H_{arom}); 7.71 (d, 4 H, H_{arom}, $J = 7$); 8.01 (d, 2 H, H_{arom}, $J = 8$); 8.50 (s, 2 H, CH=N); 9.07 (s, 2 H, NH)	108.53, 116.418, 119.448, 121.62, 121.93, 124.42, 127.75, 128.02, 128.32, 130.61, 132.90, 133.36, 137.51, 142.67, 146.17, 153.67 (C=N), 159.57 (C=O)
8	699.17 $[M + H]^+$	1.83 (s, 6 H, CH_3); 6.32 (d, 2 H, H_{arom}, $J = 4$); 6.74 (d, 2 H, H_{arom}, $J = 4$); 6.93 (m, 2 H, H_{arom}); 7.06—7.18 (m, 14 H, H_{arom}); 7.99 (d, 2 H, H_{arom}, $J = 8$); 8.18 (s, 2 H, CH=N); 8.22 (s, 2 H, NH)	29.27 (CH_3, acetone), 36.10 (2 CH_3), 107.96, 118.07, 119.04, 120.86, 125.11, 126.01, 127.89, 129.72, 130.03, 130.94, 134.20, 142.29, 144.30, 144.79, 150.70 (C=N), 159.61 (C=O)
9	769.16 $[M + H]^+$	1.05 (t, 6 H, $CH_2C\underline{H}_3$, $J = 7$); 1.68 (m, 4 H, $C\underline{H}_2CH_3$); 2.10 (s, 6 H, CH_3); 2.80 (t, 4 H, CCH_2, $J = 7$); 7.13—7.28 (m, 16 H, H_{arom}); 8.10 (d, 2 H, H_{arom}, $J = 4$); 8.42 (s, 2 H, CH=N); 8.85 (s, 2 H, NH)	159.55 (C=O), 146.11 (C=N), 145.95, 140.60, 134.45, 133.50, 133.25, 132.52, 130.09, 128.33, 127.74, 127.67, 126.34, 126.22, 124.94, 121.11, 120.38, 116.26, 26.23 (2 CH_3), 24.75 (2 $\underline{C}H_2CH_2CH_3$), 14.07 (2 $\underline{C}H_2CH_3$), 10.29 (2 $CH_2\underline{C}H_3$)
10	659.2** $[M + H]^+$	7.15—7.42 (m, 20 H, H_{arom}); 7.99 (d, 2 H, H_{arom}, $J = 8$); 8.55 (s, 2 H, CH=N); 9.72 (s, 2 H, NH)	112.25, 117.22, 120.25, 123.10, 124.95, 127.05, 127.33, 129.79, 132.59, 133.13, 134.01, 140.36, 144.48, 147.09, 151.65 (C=N), 159.12 (C=O)

* Solvents: DMSO-d_6 (compounds **3**, **4**, **7**, **10**), $CDCl_3$ (compounds **5**, **8**, **9**), DMSO-d_6—1% HCl in H_2O (compound **6**).
** Mass spectrum ESI(+).

amount of anhydrous 1,4-dioxane (10—15 mL) was stirred for 16 h at room temperature. A precipitated product was filtered off. Compounds **3—7** are solid yellow powders well soluble in the most part of polar aprotic organic solvents. The analytical and spectral data are presented in Tables 1 and 2, and the yields are given in Scheme 3.

Macrocycles 4—6 and 2,29-dioxo-31,32-diphenyl-3,10,21,28-tetraaza-34,35-dioxa-33-thiahexacyclo[29,2,1,$1^{12,15}$,$1^{16,19}$,$0^{4,9}$,$0^{22,27}$]pentatriaconta-5,7,9(4),10,12,14,16,18,20,22,24,26,30,32-tetradecaene (10) (general procedure). An acid (0.25 mmol) was added to a mixture of compound **1** (51 mg, 0.1 mmol) and diformyl derivative (0.1 mmol) in anhydrous methanol (50—100 mL). After stirring for 16 h at room temperature, the product was filtered off from the reaction mixture. Compounds **4—6** and **10** are solid yellow powders well soluble in the most part of polar aprotic organic solvents. The analytical and spectral data for the products are presented in Tables 1 and 2, and the yields and used protic acids are given in Scheme 4.

Macrocycle 3 and 16,16-dimethyl-2,30-dioxo-32,33-diphenyl-3,10,22,29,35,36-hexaaza-34-thiahexacyclo[29,2,1,$1^{12,15}$,$1^{17,20}$,$0^{4,9}$,$0^{23,28}$]hexatriaconta-5,7,9(4),10,12,14,17,19,21,23,25,27,31,33-tetradecaene (8), and 14,17-dimethyl-2,29-dioxo-31,32-diphenyl-13,18-dipropyl-3,10,21,28,34,35-hexaaza-33-thiahexacyclo[29,2,1,$1^{12,15}$,$1^{16,19}$,$0^{4,9}$,$0^{22,27}$]pentatriaconta-5,7,9(4),10,12,14,16,18,20,22,24,26,30,32-tetradecaene (9) (general procedure). An acid (0.25 mmol) was added to a mixture of compound **1** (51 mg, 0.1 mmol) and dialdehyde (0.1 mmol) in anhydrous methanol (50—100 mL). After stirring for 16 h at room temperature, the precipitated protonated macrocycle was filtered off from the reaction mixture. A suspension of the salt of the product in anhydrous CH_2Cl_2 was treated with triethylamine (0.20 mmol). A transparent solution that formed was passed through a thin silica gel layer. The solvent was distilled off on a rotary evaporator, and the substance was dried *in vacuo* using a water-jet pump. Compounds **3**, **8**, and **9** are solid yellow powders well soluble in the most part of polar aprotic organic solvents. The analytical and spectral data of the products are presented in Tables 1 and 2, and the yields and protic acids used are given in Scheme 4.

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