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A Direct Synthetic Approach to Novel Quadrupolar [14]Azolophanes[1]

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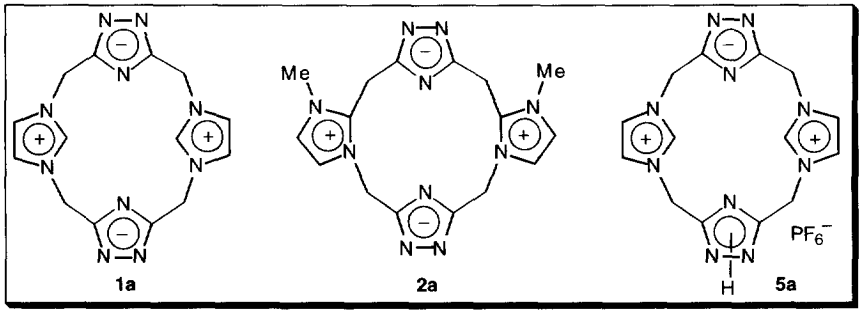
Abstract: A convergent '3+1' synthesis allowed a simple entrance to the first examples of [14]*meta*azolophanes **1** and [14](*meta-ortho*)$_2$azolophanes **2** built up from heterocyclic betaine subunits, illustrating a prototype of phanes constructed by both highly π-excessive and highly π-deficient heteroaromatic moieties linked in a 1,3-alternating fashion.

The inexhaustible diversity of molecular architectures in macrocyclic systems –natural and synthetic– allows the design of novel substrates whose chemical facets have a dominant influence upon specific biological and physical properties. Cyclophanes, phanes and heterophanes,[2a-c] together with different types of calixarenes[3a-d] represent a broad array of molecules and shapes but none is related to the quadrupolar [14]heterophanes **1** and **2**. The ring components present in heterophanes[2] are normally uncharged heteroaromatic moieties and in the few cases in which they bear a charge, they are commonly quaternary pyridinium nuclei.[4,5]

To seek further insight into the chemistry of heterocyclic betaines,[6] we have now investigated the first examples of macrocyclic systems with heterocyclic betaines as building blocks: the quadrupolar [14]*meta*heterophane **1a** and the [14](*meta-ortho*)$_2$heterophane **2a**, the corresponding immediate precursors **3a**, **4a** and the dipolar [14]*meta*heterophane **5a** together with their alkyl-substituted derivatives (see Scheme 1). Considering their constitution, the [14]*meta*heterophanes **1** are built up from heterocyclic betaine subunits, for which the two atoms linking the highly π-deficient imidazolium nuclei and the methylene bridge formed *C-N' bonds*, while the [14](*meta-ortho*)$_2$heterophanes **2** contain a 3,5-bis[1-methyl-2-imidazoliomethyl]-1,2,4-triazolate moiety, in which the imidazolium nuclei and the interannular spacer are linked by *C-C' bonds*, the other two bridges being *C-N' bonds*.

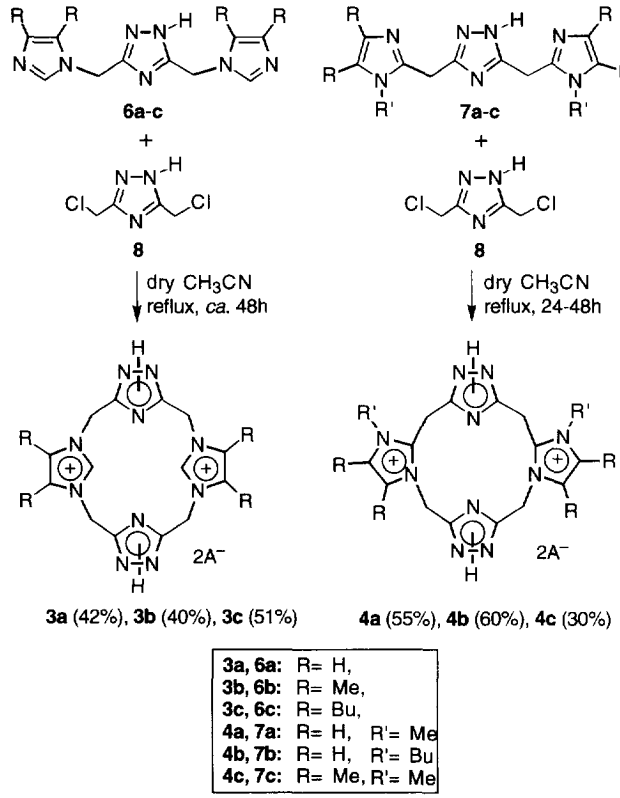


1a **2a** **5a**

Results and Discussion

A simple strategy was applied for the synthesis of the key-azolophanes **3** and **4** with two quaternary heteroaromatic subunits; using a '3+1' convergent stepwise synthesis, which implies joining a trinuclear protoheterophane **6** and **7** with a *bis*-chloromethyl monomer **8**.[7]

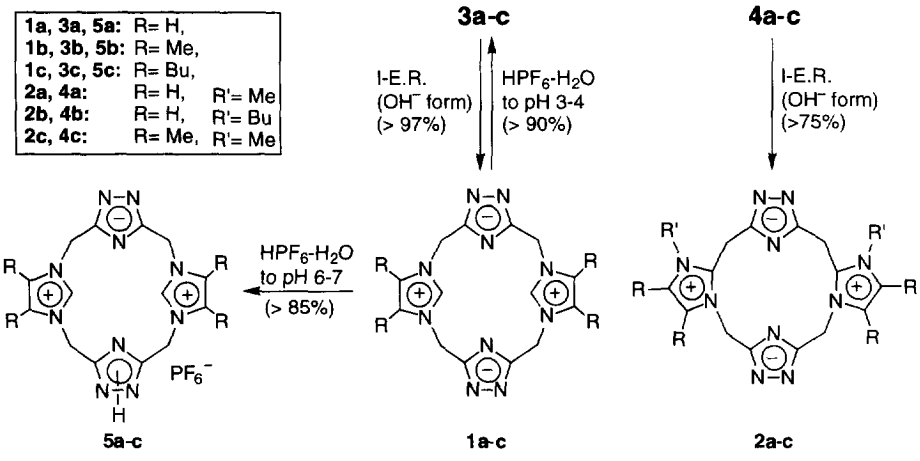
Condensation of protophanes **6a-c** with the 3,5-bis(chloromethyl)-1,2,4-triazole **8**[8] produced the azolophanes **3a-c** with two quaternary imidazolium subunits (> 40%).[9a] For the key-macrocycles **4a-c**, a similar '3+1' approach was followed (Scheme 1). Thus, condensation of the trinuclear compounds **7a-c** with compound **8**[8] produced the cationic azolophanes **4a-c** in remarkably good yields for macrocyclization (*e.g.* 55% for **4a**). Although the azolophane **4c** was obtained in 30% yield, the macrocyclization can still be considered reasonably satisfactory. Both protophane **7c** and heterophane **4c** afforded the poorest yields of the series, owing to the presence of 1,4,5-trimethylimidazole moieties.[10]



Scheme 1. '3+1' Convergent synthesis of [1$_4$]azolophanes **3** and **4** containing two quaternary heteroaromatic subunits

Transformation of the key-macrocycles **3a-c** into the quadrupolar [1$_4$]*meta*heterophanes **1a-c** was achieved using an ion exchange III resin (OH^- form).[11] Moreover, by acidification of the macrocyclic *bis*-betaines under carefully controlled pH conditions using HPF_6-H_2O, it was possible to isolate the macrocyclic dipolar betaines **5a-c** (Scheme 2). It is noteworthy that by the reported synthetic route it was not possible to

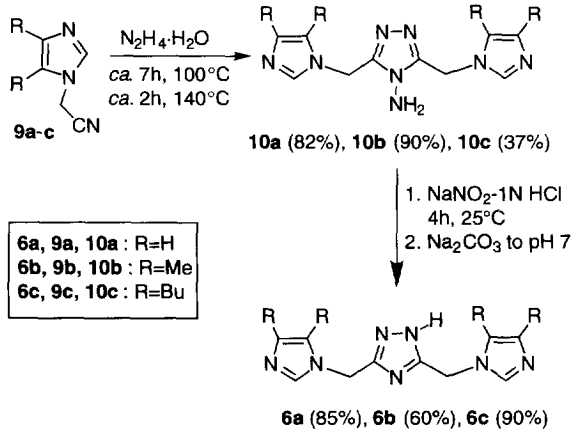
obtain an analytically pure sample of macrocycle **3a** because of the similar solubility of the ionic species present in the reaction mixture,[9a] in clear contrast with its alkyl derivatives **3b** and **3c**.



Scheme 2. Access to quadrupolar [1$_4$]azolophanes **1** and **2** together with dipolar [1$_4$]azolophanes **5**

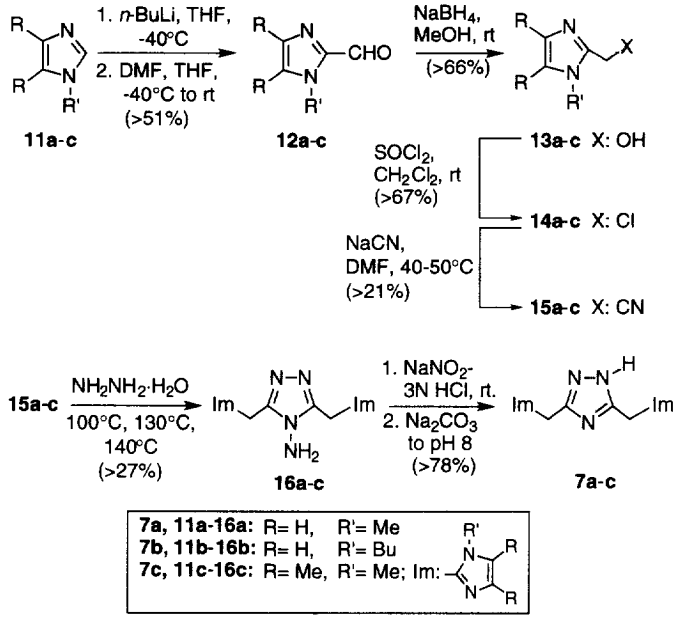
In a similar way, the quadrupolar heterophanes **2a-c** were prepared from macrocycles **4a-c** (Scheme 2). Moreover, acidification of the *bis*-betaines **2a,b** with HPF_6-H_2O to pH *ca.* 3, rigorously monitored by a pH meter, allowed the isolation of pure compounds **4a,b** as the bis(hexafluorophosphate) salts. However, when the acidic treatment of **2a** was controlled to a pH range between 6 and 7, isolation of the betaine —analogue to the dipolar compounds **5**— was precluded.

The synthetic "3+1" approach first involves the preparation of the trinuclear compounds **6** and **7** (see also, Scheme 1). Compounds **6a-c** were obtained in two steps (>33%) according to the literature procedure for the generation of 3,5-bis(substituted)-1,2,4 triazoles;[12] the starting materials were the *N*-cyanomethylimidazoles **9a**,[13] **9b** and **9c** (Scheme 3).



Scheme 3

A more elaborate process was necessary for the synthesis of the trinuclear protophanes **7a-c**, which requires six reaction steps (Scheme 4). Preparation of 2-cyanomethylimidazoles **15a-c** started with the *N*-alkylimidazoles **11a-c** and followed a standard four-step procedure.[14] Cyanomethyl compounds **15a-c** were then transformed to the trinuclear compounds **7a-c** by a similar two-step sequence to that used for the trinuclear analogues **6** (*vide supra*).

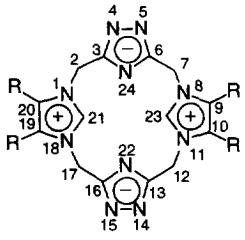


Scheme 4

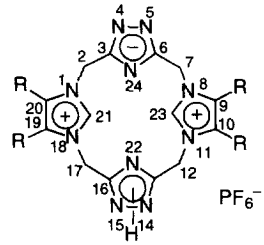
The structures of the new compounds were unambiguously characterized on the basis of their spectroscopic data. Either the quadrupolar or the dipolar character of the azolophanes **1a-c**, **2a-c** and **5a-c** is discussed mainly in terms of the spectroscopic ^1H and ^{13}C NMR parameters, and the molecular structure of the [1$_4$]heterophanes **1a**,[9b] **5a**[9b] and **2a**[9c] were secured by X-ray crystallographic diffraction. The IR spectra of the immediate precursors of macrocycles **3a-c**, and **4a-c** showed absorptions in the range of 3500-3400 cm^{-1} (ν_{NH}) and 2800-2500 cm^{-1} (hydrochlorides), while these bands were absent for the targeted azolophanes **1a-c** and **2a-c**. The ^1H and ^{13}C NMR chemical shifts established the quadrupolar and dipolar nature of compounds **1a-c**, **2a-c** and **5a-c** as well as the betaine building blocks.[6,15]

For the [1$_4$]*meta*azolophanes, the ^1H NMR spectra (20 °C) in D_2O at 200 or 500 MHz (*i.e.* **1a**, **3a**, **5a**) showed a sharp singlet for the methylene protons. Similar conformational behaviour has been reported for the parent [1$_4$]*meta*cyclophane.[16] Comparison of the proton chemical shifts of macrocyclic *bis*–betaines **1a-c** with those of their corresponding precursors **3a-c** and the corresponding betaines **5a-c** reveals that the δH values of the methylene spacers and those of δH-21 and δH-23 (Im$^+$) are the most affected; moving to lower frequencies (Δδ**H** in Table 1). For example, the proton chemical shift differences in D_2O between the bis–betaine **1a** and its corresponding macrocyclic precursor **3a** were found to be Δδ CH_2 = –0.26 ppm and Δδ H-21,23 = –0.87 ppm. For betaine **5a**, these differences were Δδ CH_2 = –0.12 ppm and Δδ H-21,23 = –0.44 ppm. The ^1H and ^{13}C NMR chemical shifts are listed in Tables 1 and 2.

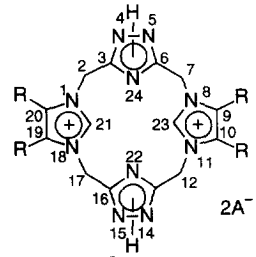
Table 1. ^{1}H NMR Data of bis-Betaines **1a-c**, Betaines **5a-c** and Macrocycles **3a-c**



1a-c



5a-c



3a-c

Compd	Solvent	R	CH_2	H-21, 23	R
1a	D_2O	H	5.19	7.91	7.42
5a	D_2O	H	5.33	8.34	7.45
3a	D_2O	H	5.45	8.78	7.48
$\Delta\delta^a$			- 0.26	- 0.87	- 0.06
$\Delta\delta^b$			- 0.12	- 0.44	- 0.03
1a	DMSO-d_6	H	5.28	8.79	7.79
3a	DMSO-d_6	H	5.61	9.12	7.80
$\Delta\delta^a$			- 0.33	- 0.33	- 0.01
1b	D_2O	CH_3	5.05	7.87	2.00
5b	D_2O	CH_3	5.17	8.23	1.98
3b	D_2O	CH_3	5.32	8.63	1.95
$\Delta\delta^a$			- 0.27	- 0.76	- 0.05
$\Delta\delta^b$			- 0.15	- 0.40	- 0.02
1b	DMSO-d_6	CH_3	5.10	8.32	2.3
3b	DMSO-d_6	CH_3	5.53	9.02	2.16
$\Delta\delta^a$			-0.43	- 0.7	0.14
1c	D_2O	C_4H_9	5.16	8.55	2.28[c]
5c	D_2O	C_4H_9	5.26	8.73	2.29[c]
3c	D_2O	C_4H_9	5.40	8.95	2.32[c]
$\Delta\delta^a$			- 0.24	- 0.40	- 0.04
$\Delta\delta^b$			- 0.14	- 0.22	- 0.01
1c	DMSO-d_6	C_4H_9	5.11	8.39	2.70[c]
3c	DMSO-d_6	C_4H_9	5.60	9.15	2.55[c]
$\Delta\delta^a$			-0.49	-0.76	-0.08

[a]$\Delta\delta$: observed chemical shifts difference between *bis*-betaines **1a-c** and the macrocycles **3a-c** ($\delta H_{bis\text{-}betaine}$ - $\delta H_{macrocycle}$). [b]$\Delta\delta$: observed chemical shifts difference between betaines **5a-c** and the macrocycles **3a-c** ($\delta H_{betaine}$-$\delta H_{macrocycle}$). [c]Only δ for the α-protons to nitrogen are listed.

Table 2. ^{13}C NMR Data of bis-betaines **1a-c**, betaines **5a-c**, and macrocycles **5a-c**[a]

Compd	R	C-21, 23	C-9, 10, 19, 20	CH_2	C-3, 5, 13, 16	R
1a	H	141.7	129.9	53.7	165.1	--
5a	H	143.0	130.2	52.9	163.2	--
3a	H	144.3	130.3	52.4	161.9	--
$\Delta\delta^b$		-2.6	-0.4	+1.3	+3.2	
$\Delta\delta^c$		-1.3	-0.1	+0.5	+1.3	
1b	CH_3	140.5	134.3	50.6	164.7	14.4
5b	CH_3	141.3	134.4	50.2	163.7	14.3
3b	CH_3	142.7	134.6	49.6	162.0	14.3
$\Delta\delta^b$		-2.2	-0.3	+1.0	+2.7	-0.1
$\Delta\delta^c$		-1.4	-0.2	+0.6	+1.7	0
1c	n-C_4H_9	142.3	138.2	51.3	165.2	37.4[d]
5c	n-C_4H_9	143.2	138.2	50.5	163.8	37.5[d]
3c	n-C_4H_9	144.2	138.3	49.7	162.5	37.5[d]
$\Delta\delta^b$		-1.9	-0.1	-1.6	+2.7	-0.1
$\Delta\delta^c$		-1.0	-0.1	-0.8	+1.3	0

[a]In D_2O. [b]$\Delta\delta$: observed chemical shifts difference between *bis*-betaines **1a-c** and the macrocycles **3a-c** ($\delta C_{bis\text{-}betaine} - \delta C_{macrocycle}$). [c]$\Delta\delta$: observed chemical shifts difference between betaines **5a-c** and the macrocycles **3a-c** ($\delta C_{betaine} - \delta C_{macrocycle}$). [d]Only δ for the α -carbons to nitrogen are listed.

For the [1$_4$](*meta-ortho*)$_2$heterophanes described, individual assignments were made by using HMQC, HMBC and NOESY NMR techniques applied to **2a** and **4a** (Figure 1) except for the NH proton in the 1,2,4-triazole subunit.

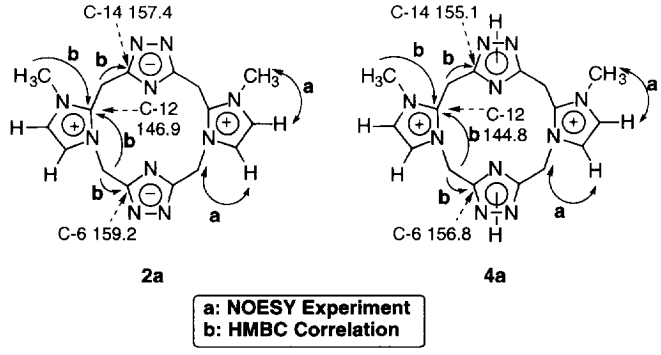
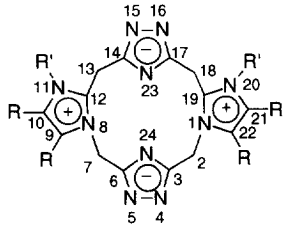


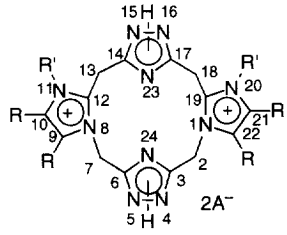
Figure 1. Key NMR responses for bis-betaine **2a** and macrocycle **4a**

Their ^{1}H NMR spectra (20 °C) in D_2O at 200 MHz or 500 MHz (*i.e.* **2a**, **4a**) showed two sharp singlets for the methylene protons atoms. Comparison of the proton chemical shifts of macrocyclic bis–betaines **2a-c** with those of their corresponding precursors **4a-c** reveals that the δH values of the methylene spacers are the most affected; they shift to lower frequencies (ΔδH in Table 3). For example, the proton chemical shift differences for *bis*–betaine **2a** and macrocyclic precursor **4a** were found to be Δδ CH_2-2,7 = –0.27 ppm and Δδ CH_2-13,18 = –0.3 ppm. The ^{1}H and ^{13}C NMR chemical shifts are shown in Table 3.

Table 3. ^{1}H and ^{13}C NMR Data of bis-Betaines **2a-c**, and Macrocycles **4a-c** in D_2O



2a-c



4a-c

Compd	R	R'	H-9,22	H-10,21	CH_2-2,7	CH_2-13,18	R'	R(10,21)	R(9,22)
2a	H	Me	7.37[b]	7.23[b]	5.11	4.13	3.68	–	–
4a	H	Me	7.51[b]	7.37[b]	5.38	4.43	3.72	–	–
Δδ[c]			-0.14	-0.14	-0.27	-0.3	-0.04		
2b	H	Bu	7.36	7.28	5.10	4.15	3.975[d]	–	–
4b	H	Bu	7.51	7.42	5.36	4.42	3.99[d]	–	–
Δδ[c]			-0.15	-0.14	-0.26	-0.27	-0.015		
2c	Me	Me	–	–	4.99	4.12	3.54	2.08	2.11
4c	Me	Me	–	–	5.235	4.38	3.59	2.11	2.13
Δδ[c]					-0.245	-0.26	-0.05	-0.03	-0.02

			C-3,6	C-9,22	C-10,21	C-12,19	C-14,17	CH_2-2,7	CH_2-13,18	R'
2a[e]	H	Me	159.2	126.0	125.3	146.9	157.4	49.5	25.6	38.0
4a[e]	H	Me	156.8	126.7	126.3	144.8	155.1	47.7	24.6	36.3
Δδ[c]			+2.4	-0.7	-1.0	+2.1	+2.3	+1.8	+1.0	+1.7
2b	H	Bu	159.1	126.2	124.0	146.2	157.35	49.3	25.3[f]	51.3[d]
4b	H	Bu	156.8	126.9	124.9	144.35	155.2	47.6	24.5	51.6[d]
Δδ[c]			+2.3	-0.7	-0.9	+1.85	+2.15	+1.7	+0.8	-0.3

[a]In D_2O at 300 MHz. [b]Assignation of signals by NOESY. [c]Δδ: observed chemical shifts difference between *bis*-betaines **2a-c** and the macrocycles **4a-c** ($\delta_{bis\text{-}betaine}$-$\delta_{macrocycle}$). [d]Only δ for the α-atoms to nitrogen are listed. [e]Assignation of signals by HMBC and HMQC. [f]Broad signal.

From the ^{1}H NMR data, a shielding effect for the CH and CH_2 protons of the quadrupolar systems **1a-c** and **2a-c** in D_2O was observed. This is the first time that the tendency for hydration[6,11b] has been overcome

and the [1_4]heterophane framework within compounds **1a-c** and **2a-c** modulates the susceptibility to form *salt-type associates* —e.g. quaternary ammonium hydroxides may be formed in water—. A different behaviour was found for the corresponding building blocks, the heterocyclic betaines of imidazolium azolate with a methylene interannular spacer,[15] since *anhydrous* sample should be used and the NMR solvent has to be dried with activated molecular sieve 3Å to reduce the presence of water as far as possible. Unfortunately, it was not possible to carry out a dynamic NMR study due to their insolubility in low-melting-point solvents.

Conclusions

A convergent '3+1' synthesis allowed a simple entrance to first [1_4]*meta*azolophanes **1** and [1_4](*meta-ortho*)$_2$azolophanes **2** with heterocyclic betaines as building blocks, which can be considered unconventional phanes[2-5] constructed by both highly π-excessive and highly π-deficient heteroaromatic moieties linked in a 1,3-alternating manner. The ^{1}H NMR chemical shifts provided evidence of charge distribution within the novel quadrupolar macrocyclic systems. The bis–betaines **1** and **2** emerge as a novel family within [1_n]heterophanes and their quadrupolar nature should confer unusual properties to the *host* molecular architecture, and reasonably permit the formation of *host–guest* complexes. Efforts are under way to expand this work in to related systems, seeking further insight with regards to their structural and physical facets, together with their capacity for specific molecular recognition behaviour.

Experimental Section.

General Methods. Melting point: CTP–MP 300 hot-plate apparatus with ASTM 2C thermometer (given in Table 1). IR (KBr disks): Perkin Elmer 1430 spectrophotometer. ^{1}H NMR: Varian Gemini 200 and Varian Unity 300 spectrometers (200 MHz and 300 MHz). ^{13}C NMR: Varian Gemini 200 spectrometer (50.3 MHz). NOE ^{1}H{^{1}H}: Varian Unity 300 spectrometer (2300 MHz). HMQC, HMBC and NOESY: Varian VXR-500 spectrometer (500 MHz). NMR spectra were determined in dimethyl-d_6 sulfoxide and deuterium oxide, and chemical shifs are expressed in parts per million (δ) relative to the central peak of dimethyl-d_6 sulfoxide. TLC: Merck precoated silica gel 60 F_{254} plates; solvent systems, A, methanol-ammonium chloride 2M-nitrometane (6:3:1); B, methanol-ammonium chloride 2M-nitrometane (6:1:3); C, chloroform-methanol (1:1); D, chloroform-methanol (8:2); detection by UV light. Chromatography : Merck Aluminium oxide 90 activity II-III (70-230 mesh ASTM). Ion-exchange resin (I-E.R.): A column (0.5-in. diameter) was packed with ion exchange III resin (OH^- form)[11] up to a height of 5 in (*vide infra*). Microanalyses were performed on a Carlo Erba 1106 analyzer. Physical data of the new compounds described in this work are listed in Table 4, and all the products isolated were analytically pure.[9a]

Materials. 3,5-bis(chloromethyl)-1,2,4-triazole (**8**),[8] 4,5-dimethyl-1*H*-imidazole hydrochloride[17a] and 4,5-dibutyl-1*H*-imidazole hydrochloride[17b] were prepared as described in the literature. 1*H*-imidazole, *N*-butyl and *N*-methylimidazole were purchased from commercial sources.

***bis*-Betaines 1a-c and *bis*-Betaines 2a-c (Table 4)**: A column packed with ion exchanger III (Merck) resin chloride form was converted to the hydroxide form. The resin (75 g) was washed with aqueous 10% NaOH (ca. 3 L) until it was free of halide ion ($AgNO_3$-HNO_3 test) with water until the eluant was no longer alkaline (pH 7) and then stored in water. A column (0.5-in. diameter) was packed with ion exchanger III resin (OH^- form) up to a height of 5 in and the column bed equilibrated with the following eluants: H_2O (20 mL), 20% ethanol (20 mL), 60% ethanol (20 mL), 80% etanol (20 mL) and 96% ethanol (20 mL). A solution of macrocycles **3a-c** or **4a-c** (100 mg) in 80% ethanol for **3a,b**, **4a-c**, and in 96% ethanol for **3c** (50 mL) was passed through the column. The neutral eluates were evaporated to dryness to give white solids of the corresponding inner salts **1a-c** or **4a-c**.

Macrocycles 3a-c (Table 4): A stirred solution of 3,5-bis(chloromethyl)-1,2,4-triazole **8**[8] (146 mg, 0.9 mmol) in dry acetonitrile (40 mL) was added dropwise to a suspension of protophanes **6a,b,c** (0.9 mmol; 202 mg of **6a**, 251 mg of **6b**, 400 mg of **6c**) in dry acetonitrile (350 mL) at 25 °C, under an atmosphere of nitrogen, and the mixture was then maintained in a bath at *ca.* 85 °C for 48h. For compound **3a** the resulting suspension was filtered, the crude solid was washed with 70% ethanol (5 x 10 mL) and the mother liquors were evaporated to dryness to afford macrocycle **3a·2Cl**. For compound **3b** the resulting suspension was filtered, and the mother liquors were evaporated to dryness and the the crude solid was crushed with acetonitrile (4 x 10 mL) to give macrocycle **3b·2Cl**. As for the resulting solution of compound **3c**, the solvent was removed in a rotary evaporator and the solid residue was crushed with dry acetone (2 x 10 mL) and then filtered to afford macrocycle **3c·2Cl**. Macrocycles **3a-c·2Cl** were recrystallized.

The macrocycles **3a,b·2Cl** were purified by gel-filtration chromatography on a column of Sephadex LH-20 with water as eluent, and for **3b·2Cl** was also purified using Sephadex G-10. Unfortunately, the macrocycles **3a,b·2Cl** did not give satisfactory elemental analysis.

A solution of *bis*-betaines **1a,b,c** (100 mg) in water (50 mL) was acidified with 1 % aqueous hexafluorophosphoric acid to pH *ca.* 3, and the solvent was removed in a rotary evaporator and the solid was recrystallized to afford pure macrocycles **3a-c·2PF$_6$**.

Synthesis of macrocycle 3b·2Cl under *high dilution conditions*: A solution of 3,5-bis(chloromethyl)-1,2,4-triazole **8**[8] (55 mg, 0.3 mmol) and protophane **6c** (150 mg, 0.3 mmol) in separate 50-mL portions of dry acetonitrile were simultaneously added over a period of 8 h to a vigorously stirred refluxing solution of dry acetonitrile (50 mL), under an atmosphere of nitrogen. After being boiled for additional 40 h, the reaction mixture was cooled, the solvent was removed to dryness and the solid residue triturated with acetone (3 x 10 mL) and filtered to yield compound **3c·2Cl** in 49%.

Macrocycles 4a-c (Table 4): A stirred solution of 3,5-bis(chloromethyl)-1,2,4-triazole **8**[8] (0.18 g, 1.1 mmol) in dry acetonitrile (45 mL) was added dropwise to a solution of protophanes **7a,b,c** (1.1 mmol; 0.29 g of **7a**, 0.37 g of **7b**, 0.35 g of **7c**) in dry acetonitrile (450 mL) at 25 °C, under an atmosphere of nitrogen, and the mixture was then maintained in a bath at *ca.* 85 °C for the time specified in Table 1.

For compound **4a** the resulting suspension was filtered, the crude solid was recrystallized to afford pure macrocycle **4a·2Cl**. For the resulting resulting solution of compound **4b**, the solvent was removed in a rotary evaporator and the solid residue was crushed with dry acetone (50 mL) and then filtered under an atmosphere

of nitrogen. The collected white solid was washed with acetone (2 x 10 mL) and dried to give a pale brown hygroscopic solid of **4b·2Cl**.

The cold solution of macrocycle **4c·2Cl** was evaporated to dryness, triturated with acetone (50 mL) and filtered. The crude solid was washed with acetone (3 x 5 mL) and then dissolved in 50 mL of 96% ethanol-H_2O (8:2). The ethanolic solution was passed through a column packed with ion exchanger III resin (OH^--form), the neutral eluates were evaporated to dryness and water (20 mL) was added. The aqueous solution was acidified with 1 % aqueous hexafluorophosphoric acid to pH *ca.* 4 and the solvent was removed. The residue was triturated with acetone (10 mL), filtered and then washed with acetone (2 x 1 mL) to yield compound **4c·2PF$_6$** in 49%.

A solution of *bis*-betaines **2a,b** (100 mg) in water (50 mL) was acidified with 1 % aqueous hexafluorophosphoric acid to pH *ca.* 3, and the solvent was removed in a rotary evaporator and the solid was recrystallized to afford pure macrocycles **3a,b·2PF$_6$**.

Betaines 5a-c (Table 4): A solution of *bis*-betaines **1a,b,c** (100 mg) in water (50 mL) was acidified with 1 % aqueous hexafluorophosphoric acid to pH 6, and the solvent was then evaporated to dryness to give betaines **5a,b,c**.

Protophanes 6a,b (Tables 4 and 5): To a cold solution of 5 mmol of the *N*-amino-1,2,3-triazole **10a** or **10b** (1.25 g or 1.5 g) in 1 N HCl (66.0 mL) was added portionwise a solution of $NaNO_2$ (10 mmol, 0.75 g) in H_2O (30 mL) maintaining the temperature at 0 to 10 °C and then, warmed to rt for 5 h. The mixture was treated with Na_2CO_3 to pH 7 and evaporated to dryness. For compound **6a**, the residue was crushed with dry isopropanol, filtered and dried; after several assays of recrystallization with different alcoholic mixtures the product gave unsatisfactory elemental analysis, but the material was used directly in the macrocyclization reaction. For compound **6b**, the residue was crushed with dry acetonitrile at 50 °C and the solvent was removed; then the gummy residue was triturated with dry acetone (3 x 10 mL) to give a pale solid, which was recrystallized.

Protophane 6c (Tables 4 and 5): To a cold solution of the *N*-amino-1,2,3-triazole **10c** (1.6 mmol, 0.74 g) in 1 N HCl (100.0 mL) was added portionwise a solution of $NaNO_2$ (6.3 mmol, 0.436 g) in water (30 mL) maintaining the temperature at 0 to 10 °C and then, warmed to rt for 10 h. The mixture was treated with Na_2CO_3 to pH 7 and extracted with dichloromethane (3 x 100 mL). The organic layers were dried (Na_2SO_4), filtered and the solvent was removed to afford pure compound **6c**.

Protophanes 7a-c (Tables 4 and 6): To a cold solution of the *N*-amino-1,2,3-triazoles **16a-c** (2.8 mmol, 0.8 g or 0.6 g or 0.8 g) in 3 N HCl (50 mL) was added portionwise a solution of $NaNO_2$ (3.9 mmol, 0.3 g) in water (25 mL) maintaining the temperature at 0 to 10 °C and then, warmed to rt for the time specified in Table 1. The mixture was treated with Na_2CO_3 to pH 8.

For compound **7a**, the reaction mixture was evaporated to dryness and 150 mL of dichloromethane was added to the cake and digested at 55 °C for *ca.* 2 h, and this was repeated three times more. Then, the organic layers (4 x 150 mL) were dried (Na_2SO_4), the solvent was removed and the residue washed with dry acetone (2 x 2 mL), recrystallization afforded pure compound **7a**.

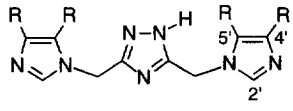
For compounds **7b** and **c**, the solvent of the reaction mixture of was concentrated to reduce half of the volume (the volume to one half) and extracted with dichloromethane (4 x 60 mL). The organic layers were dried (Na_2SO_4), and the solvent was removed. Then, the residue was triturated with ethyl acetate to give protoheterophanes **7b** and **c**.

Table 4. Physical Data of Compounds **1-7**

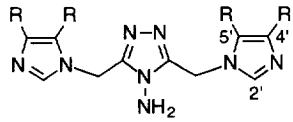
Compd	Yield (%)[a]	mp (°C) [solvent][b]	Reaction time (h)	TLC[c]	molecular formula[d]
1a	97	>300	*c*	A	$C_{14}H_{14}N_{10}\cdot 4H_2O$
1b	98	–	*c*	A	*e*
1c	98	244	*c*	A	$C_{30}H_{46}N_{10}\cdot H_2O$
2a	90	>300 [i]	*c*	B	$C_{16}H_{18}N_{10}\cdot 4H_2O$
2b	85	200	*c*	B	$C_{22}H_{30}N_{10}\cdot 2H_2O$
2c	75	–	*c*	B	*e*
3a·2Cl	42	>300 [iii]	48	A	*e*
3a·2PF$_6$	93	>300 [ii]	–	A	$C_{14}H_{16}N_{10}P_2F_{12}\cdot 3H_2O$
3b·2Cl	40	>300 [iii]	48	A	*e*
3b·2PF$_6$	90	>300 [ii]	–	A	$C_{18}H_{24}N_{10}P_2F_{12}$
3c·2Cl	51	273-74	48	A	$C_{30}H_{48}N_{10}Cl_2\cdot H_2O$
3c·2PF$_6$	91	210-11 [iii]	–	A	$C_{30}H_{48}N_{10}P_2F_{12}$
4a·2Cl	55	>300 [ii]	24	B	$C_{16}H_{20}N_{10}Cl_2\cdot 3H_2O$
4a·2PF$_6$	90	>300	*c*	B	$C_{16}H_{20}N_{10}P_2F_{12}\cdot H_2O$
4b·2Cl	60	*f*	48	B	*e*
4b·2PF$_6$	95	236	*c*	B	$C_{22}H_{32}N_{10}P_2F_{12}\cdot H_2O$
4c·2PF$_6$	30	–	24[c]	B	*e*
5a	87	*f* [iii]	*c*	A	$C_{14}H_{15}N_{10}PF_6$
5b	85	*f*	*c*	A	*e*
5c	91	231	*c*	A	$C_{30}H_{49}N_{10}PF_6$
6a	85	–	5	C	*e*
6b	60	196 [iv]	5	C	$C_{14}H_{19}N_7$
6c	90	81	10	D	$C_{26}H_{43}N_7\cdot H_2O$
7a	78	185 [v]	3	C	$C_{12}H_{15}N_7$
7b	78	95 [vi]	2	C	$C_{18}H_{27}N_7$
7c	82	190	4	C	$C_{16}H_{23}N_7\cdot H_2O$

[a]Yields were not optimized. [b]Recrystallization solvent: (i) ethanol; (ii) 2-methyl-2,4-pentanediol; (iii) i-PrOH-water (8:2); (iv) acetonitrile-water (9:1); (v) acetonitrile; (vi) ethyl acetate-methanol (9:1). [c]See Experimental Section. [d]Satisfactory analytical data (± 0.4% for C, H, N) were obtained for new compounds. [e]Not satisfactory analytical data were obtained. [f]Hygroscopic solid.

Table 5. Selected ^{1}H NMR and ^{13}C NMR Data of compounds **6a-c** and **10a-c** in DMSO-d_6



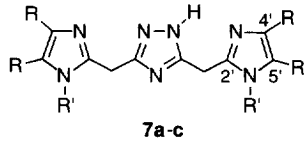
6a-c



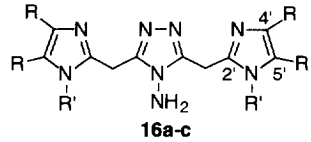
10a-c

Compd	CH_2	H-2'	R-(C-4')	R-(C-5')	NH_2	CH_2	C-2'	C-3(5)
6a	4.97	7.57	6.78	7.08	–	44.8	137.4	158.8
6b	5.10	7.43	1.97	2.01	–	41.1	135.7	156.9
6c	5.17	7.65	2.30-2.43		–	41.1	135.9	156.7
10a	5.37	7.77	6.92	7.23	6.19	40.1	137.9	151.9
10b	5.23	7.53	2.02	2.13	6.15	37.9	135.8	151.8
10c	5.18	7.44	2.29-2.59		6.08	37.9	136.0	151.8

Table 6. Selected ^{1}H NMR and ^{13}C NMR Data of compounds **7a-c** and **16a-c** in DMSO-d_6



7a-c



16a-c

Compd	CH_2	R-(C-4')	R-(C-5')	R'	NH_2	CH_2	C-2'	C-3(5)
7a	4.05	6.71	7.02	3.58	–	25.7	143.8	155.5
7b	4.04	6.73	7.05	3.88	–	25.9[a]	143.2	*b*
7c	3.98	1.94	2.02	3.39	–	26.0	141.2	156.6[a]
16a	4.17	6.74	7.07	3.63	6.05	22.7	143.1	151.8
16b	4.18	6.76	7.10	3.95	6.15	22.7	142.6	151.8
16c	4.10	1.94	2.03	3.42	6.09	23.0	140.5	151.8

[a]Broad signal. [b]Not observed signal.

1-Cyanomethylimidazoles 9a,b (Table 7): A stirred suspension of 52 mmol of 1*H*-imidazole (3.6 g) or 4,5-dimethyl-1*H*-imidazole hydrochloride (5.0 g) and powdered KOH (67.7 mmol, 4.5 g, or 135.2 mmol, 8,9 g) in dry acetonitrile (300 mL) under an atmosphere of nitrogen was maintained at rt for 1.5 h.

Next, a solution of chloroacetonitrile (4 mL, 63.8 mmol) in dry acetonitrile (40 mL) was added portionwise over 0.5 h to the slurry and stirred at rt for 6 h. The reaction mixture was filtered and the filtrate was evaporated to dryness. The solid residue was dissolved in water (200 mL) and extracted with 4 x 200 mL portions of dichloromethane and the combined extracts were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was chromatographed: for compound **9a**, dichloromethane-96% ethanol, 9.8: 0.2; for compound **9b**, dichloromethane, dichloromethane-96% ethanol, 9.8: 0.2; dichloromethane-96% ethanol, 9.5: 0.5. The eluates were evaported to dryness to give the solid compounds **9a** and **9b**. Compound **9a**: mp. 50°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.94 (s, 2H, CH_2), 7.06 (s, 1H, H-5), 7.16 (s, 1H, H-4), 7.59 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 34.2 (CH_2), 113.8 (CN), 118.8 (C-5), 130.5 (C-4), 136.9 (C-2); Anal. Calcd. for $C_5H_5N_3$: C, 56.1; H, 4.7; N, 39.2. Found: C, 55.9; H, 4.7; N, 39.0. Compound **9b**: mp. 60°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.16 (s, 3H, C$\underline{H}_3$-(C-4)), 2.22 (s, 3H, C$\underline{H}_3$-(C-5)), 4.78 (s, 2H, CH_2), 7.40 (s, 1H, C-2); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 7.9 ($\underline{C}H_3$-(C-5)), 12.5 ($\underline{C}H_3$-(C-4)), 32.6 (CH_2), 113.8 (CN), 121.9 (C-5), 134.7 (C-2), 135.1 (C-4). Anal. Calcd. for $C_7H_9N_3$: C, 62.2; H, 6.7; N, 31.1. Found: C, 62.2; H, 6.7; N, 31.0.

1-Cyanomethylimidazole 9c (Table 7). A stirred suspension of 4,5-dibutyl-1*H*-imidazole hydrochloride (5.0 g, 23.0 mmol) and finely powdered KOH (4.0 g, 59.8 mmol) in dry acetonitrile (200 mL) under an atmosphere of nitrogen was maintained at rt for 1.25 h. To this, a solution of chloroacetonitrile (1.9 mL, 29.9 mmol) in dry acetonitrile (40 mL) was added portionwise over 0.5 h to the slurry and stirred at rt for 6 h. The reaction mixture was filtered and the filtrate was evaporated to dryness. The solid residue was dissolved in water (200 mL) and extracted with 3 x 200 mL portions of dichloromethane and the combined extracts were dried (Na_2SO_4) and the solvent was removed *in vacuo*. Distillation of the residue (Kulgelrohr) gave a yellow oil with a bp *ca.* 150 °C /0.5 mm, which was then chromatographed: dichloromethane-99% ethanol, 9.9: 0.1. The eluates were evaported to dryness to yield the oily compound **9c**. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.91 (m, 6H, CH_3), 1.43 (m, 8H, Me-(C$\underline{H}_2$)$_2$), 2.46 (t, *J*= 7.9 Hz, 2H, CH_2-(C-4)), 2.58 (t, *J*= 8.2 Hz, 2H, CH_2-(C-5)), 4.78 (s, 2H, CH_2CN), 7.43 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 13.59 (CH_3), 13.79 (CH_3), 22.25 (CH_2), 22.31 (CH_2), 26.78 (CH_2), 31.79 (CH_2), 31.9 (CH_2), 32.4 ($\underline{C}H_2$-CN), 114,0 (CH_2-$\underline{C}N$), 126.1 (C-5), 135.1 (C-2), 139.9 (C-4); Anal. Calcd. for $C_{13}H_{21}N_3 \cdot 1/2H_2O$: C, 68.4; H, 9.7; N, 18.4. Found: C, 68.6; H, 9.8; N, 18.6.

4-Amino-3,5-bis(1-imidazolylmethyl)-4*H*-1,2,4-triazoles 10a,b (Tables 5 and 7). A stirred solution of 10 mmol of 1-cyanomethylimidazoles **9a** or **9b** (1.1 g or 1.35 g) and hydrazine hydrate (2 mL, 41.2 mmol) was maintained at 100 °C for 6.5 h. Then, the bath temperature was raise to 140 °C, the excess of hydrazine and water were distilled off over 4 h. The residue was triturated with dry acetone (3 x 15 mL) or dry diethyl ether (3 x 15 mL) to afford compounds **10a** and **10b** respectively as white solids.

4-Amino-3,5-bis(4,5-dibutyl-1-imidazolylmethyl)-4*H*-1,2,4-triazole 10c (Tables 5 and 7). A stirred solution of 4,5-dibutyl-1-cyanomethylimidazole (**9c**) (5.7 mmol, 1.25 g), hydrazine hydrate (2 mL, 41.2 mmol) and 96% ethanol (2 mL) was maintained at 100 °C for 10 h. Then, the bath temperature was raised to 140 °C, and the excess of hydrazine and water were distilled off over 4 h. The residue was dissolved in dichloromethane (75 mL) and washed with a saturated aqueous solution of NaCl (3 x 50 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo*. The oily residue was chromatographed:

dichloromethane; dichloromethane-96% ethanol, 9.5: 0.5; dichloromethane-96% ethanol, 9: 1. The eluates were evaported to dryness and the residue was then crushed with hexane to give the white solid compound **10c**.

1,4,5-Trimethylimidazole 11c: To a cold suspension of 21.0 mL (300.0 mmol) of formaldehyde, 36.5 g (540.0 mmol) of methylamine hydrochloride and 150.0 mL of ammonium hydroxide was added 15.8 mL (180.1 mmol) of butandione and the mixture was then maintained in a bath at *ca.* 100 °C for 15 min.

The cold reaction mixture was extracted with dichloromethane (4 x 100 mL). The organic layers were dried (Na_2SO_4) and the solvent was removed. Vacuum distillation of the residue (Kugelrohr) afforded compound **11c** (30%), bp 100 °C/1 Torr. ^1H NMR ($CDCl_3$, 200 MHz) δ 2.11 (s, 3H, CH_3-(C-5)), 2.15 (s, 3H, CH_3-(C-4)), 3.49 (s, 3H, CH_3N), 7.28 (s, 1H, H-2).

1-Alkylimidazole-2-carbaldehydes 12a-c (Table 7): A stirred solution of 145.2 mmol of 1-alkylimidazoles **11a-c** (**11a**: 11.4 mL; **11b**: 19.0 mL; **11c**: 16.0 g) in dry THF (150 mL) was cooled to -40 °C, then 100 mL (160.0 mmol) of 1.6 M nBuLi in hexane (160.0 mmol) was slowly added under an argon atmosphere and the reaction mixture maintained at -40 °C for 1h. To this was added dry DMF (160 mmol, 12.3 mL) in dry THF (25 mL). After the solution was kept at rt for the time specified in Table 11, it was quenched with 200 mL of H_2O and extracted with chloroform (6 x 250 mL). The organic layers were dried (Na_2SO_4) and the solvent was removed. Vacuum distillation of the residue (Kugelrohr) afforded compound **12a**, bp 40-45 °C/1.5 Torr or **12b** bp 67-75 °C/1.5 Torr. For imidazolecarbaldehyde **12c**, the residue was purified by chromatography: ethyl acetate-hexane, 1:1.The eluates were evaported to dryness to give compound **12c** as a yellow solid. Compound **12a**: ^1H NMR (DMSO-d_6, 200 MHz) δ 3.92 (s, 3H, CH_3N), 7.24 (s, 1H, H-4), 7.57 (s, 1H, H-5), 9.67 (s, 1H, CHO); ^{13}C NMR (DMSO-d_6, 50.3 MHz) δ 34.7 (CH_3N), 128.7 (C-5), 131.1 (C-4), 143.5 (C-2), 182.1 (CHO). Compound **12b**: ^1H NMR (DMSO-d_6, 200 MHz) δ 0.86 (t, J= 7.7 Hz, 3H, CH_3), 1.22 (m, 2H, Me-CH_2), 1.66 (m, 2H, Et-CH_2), 4.34 (t, J= 6.8 Hz, 2H, (Pr-CH_2N), 7.26 (s, 1H, H-4), 7.66 (s, 1H, H-5), 9.67 (s, 1H, CHO); ^{13}C NMR (DMSO-d_6, 50.3 MHz) δ 13.6 (CH_3), 19.2 (Me-CH_2), 32.7 (Et-CH_2), 46.8 (Pr-CH_2N), 127.9 (C-5), 131.3 (C-4), 142.9 (C-2), 182.0 (CHO). Compound **12c**: mp. 82°C; ^1H NMR (DMSO-d_6, 200 MHz) δ 2.12 (s, 3H, CH_3-(C-4)), 2.17 (s, 3H, CH_3-(C-5)), 3.81 (s, 3H, CH_3N), 9.49 (s, 1H, CHO); ^{13}C NMR (DMSO-d_6, 50.3 MHz) δ 8.3 (CH_3-(C-5)), 12.8 (CH_3-(C-4)), 31.7 (CH_3N), 132.9 (C-5), 137.6 (C-4), 141.6 (C-2), 180.65 (CHO). Anal. Calcd. for $C_7H_{10}N_2O$: C, 60.8; H, 7.3; N, 20.3. Found: C, 60.7; H, 7.4; N, 20.3.

1-Alkyl-2-(hydroxymethyl)imidazoles 13a-c (Table 7): To a stirred solution of 49.4 mmol of 1-alkylimidazole-2-carbaldehydes **12a-c** (**12a**: 5.4 g; **12b**: 7.5 g; **12c**: 6.8 g) in dry methanol (40 mL) was cooled to ca. -10 °C, then 74.0 mmol of $NaBH_4$ (2.8 g) was slowly added and the reaction mixture was maintained at rt under a nitrogen atmosphere for the time specified in Table 11. H_2O (40 mL) was added and then was evaporated to dryness, the residue was dissolved in H_2O (175 mL) and extracted with chloroform (6 x 200 mL). The organic layers were dried (Na_2SO_4), the solvent was removed and the residue was purified by chromatography: dichloromethane-96% ethanol, 9.5: 0.5. The eluates were evaported to dryness and the residue was then crushed with hexane to give compounds **13a-c**. Compound **13a**: ^1H NMR (DMSO-d_6, 200 MHz) δ 3.62 (s, 3H, CH_3N), 4.45 (d, J= 5.6 Hz, 2H, CH_2-OH), 5.35 (t, J= 5.6 Hz, 1H, CH_2-OH), 6.74 (s, 1H, H-4), 7.05 (s, 1H, H-5); ^{13}C NMR (DMSO-d_6, 50.3 MHz) δ 32.6 (CH_3N), 55.7 (CH_2OH), 122.1 (C-

5), 126.3 (C-4), 147.6 (C-2); Anal. Calcd. for $C_5H_8N_2O$: C, 53.5; H, 7.2; N, 25.0. Found: C, 53.5; H, 7.2; N, 25.0. Compound **13b**: mp. 110°C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 0.88 (t, J= 7.3 Hz, 3H, CH_3), 1.26 (m, 2H, Me-C$\underline{H}_2$), 1.67 (m, 2H, Et-C$\underline{H}_2$), 3.95 (t, J= 7.4 Hz, 2H, Pr-C$\underline{H}_2$N), 4.44 (d, J= 5.5 Hz, 2H, C$\underline{H}_2$OH), 5.27 (t, J= 5.5 Hz, 1H, CH$_2$O$\underline{H}$), 6.76 (s, 1H, H-4), 7.11 (s, 1H, H-5); ^{13}C NMR (DMSO-d_6, 50.3 MHz) δ 13.8 (CH_3), 19.6 (Me-$\underline{C}H_2$), 32.9 (Et-$\underline{C}H_2$), 45.3 (Pr-$\underline{C}H_2$N), 55.8 (CH_2OH), 120.7 (C-5), 126.4 (C-4), 147.2 (C-2); Anal. Calcd. for $C_8H_{14}N_2O$: C, 62.3; H, 9.1; N, 18.2. Found: C, 62.3; H, 9.1; N, 18.1. Compound **13c**: mp. 134°C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.95 (s, 3H, C$\underline{H}_3$-(C-4)), 2.03 (s, 3H, C$\underline{H}_3$-(C-5)), 3.43 (s, 3H, CH_3N), 4.36 (d, J= 5.7 Hz, 2H, C$\underline{H}_2$OH), 5.10 (t, J= 5.7 Hz, 1H, CH$_2$O$\underline{H}$); ^{13}C NMR (DMSO-d_6, 50.3 MHz) δ 8.6 ($\underline{C}H_3$-(C-5)), 12.6 ($\underline{C}H_3$-(C-4)), 30.2 (CH_3N), 55.9 (CH_2OH), 123.3 (C-5), 130,2 (C-4), 145.3 (C-2); Anal. Calcd. for $C_7H_{12}N_2O$: C, 60.0; H, 8.6; N, 20.0. Found: C, 60.3; H, 8.5; N, 19.9.

1-Alkyl-2-(chloromethyl)imidazoles hydrochlorides 14a-c (Table 7): To a stirred solution of 173.7 mmol of thionyl chloride (12.6 mL) in dry dichloromethane (20 mL) was added dropwise a solution of 12.6 mmol of 1-Alkyl-2-(hydroxymethyl)imidazoles **13a-c** (**13a**: 1.4 g; **13b**: 1.9 g; **13c**: 1.7 g) in dry dichloromethane (40 mL) at 0 °C, and then maintained at rt for 5 h. The reaction mixture was evaporated to dryness and the residue was triturated with dichloromethane for compounds **14a,b** or with acetonitrile for compound **14c**, affording the desired chloromethyl products **14a-c**. Compound **14a**: mp. 174°C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.87 (s, 3H, CH_3N), 5.21 (s, 2H, CH_2-Cl), 7.70 (s, 1H, H-4), 7.05 (s, 1H, H-5); ^{13}C NMR (DMSO-d_6, 50.3 MHz) δ 31.8 (CH_2Cl), 34.5 (CH_3N), 119.3 (C-5), 125.0 (C-4), 141.6 (C-2); Anal. Calcd. for $C_5H_8N_2Cl_2$: C, 35.9; H, 4.8; N, 16.8. Found: C, 35.8; H, 4.8; N, 16.7. Compound **14b**: mp. 165°C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 0.90 (t, J= 7.12 Hz, 3H, CH_3), 1.30 (m, 2H, Me-C$\underline{H}_2$), 1.78 (m, 2H, Et-C$\underline{H}_2$), 4.20 (t, J= 7.56 Hz, 2H, Pr-C$\underline{H}_2$N), 5.19 (s, 2H, CH_2Cl), 7.74 (s, 1H, H-4), 7. 84 (s, 1H, H-5); ^{13}C NMR (DMSO-d_6, 50.3 MHz) δ 13.6 (CH_3), 19.2 (Me-$\underline{C}H_2$), 31.5 (Et-$\underline{C}H_2$), 31.65 (CH_2Cl), 47.1 (Pr-$\underline{C}H_2$N), 119.9 (C-5), 123.6 (C-4), 141.3 (C-2); Anal. Calcd. for $C_8H_{14}N_2Cl_2$: C, 45.9; H, 6.7; N, 13.4. Found: C, 45.9; H, 6.8; N, 13.4. Compound **14c**: mp. 168°C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.21 (s, 6H, C$\underline{H}_3$-(C-4,5)), 3.71 (s, 3H, CH_3N), 5.17 (s, 2H, CH_2Cl); ^{13}C NMR (DMSO-d_6, 50.3 MHz) $\delta\delta$ 8.1 ($\underline{C}H_3$-(C-5)), 9.0 ($\underline{C}H_3$-(C-4)), 31.8 (CH_3N), 32.2 (CH_2Cl), 124.9 (C-5), 128.2 (C-4), 138.9 (C-2); Anal. Calcd. for $C_7H_{12}N_2Cl_2$: C, 43.1; H, 6.2; N, 14.4. Found: C, 43.3; H, 6.2; N, 14.2.

2-Cyanomethylimidazoles 15a,b (Table 7): Chloromethylimidazole hydrochlorides **14a** or **14b** (**14a**: 5.2 g, 30.9 mmol; **14b**: 2.0 g, 9.6 mmol) were dissolved in dry DMF at 40 °C (**14a**: 200 mL; **14b**: 75 mL) under an atmosphere of nitrogen. The solution was added dropwise to a suspension of NaCN (**14a**: 57.7 g, 157.1 mmol; **14b**: 2.3 g, 47.8 mmol) in dry DMF (50 mL). The reaction mixture was maintained at 45 °C for 4 h, then a saturated aqueous solution of Na_2CO_3 (100 mL) was added and the solvent was removed in a rotary evaporator. The residue was dissolved in H_2O (100 mL) and extracted with 5 x 75 mL portions of dichloromethane and the combined extracts were dried (Na_2SO_4) and the solvent was removed *in vacuo*. Purification was carried out by chromatography: for compound **15a**, dichloromethane-96% ethanol, 9.9: 0.1; for compound **15b**, ethyl acetate-hexane, 1:1. The eluates were evaported to dryness to give compounds **15a** and **15b**. Compound **15a**: ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.58 (s, 3H, CH_3N), 4.19 (s, 2H, CH_2CN), 6.81 (s, 1H, H-4), 7.13 (s, 1H, H-5); ^{13}C NMR (DMSO-d_6, 50.3 MHz) δ 16.4 ($\underline{C}H_2$CN), 32.6 (CH_3N),

116.95 (CH_2CN), 122.8 (C-5), 127.1 (C-4), 137.9 (C-2); Anal. Calcd. for $C_6H_7N_3 \cdot 1/3H_2O$: C, 56.7; H, 6.0; N, 33.1. Found: C, 56.6; H, 5.9; N, 33.6.

Table 7. Physical Data of Compounds **9**, **10** and **12-16**

Compd	Yield (%)[a]	mp (°C) [solvent][b]	Reaction time (h)[c]	TLC[d]	molecular formula[e]
9a	40	50	7.5	A	$C_5H_5N_3$
9b	48	60	7.5	B	$C_7H_9N_3$
9c	63	*f*	7	C	$C_{13}H_{21}N_3 \cdot 0.5H_2O$
10a	82	195	6.5(100); 3(140)	A	$C_{10}H_{22}N_8$
10b	90	126	6.5(100); 2(140)	B	$C_{14}H_{20}N_8 \cdot H_2O$
10c	37	107	10(100); 2(140)	D	$C_{26}H_{44}N_8$
12a	52	*f*	18	B	*g*
12b	75	*f*	20	B	*g*
12c	51	82	24	E	$C_7H_{10}N_2O$
13a	66	110	20	D	$C_5H_8N_2O$
13b	68	*f*	26	D	$C_8H_{14}N_2O$
13c	78	134	18	D	$C_7H_{12}N_2O$
14a	86	174	5	A	$C_5H_8N_2Cl_2$
14b	83	165	5	A	$C_8H_{14}N_2Cl_2$
14c	67	168	5	A	$C_7H_{12}N_2Cl_2$
15a	87	*f*	3	E	$C_6H_7N_3 \cdot 0.3H_2O$
15b	80	*f*	4	E	$C_9H_{13}N_3 \cdot 0.25H_2O$
15c	21	117	1	A	$C_8H_{11}N_3$
16a	67	220	6(100); 6(130)	A	$C_{12}H_{16}N_8 \cdot H_2O$
16b	70	76	6(100); 4(130)	A	$C_{18}H_{28}N_8 \cdot H_2O$
16c	27	221 [i]	6(100); 2(140)	A	$C_{16}H_{24}N_8$

[a]Yields were not optimized. [b]Recrystallization solvent: (i) acetone. [c]Between claudators reaction temperature. [d]A: Chloroform-methanol (8:2); B: Chloroform-methanol (1:1); Dichloromethane-ethanol (99:1); D: Dichloromethane-ethanol (9:1); E: Ethyl acetate-hexane (1:1). [e]Satisfactory analytical data (± 0.4% for C, H, N) were obtained for new compounds. [f]Oily Compound. [g]Not satisfactory analytical data were obtained.

Compound **15b**: ^{1}H NMR (DMSO-d_6, 200 MHz) δ 0.91 (t, J= 7.3 Hz, 3H, CH_3), 1.28 (m, 2H, Me-CH_2), 1.65 (m, 2H, Et-CH_2), 3.93 (s, 2H, CH_2CN), 4.23 (t, J= 7.6 Hz, 2H, Pr-CH_2N), 6.84 (s, 1H, H-4),

7.21 (s, 1H, H-5); ^{13}C NMR (DMSO-d_6, 50.3 MHz) δ 16.5 ($\underline{C}H_2CN$), 13.7 (CH_3); 19.4 (Me-$\underline{C}H_2$), 32.4 (Et-$\underline{C}H_2$), 45.3 (Pr-$\underline{C}H_2N$), 117.2 ($CH_2\underline{C}N$), 121.5 (C-5), 127.4(C-4), 137.4 (C-2); Anal. Calcd. for $C_9H_{13}N_3 \cdot 1/4H_2O$: C, 64.4; H, 7.8; N, 25.0. Found: C, 64.6; H, 8.1; N, 25.2.

2-Cyanomethylimidazole 15c (Tables 7): Chloromethylimidazole hydrochloride **14c** (6.5 g, 3.3 mmol) was dissolved in dry DMF (150 mL) at rt under an atmosphere of nitrogen. The solution was added dropwise to a suspension of NaCN (8.2 g, 177.3 mmol) in dry DMF (50 mL). The stirred mixture was maintained at rt for 1 h, then a saturated aqueous solution of Na_2CO_3 (100 mL) was added and the solvent was removed in a rotary evaporator. The residue was dissolved in H_2O (150 mL) and extracted with 3 x 100 mL portions of dichloromethane and the combined extracts were dried (Na_2SO_4) and the solvent was removed *in vacuo*. Purification was carried out by chromatography: ethyl acetate-hexane, 1:1. The eluates were evaported to dryness to give compound **15c**. mp. 117°C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.98 (s, 3H, $C\underline{H}_3$-(C-4)), 2.04 (s, 3H, $C\underline{H}_3$-(C-5)), 3.39 (s, 3H, CH_3N), 4.10 (s, 2H, CH_2CN); ^{13}C NMR (DMSO-d_6, 50.3 MHz) δ 8.6 ($\underline{C}H_3$-(C-5)), 12.6 ($\underline{C}H_3$-(C-4)), 16.7 ($\underline{C}H_2CN$), 30.3 (CH_3N), 117.1 ($CH_2\underline{C}N$), 124.0 (C-5), 131.2 (C-4), 135.1 (C-2); Anal. Calcd. for $C_8H_{11}N_3$: C, 64.4; H, 7.4; N, 28.2. Found: C, 64.6; H, 7.4; N, 28.0.

4-Amino-3,5-bis[2-(1-alkyl-imidazolyl)methyl]-4*H*-1,2,4-triazoles 16a,b (Tables 6 and 7). A stirred solution of 12.7 mmol of 2-cyanomethylimidazoles **15a** or **15b** (1.5 g or 2.1 g) and hydrazine hydrate (2.0 mL, 41.2 mmol) was maintained at 100 °C for the time specified in Table 11, and then, the bath temperature was raised to 130 °C for the time specified in Table 11. At 145 °C, the excess of hydrazine and water were distilled off over 3.5 h. For compound **16a** the reaction mixture was triturated with dry dichloromethane (25 mL) to give a pure white solid. For compound **16b** H_2O (2 mL) was added first and then diethyl ether (10 mL) to afford pure compound **16b** as a pale brown solid.

4-Amino-3,5-bis[2-(1-alkyl-imidazolyl)methyl]-4*H*-1,2,4-triazole 16c (Tables 6 and 7). To a stirred solution of 2-cyanomethylimidazole (**15c**) (2.9 mmol, 0.4 g) in 96% ethanol (10 mL), hydrazine hydrate (1.5 mL, 30.9 mmol) was added and the reaction mixture was maintained at 100 °C for 6 h. Then raising up the bath temperature to 140 °C, the excess of hydrazine and water were distilled off over 2 h. The mixture was crushed with dry acetone (2 x 2 mL) to give a white solid which was recrystallized.

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