Application of the Kauffmann Areno-Analogy Principle − Stability towards Oxidation of the Methylene Spacers in Quadrupolar [1$_4$]Heterophane Frameworks Incorporating 4- or 3-Pyridiniomethyl-1,2,4-triazolate Betaine Units

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Incorporation of 3,5-bis-3(4)-pyridiniomethyl-1,2,4-triazolate units into the structures of novel bis-betaines in [1$_4$](*meta*-*para*)$_2$heterophane systems has shown that the structural features conferred by the heterophane framework result in macrocycles that, in contrast to their building blocks, are stable towards oxidation. The stability of [1$_4$]*meta*heterophanes is consistent with their betaine subunits.

Introduction

Diversity of molecular architectures in macrocycles permits the design of novel systems with capacity for specific physical or biological behavior.[2a−2c] In this context, the synthesis and properties of different 1,2,4-triazole-containing macrocycles has been reported.[1,2d,2e] On the other hand, the background offered by Kauffmann's areno-analogy principle allows heteroaromatic fragments to be correlated with classical functional groups.[3] Accordingly, the 1-alkyl-4(3)-(1*H*-1,2,4-triazolylmethyl)pyridinium salts **1·X** and **3·X** are monocationic building blocks bearing both highly π-deficient (acceptor group) and π-rich (donor group) heteroaromatic rings on the same carbon.[3,4] The combination of the areno-analogy principle[4] and the effects of electronic stabilization of carbon-centered radicals[5] has been achieved in several salts, such as **1·X** and **3·X**. Thus, the propensity of the methylene spacer towards spontaneous oxidation may be controlled by changing the nature of the non-classical acceptor and donor heteroaromatic fragments.[6] As shown in Figure 1, air was sufficient for oxidation of 4-pyridinium compounds **1·X** to their corresponding oxomethyl analogues **2·X**, whereas the 3-pyridinium monocations **3·X** were very stable to air oxidation. The fact that this chemical stability persisted in the corresponding betaines **4** is noteworthy and the synthetic utility of this spontaneous oxidation appears to be an attractive way to functionalize the $C-CH_2-C'$ bond type linker.[6b] Considering the pro-radical aspect of the methylene spacer, more elaborated multicharged systems have been studied;[7a] these include the dicationic [1$_4$](*meta*-*para*)$_2$heterophanes **5·2Cl** and **6·2Cl** and [1$_4$]*meta*heterophanes **7·2Cl** and **8·2Cl**, together with the novel bis-betaines **9** and **10**.

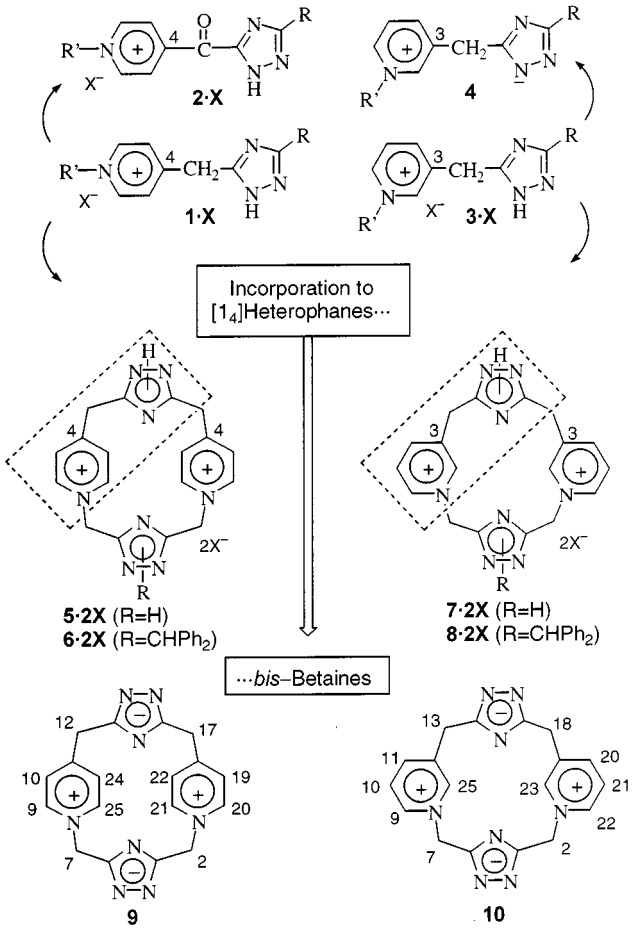

Figure 1. From betaine building blocks to [1$_4$]heterophanes containing methylene spacers *stable* to oxidation

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Results and Discussion

Synthesis

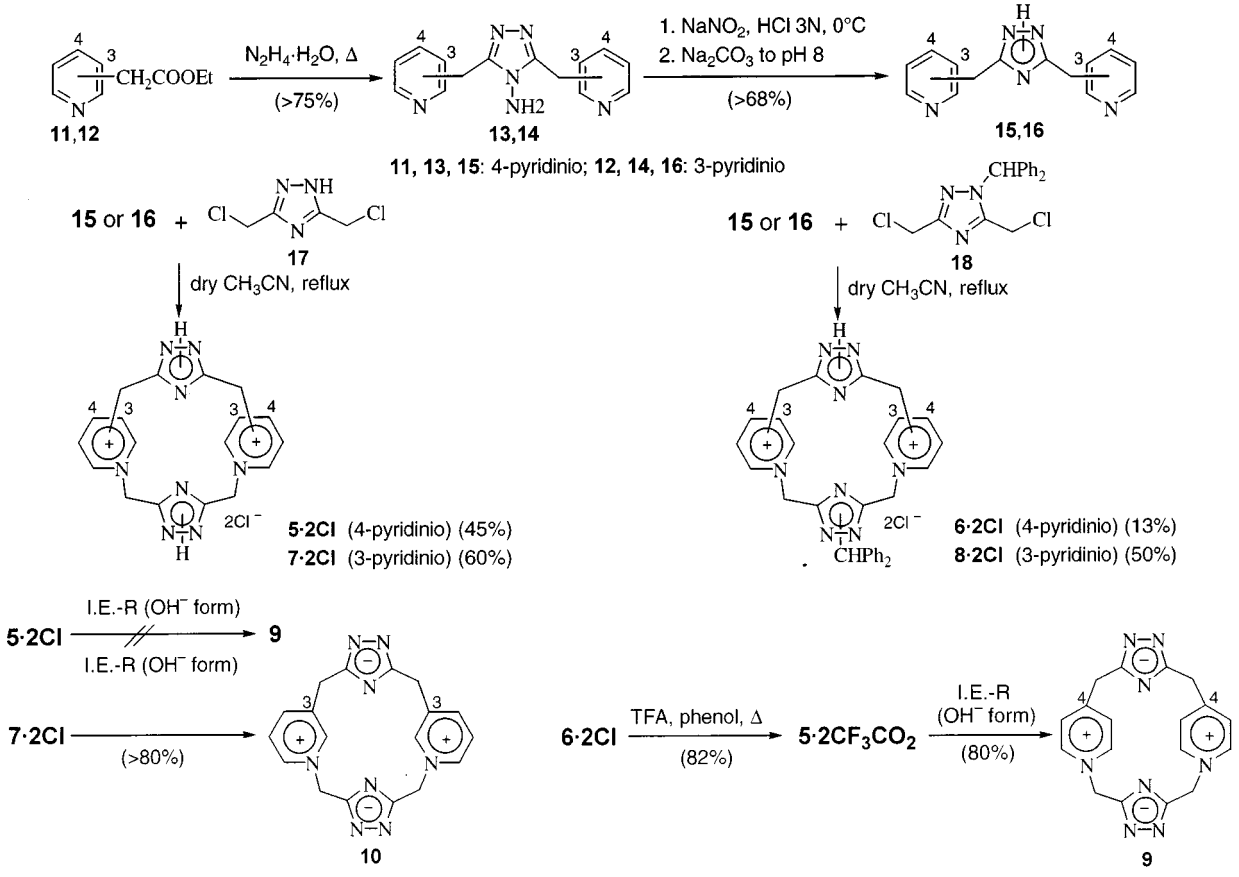
The key trinucleating systems **15** and **16** were obtained by a two-step procedure starting from ethyl 4- and 3-pyridylacetates **11** and **12**, respectively (Scheme 1). Thus, treatment of compounds **11** and **12** with an excess of hydrazine hydrate gave the 4-amino-3,5-bis-[3(4)-pyridylmethyl]-1,2,4-triazoles **13** and **14**, which were deaminated to afford the key protophanes **15** and **16** in overall yields of ≥ 50%. By a '3+1' convergent stepwise synthesis,[7b] dicationic [1$_4$]heterophanes **5·2Cl** and **7·2Cl** were prepared by coupling of protophanes **15** or **16** to 3,5-bis(chloromethyl)-1*H*-1,2,4-triazole **17**.[8] The macrocyclization was conducted with equimolar amounts of reactants **15/16** and **17** in refluxing acetonitrile and proceeded in good yields (> 45%).

The insolubility of the macrocyclic dication **5·2Cl** in alcohols and water, however, precluded its transformation into the corresponding quadrupolar [1$_4$](*meta-para*)$_2$heterophane **9**, although dication **7·2Cl** could be converted into the bis-betaine **10** with the aid of an anion-exchange resin (OH^- form). An alternative pathway to bis−betaine **9** was therefore developed. Protophane **15** was coupled with 1-benzhydryl-3,5-bis(chloromethyl)-1*H*-1,2,4-triazole (**18**),[7c] and the *N*-benzhydryl dication **6·2Cl** was obtained in moderate yields. Removal of the *N*-benzhydryl group with trifluoroacetic acid provided the bistrifluoroacetate dication **5·2CF$_3$CO$_2$**. This was much more soluble in alcohols and/or water than its dichloride counterpart **5·2Cl**, and the quadrupolar heterophane **9** could thus be obtained as shown in Scheme 1. Moreover, the coupling of protophane **16** with compound **18** afforded the macrocyclic dication **8·2Cl** in 50% yield.

Stability towards Oxidation

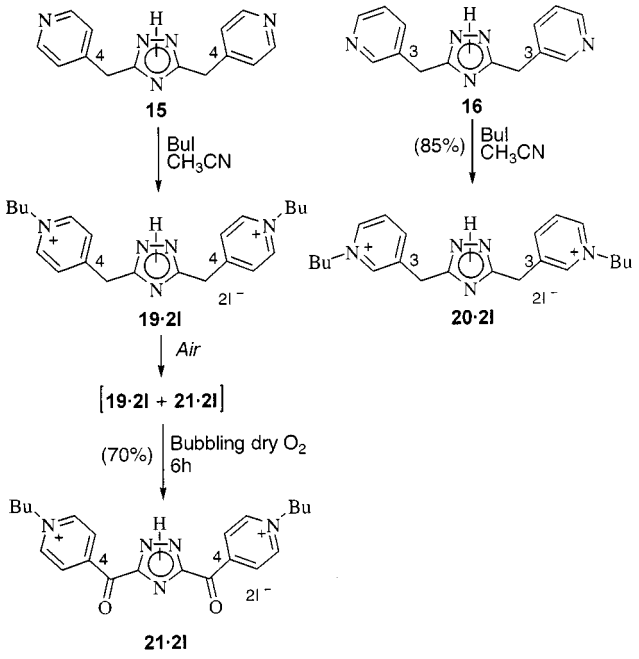
Both macrocyclic dications **5·2Cl**−**8·2Cl** and bis-betaines **9** and **10** were stable in air. Unlike the betaine building block **1·X**,[6] the [1$_4$](*meta-para*)$_2$heterophane framework was stable towards spontaneous oxidation not only in the dications **5·2X** and **6·2Cl** but also in the bis-betaine **9**. The chemical stability observed in the [1$_4$]*meta*heterophanes − dications **7·2Cl** and **8·2Cl** and bis-betaine **10** − was unsurprising, since atmospheric oxidation had also not been observed for the betaine counterpart **4**.

With these results in mind, the course of quaternization of the acyclic trinucleating building blocks **15** and **16** was then examined, by using 1-iodobutane as an alkylating agent under standard conditions. Once the open-chain dications **19·2I** and **20·2I** had been obtained, different chemical stabilities were observed (Scheme 2). The presence of 4-pyridinio fragments in dication **19·2I** favored its oxidation and consequently yielded a mixture of dication **19·2I** and its dioxomethyl counterpart **21·2I** in 40:60 ratio. Conditions more forcing than atmospheric induced complete oxidation



Scheme 1. Route to macrocyclic bis-betaines **9** and **10** from dicationic [1$_4$]heterophanes **5·2Cl**−**8·2Cl** by a '3+1' convergent synthesis

of the mixture, and pure dication **21·2I** was formed by bubbling oxygen through the reaction mixture. In the case of the dicationic open-chain system **20·2I**, with 3-pyridinio fragments, no aerial oxidation was observed and the diiodide **20·2I** was stable.



Scheme 2. Chemical behavior of model trinucleating open−chain dications **19·2I** and **20·2I** regarding spontaneous oxidation

Spectroscopic Methods

The molecular structures of the new macrocycles were unambiguously characterized on the basis of their spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, ESI-MS). Unfortunately, it was impossible to obtain single crystals of the targeted [1$_4$]heterophanes for X-ray structure analysis either with the dications **5·2Cl−8·2Cl** or with the bis-betaines **9** and **10**. The IR spectra of compounds **5·2Cl−8·2Cl** showed absorption bands in the 3200−3000 cm^{-1} range (ν_{NH}), which were absent in the bis-betaines **9** and **10.** On the other hand, dication **5·2CF$_3$CO$_2$** also showed absorption bands in the 3200−3000 cm^{-1} (ν_{NH}) and the 1700−1650 cm^{-1} ranges (ν_{CO}), corresponding to the trifluoroacetate anions.

NMR Spectroscopy

The ^{1}H and ^{13}C NMR chemical shifts of the macrocycles reported were crucial for structural characterization and accorded well with the nature of the π-excessive and π-deficient heteroaromatic fragments, as well as with data for related macrocyclic systems. The ^{1}H NMR spectroscopic data of the [1$_4$]heterophanes are given in Table 1, and the ^{13}C NMR parameters are listed in the Supporting Information.

In contrast to what had been observed with the betaine building blocks,[6] the tendency towards hydration was minimal, the NMR spectra recorded in D_2O were reliable, and a pronounced shielding effect for the CH and CH_2 protons atoms of bis-betaines **9** and **10** was observed in D_2O, decreasing in [D$_6$]DMSO (see Table 1).

The ^{1}H NMR spectra (22 °C) of the [1$_4$]heterophanes in D_2O showed that the methylene protons appeared as two sharp singlets, corresponding to the $C-CH_2-C'$ and the $C-CH_2-N'$ bond-type spacers. Their insolubility in low melting solvents precluded a dynamic NMR study, however. Similar conformational mobility has been observed in related [1$_4$]heterophane systems.[7b] Comparison of the proton chemical shifts of bis-betaines **9** and **10** with those of the corresponding dicationic precursors **5·2CF$_3$CO$_2$** and **7·2Cl** revealed that the δH values of the bridging protons were among those most affected, with the CH_2 protons moving upfield (see ΔδH in Table 1 and Figure 2). For example, the differences in proton chemical shifts between bis-betaine **9** and dication **5·2CF$_3$CO$_2$** were $\Delta\delta CH_2 = -0.24$ ppm. For compound pair **7·2Cl** and **10**, enhanced shielding effects were observed for the pyridinium protons H(23) and H(25): $\Delta\delta = -0.71$ ppm. Individual assignments could be made for the *N*-benzhydryl dications **6·2Cl** and **8·2Cl**, except for the NH proton in the 1-*H*-1,2,4-triazole subunit, with the aid of NMR experiments (NOESY, HMQC and HMBC) and the key NMR responses of dication **6·2Cl** are shown in Figure 2.

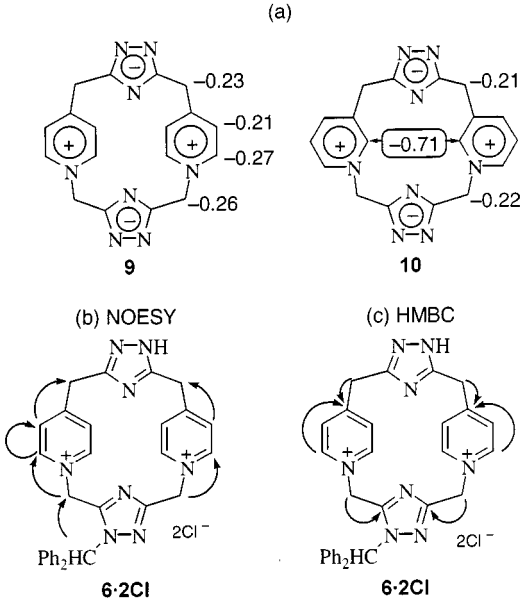


Figure 2. (a) Chemical shift differences (Δδ, ppm) in D_2O between bis-betaines **9** and **10** and their dicationic precursors **5·2Cl** and **7·2Cl**. Key NMR responses for dication **6·2Cl**: (b) NOESY experiment; (c) HMBC correlation

Table 2 shows the relevant ^{1}H and ^{13}C NMR parameters of the acyclic polydentates **13−16** and the dications **20·2I** and **21·2I** in [D$_6$]DMSO. For the 3(4)-pyridine/pyridinium rings, the δH values of the α-CH protons are similar to those observed for their building block counterparts[6] (e.g., **1·2X** and **3·2X** for pyridinium monocations), whereas the [1$_4$]heterophane framework produced a shielding effect, the α-CH protons moving upfield especially in bis-betaine **10**, in which δH(23,25) appeared at δ = 8.69 in [D$_6$]DMSO (δ = 7.85 in D_2O, Table 1 and Table 2).

Table 1. ^{1}H NMR spectroscopic data of quadrupolar bis-betaines **9** and **10** and the dicationic macrocycles **5·2X**−**8·2X**

Compd.	H-9,20,21,25	H-10,19,22,24 CH_2-2,7	CH_2-12,17
9[a] **I**[b]	8.22	7.40	
		5.49	3.95
5·2CF$_3$CO$_2$[a] [b]	8.49	7.61	
		5.75	4.18
Δδ[c]	−0.27	−0.21	
		−0.26	−0.23
5·2Cl[a] [d]	8.48	7.59	
		5.72	4.15
9[d] [e]	8.69	7.71	
		5.63	4.21
5·2CF$_3$CO$_2$[d] [e]	8.78	7.85	
		5.97	4.28
Δδ[c]	−0.09	−0.14	
		−0.34	−0.07
5·2Cl[e] [f]	8.81	7.86	
		6.01	4.29

Compd.	H-9,22	H-10,21	H-11,20	H-23,25	CH_2-2,7	CH_2-13,18
10[a] [d]	8.64	7.79	8.28	7.85	5.53	3.98
7·2Cl[a] [d]	8.72	7.88	8.40	8.49	5.76	4.20
Δδ[c]	−0.08	−0.09	−0.12	−0.64	−0.23	−0.22
7·2PF$_6$ [a] [d]	8.74	7.90	8.42	8.51	5.78	4.22
10[e] [f]	9.01	8.00	8.44	8.69	5.69	4.04
7·2Cl[f] [g]	9.12	8.16	8.62	8.86	6.00	4.31
Δδ[c]	−0.11	−0.16	−0.18	−0.17	−0.31	−0.27
7·2PF$_6$ [e] [f]	9.05	8.16	8.61	8.89	5.97	4.30

Compd.	H-9	H-10	H-11	H-19	H-20	H-21	H-22	H-23	H-24	H-25
6·2Cl[a] [f] [h]	8.32	7.64	−	7.72	8.58	8.58	7.72	−	7.64	8.32
8·2Cl[a] [f] [h]	8.39	7.62	8.27	−	8.48	7.97	8.80	8.52	−	8.05

Compd.	CH_2-2	CH_2-7	CH_2-12	CH_2-13	CH_2-17	CH_2-18	−$CHPh_2$
6·2Cl[a] [f] [h]	5.70	5.82	4.25	−	4.28	−	7.09, 7.18, 7.39
8·2Cl[a] [f] [h]	5.67	5.95	−	4.09	−	4.30[i]	6.85−7.33

[a] n D_2O. [b] ^{1}H NMR spectra at 300 MHz. [c] Δδ: difference in the chemical shift of bis-betaines and their corresponding salts. [d] ^{1}H NMR spectra at 200 MHz. [e] In [D_6]DMSO. [f] ^{1}H NMR spectrum at 500 MHz. [g] In [D_6]DMSO/D_2O (9:1, v/v), ca. 3 mM. [h] Assignment of the aromatic signals by NOESY. [i] Broad signal.

Table 2. Selected ^{1}H and ^{13}C NMR spectroscopic data of protophanes **13**−**16**, **20·2I**, and **21·2I** (in [D_6]DMSO at 300 MHz)

Compd.	H-2′	H-3′	H-4′	H-5′	H-6′	−CH_2−	
13	8.48	7.27	−	7.27	8.48	4.10	
14	8.50	−	7.68	7.33	8.44	4.08	
15	8.46	7.24	−	7.24	8.46	4.02[a]	
16	8.48	−	7.64	7.31	8.42	4.01	
	C-2′	C-3′	C-4′	C-5′	C-6′	−CH_2−	
13	150.1	124.7	146.2	124.7	150.1	29.2	
14	150.5	133.0	137.1	123.95	148.3	27.2	
15	149.8	124.3	147.7, 145.9	124.3	149.8	31.3, 33.5	
16	149.9	133.6	136.5	123.7	147.9	30.4	
	H-2′	H-3′	H-4′	H-5′	H-6′	−CH_2−	
20·2I	9.13	−	8.51	8.13	9.02	4.29[a]	
21·2I	9.30	8.76	−	8.76	9.30	−	
	C-2′	C-3′	C-4′	C-5′	C-6′	−CH_2−	CO
20·2I	144.7	139.8[a]	146.0	127.9	143.3	30.0	−
21·2I	145.7	128.0	150.2	128.0	145.7	−	181.2

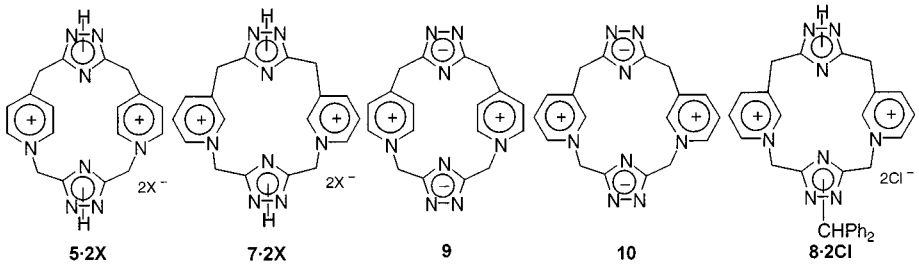
[a] Broad signal.

Electrospray Mass Spectrometry

ESI-MS was used to examine multicharged [1$_4$]*meta*heterophanes, and both dicationic macrocycles and bis-betaines produced clean positive ion ESI mass spectra. Proton-transfer reactions were observed, the two common characteristic peaks corresponding to the doubly charged and singly charged ions $[MH_2]^{2+}$ and $[M]^+$. When the cone voltage was varied from 50V to 100V, a variety of polymolecular self-assembled aggregates was observed.[9]

Positive ion ESI-MS were performed by following the same experimental methodology as previously reported.[9] Samples were dissolved in a 1:1 mixture of H_2O/CH_3CN at a concentration of 250 pmol μL^{-1} and the cone voltage was varied between 50V and 100V. The positive ion ESI response of the title bis-betaines **9** and **10** and the dications **5·2X**, **7·2X** and **8·2Cl** resulted in the appearance of the two characteristic doubly charged and singly charged species $[MH_2]^{2+}$ and $[M]^+$ (Table 3). At a cone voltage of 100V,

Table 3. Summary of data obtained from positive ion ESI-MS of **5·2X**, **7·2X**, **8·2Cl**, **9**, and **10**



5·2X **7·2X** **9** **10** **8·2Cl**

Vc [V]	Compd. (Mol. mass)[a]	Ions, *m/z* ratio Relative abundance (%)					
		$[MH_2]^{2+}$	$[Pp{\cdot}H]^+$ [b]	$[MH]^+$	$[MH_2+X]^+$	$[2M + H]^+$	
	5·2Cl						
	(417.3)	173.2	252.3	345.4	381.9	689.9	
50		*100*	[c]	6	[c]	[c]	
100		*100*	87	64	[c]	[c]	
	5·2CF$_3$CO$_2$						
	(572.4)	173.2	252.3	345.4	459.4	689.9	
50		*100*	[c]	8	[c]	[c]	
100		*100*	64	42	[c]	[c]	
	7·2Cl						
	(417.3)	173.2	252.3	345.4	381.9	689.9	
50		*100*	<1	8	[c]	<1	
100		*100*	76	37	[c]	2	
	7·2PF$_6$						
	(636.3)	173.2	252.3	345.4	491.3	689.9	
50		*100*	[c]	8	<1	[c]	
100		*100*	22	50	20	[c]	
	9						
	(344.4)	173.2	252.3	345.4	–	689.9	
50		*100*	<1	3	–	[c]	
100		5	*100*	18	–	2	
	10						
	(344.4)	173.2	252.3	345.4	–	689.9	
50		*100*	<1	7	–	<1	
100		[c]	[c]	*100*	–	19	
		$[Ph_2CH]^+$	**$[Pp{\cdot}H]^+$** [b]	**$[MH]^{2+}$**	**$[MH\text{-}Ph_2CH]^+$**	**$[M]^+$**	**$[MH+Cl]^+$**
	8·2Cl						
	(583.5)	167.2	252.3	256.3	345.4	511.6	548.0
50		*100*	1	8	86	10	<1
100		93	40	9	69	*100*	6

[a] Molecular mass and ion *m/z* values apply to the lowest mass component of any isotope distribution and are based on a scale in which the value for ^{12}C equals 12.000. [b] Protophane (Pp, $MW = 251.3$). [c] No signal observed.

besides these two common peaks, a singly charged fragment ion $[Pp{\cdot}H]^+$ at $m/z = 252.3$ was also produced; this was due to the protonated trinuclear 3,5-bis-pyridylmethyl-1*H*-1,2,4-triazole, which was the base peak for bis-betaine **9**. For bis-betaine **10**, a self-assembled aggregate due to a singly charged dimer $[2\,M + H]^+$ was produced at $m/z = 689.9$ (19%). The *N*-benzhydryl dication **8·2Cl** gave a pronounced singly charged fragment ion at $m/z = 167.2$, due to the benzhydryl cation. The uncharged 3,5-bis(pyridylmethyl)-1*H*-1,2,4-triazoles **13**–**16**, on the other hand, were studied by electron impact ionization (see Supplementary Information).

Conclusion

The bis-betaine [1$_4$] (*meta-para*)$_2$heterophane **9** and the dicationic precursors **5·2Cl** and **6·2Cl** were stable in air, in contrast to their monocationic building blocks **1·2X**. The stability of bis-betaine **10** and the dicationic [1$_4$]*meta*heterophanes **7·2Cl** and **8·2Cl** towards oxidation was as expected, since no atmospheric oxidation had been observed for their corresponding units, either the monocations **3·2X** or the betaines **4**. The [1$_4$]heterophane frameworks thus conferred stability towards oxidation on the spacer and allowed access to the model macrocyclic bis–betaines **9** and **10**. The ^1H

NMR spectroscopic data provided evidence of the charge distributions in these macrocyclic systems in solution, and the electrospray ionization mass spectrometry revealed the formation of several informative peaks in the gas phase, especially for bis-betaine **10**. Further studies are being directed towards the application of the betaine building blocks for the construction of supramolecular scaffolds, developing from quadrupolar to multipolar systems.

Experimental Section

General Remarks: Melting point: CTP-MP 300 hot-plate apparatus with ASTM 2C thermometer (Table 4). IR (KBr disks or thin film): Nicolet 205 FT 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 (75.4 MHz). HMQC, HMBC and NOESY: Varian VXR 500 spectrometer (500 MHz). NMR spectra were determined in [D_6]dimethyl sulfoxide and deuterium oxide, and chemical shifts were referenced and expressed in parts per million (δ) relative to the central peak of [D_6]dimethyl sulfoxide or deuterium oxide. ESI-MS:[9] VG-Quattro mass spectrometer (Micromass Instruments). EIMS: Hewlett−Packard HP-5988A. The pH was monitored with a CRISON micropH 2001 apparatus. TLC: Merck precoated 60 F_{254} silica gel plates. − Solvent systems: A: methanol/ammonium chloride 2 M/nitromethane (6:3:1); B: methanol/ammonium chloride 2 M/nitromethane (6:1:3); C: chloroform/methanol (1:1); D: chloroform/methanol (8:2); detection by UV light. Chromatography: Merck aluminum oxide 90 activity II−III (70−230 mesh ASTM). Ion-exchange resin[6] (I-E.R.): a column (0.5 inch diameter) was packed with ion exchanger III resin (OH^- form) up to a height of 5 inch. When a rotary evaporator was used, the bath temperature was 25 °C. In general, the compounds were dried overnight at 25 °C in a vacuum oven. Microanalyses were performed on a Carlo Erba 1106 analyzer.

Materials: Ethyl 2-(4-pyridyl)acetate (**11**) and ethyl 2-(3-pyridyl)acetate (**12**) were purchased from commercial sources. 3,5-Bis(chloromethyl)-1,2,4-triazole (**17**)[8] and 1-benzhydryl-3,5-bis(chloromethyl)-1,2,4-triazole (**18**)[7c] were prepared as described in the literature.

4-Amino-3,5-bis(4-pyridylmethyl)-4*H*-1,2,4-triazole (13) and 4-Amino-3,5-bis(3-pyridylmethyl)-4*H*-1,2,4-triazole (14): A stirred solution of ethyl pyridylacetates **11** or **12** (1.5 g, 9.1 mM) and hydrazine hydrate (0.9 mL, 18.2 mM) was maintained, under an atmosphere of nitrogen, at either 100 °C for 6 h and at 150 °C for 5 days for compound **13**, or at 100 °C for 6 h and at 140 °C for 8 days for compound **14**. During this period, 2 equivalents of hydrazine hydrate per day were added. The bath temperature was then raised to 165 °C, and the excess of hydrazine and water was distilled off over 2−3 h. The residue was triturated with dry acetone (3 × 5 mL) and dried to afford compounds **13** and **14** as solids (Table 4).

3,5-Bis(4-pyridylmethyl)-1*H*-1,2,4-triazole (15) and 3,5-Bis(3-pyridylmethyl)-1*H*-1,2,4-triazole (16): A solution of $NaNO_2$ (0.4 g, 5.8 mM) in H_2O (25 mL) was added dropwise to a cold solution of the *N*-amino-1,2,4-triazole **13** or **14** (1.0 g, 3.7 mM) and 3 N HCl (4.5 mL, 12.0 mM) in water (50-60 mL), while the temperature was maintained at 0 to 10 °C. The mixture was then allowed to warm to room temperature for 1 h. It was treated with Na_2CO_3 to pH 8 and the solvents were evaporated to dryness. In the case of compound **15**, the residue was extracted with hot dichloromethane (3 × 150 mL). The organic layers were dried (Na_2SO_4) and filtered, and the solvent was removed to afford pure **15** (Table 4). In the case of compound **16**, the residue was extracted with hot dichloromethane (3 × 100 mL). The organic layers were dried (Na_2SO_4) and filtered, and the solvent was removed to afford an oil, which was triturated with dry acetone (15 mL) to give a solid. This was filtered and washed in acetone (2 × 2 mL); recrystallization afforded pure **16** (Table 4).

Macrocycles 5·2Cl and 7·2Cl: A solution of 3,5-bis(chloromethyl)-1,2,4-triazole **17**[8] (260 mg, 1.6 mM) in dry acetonitrile (45 mL) was added dropwise to a stirred suspension of protophanes **15** or **16** (0.4 g, 1.6 mM) in dry acetonitrile (400 mL) at 25 °C, under an atmosphere of nitrogen. The mixture was then maintained in a bath at ca. 85 °C for the time specified in Table 4. The resulting suspension was filtered and the residue was washed with acetonitrile (3 × 20 mL) and dried to give pure macrocycles **5·2Cl** and **7·2Cl** (Table 4).

Macrocycles 6·2Cl and 8·2Cl: A solution of 3,5-bis(chloromethyl)-1,2,4-triazole **18**[7c] (0.4 g, 0.8 mM) in dry acetonitrile (5 mL) was added dropwise to a stirred suspension of protophanes **15** or **16**

Table 4. Physical data of compounds **5·2Cl**, **5·2CF$_3$CO$_2$**, **6·2Cl**, **7·2Cl**, **8·2Cl**, **9**, **10**, **13−16**, **20·2I**, and **21·2I**

Compd.	Yield (%)[a]	mp [°C] (solvent)[b]	Reaction time [h]	Molecular formula[c]
5·2Cl[d]	45	>300	48	$C_{18}H_{18}N_8Cl_2·4H_2O$
5·2CF$_3$CO$_2$[d]	82	267 (i)	1	[e]
6·2Cl[d]	13	>300	24	$C_{31}H_{28}N_8Cl_2·H_2O$
7·2Cl[d]	60	>300	24	$C_{18}H_{18}N_8Cl_2·3H_2O$
8·2Cl[d]	43	>300	24	$C_{31}H_{28}N_8Cl_2·5H_2O$
9[d]	80	>300	[f]	$C_{18}H_{16}N_8·3H_2O$
10[d]	84	>300 (ii)	[f]	$C_{18}H_{16}N_8·0.5H_2O$
13[g]	75	150−151 (iii)	[f]	$C_{14}H_{14}N_6$
14[g]	85	149−150 (iv)	[f]	$C_{14}H_{14}N_6$
15[g]	68	127−130	1	$C_{14}H_{13}N_5$
16[g]	84	66−67 (iii)	1	$C_{14}H_{13}N_5·H_2O$
20·2I[h]	85	[i]	24	[e]
21·2I[h]	70	[i]	24	[e]

[a] Yields not optimized. [b] Recrystallization solvent: (i) ethanol, (ii) 2-methyl-2,4-pentanediol, (iii) acetone, (iv) dichloromethane. [c] Satisfactory analytical data (±0.4% for C,H,N) were obtained for the new compounds. [d] TLC: silica gel plates, solvent system: 2-propanol/H_2O (4:1). [e] Not analyzed. [f] See Exp. Sect. [g] TLC: aluminium oxide plates, solvent system: chloroform/methanol (8:2). [h] R_f = 0 in different solvent systems. [i] Oil at 25 °C.

(0.2 g, 0.8 mM) in dry acetonitrile (60 mL), under an atmosphere of nitrogen. The mixture was then maintained in a bath at ca. 85 °C for 24 h. In the case of **6·2Cl**, the resulting suspension was filtered and the residue was purified by chromatography on an aluminium oxide column, with 2-propanol/water (4:1) as eluent, to afford **6·2Cl** (Table 4). In the case of **8·2Cl**, the resulting suspension was filtered and the crude solid was crushed with ethanol (20 mL), filtered, washed with ethanol (2 × 3 mL), and dried to give macrocycle **8·2Cl** (Table 4).

Macrocycle 5·2CF$_3$CO$_2$: A solution of macrocycle **8·2Cl** (0.15 g, 0.3 mM) and phenol (0.15 g) in trifluoroacetic acid (5 mL) was heated to reflux for 1 h. The reaction solvents were evaporated and the resulting oil was crushed with diethyl ether (3 × 10 mL), filtered, and dried to give macrocycle **5·2CF$_3$CO$_2$** (Table 4).

Bis-Betaines 9 and 10: A column packed with ion exchanger III (Merck) resin (chloride form) was converted into the hydroxide form. The resin (75 g) was washed in aqueous 10% NaOH (ca. 3 L) until it was free of halide ion ($AgNO_3$-HNO_3 test) and with water until the eluent was no longer alkaline (pH 7), and then stored in water. A column (0.5 inch diameter) was packed with ion exchanger III resin (OH^- form) up to a height of 5 inch and the column bed was equilibrated with the following eluents: H_2O (20 mL), 20% ethanol (20 mL), 60% ethanol (20 mL), 80% ethanol (20 mL), and 96% ethanol (20 mL). A solution of macrocycles **5·2CF$_3$CO$_2$** (100 mg) in ethanol/water (1:1) (50 mL) or **7·2Cl** (100 mg) in ethanol/water (1:1) (150 mL) was passed through the column. The neutral eluates were evaporated to dryness to give white solids of the corresponding inner salts **9** or **10** (Table 4).

1,1′-Dibutyl-3,3′-(1*H*-1,2,4-triazole-3,5-diyldimethyl)dipyridinium Diiodide (20·2I) and 1,1′-Dibutyl-4,4′-(1*H*-1,2,4-triazole-3,5-diyldicarbonyl)dipyridinium Diiodide (21·2I): Freshly distilled and degassed *n*-butyl iodide (0.54 mL, 4.8 mM) was added to a stirred suspension of protophanes **15** or **16** (0.1 g, 0.4 mM) in dry acetonitrile (40 mL), under an atmosphere of nitrogen, and the mixture was then maintained at ca. 85 °C in a bath for 24 h.

In the case of compound **20·2I**, the reaction solvents were evaporated, and the resulting yellow oil was washed with acetonitrile (3 × 4 mL), filtered and dried to afford **20·2I** (Table 4).

In the case of compound **21·2I**, the reaction solvents were evaporated, and the resulting slurry was crushed with ethyl acetate (20 mL) to afford a red hygroscopic solid, which was filtered and washed with ethyl acetate (2 × 1 mL) under argon atmosphere. The solid was determined by ^{1}H NMR ([D$_6$]DMSO, 200 MHz) to be a mixture (40:60) of 1,1′-dibutyl-4,4′-(1*H*-1,2,4-triazole-3,5-diyldimethyl)dipyridinium diiodide (**19·2I**) and 1,1′-dibutyl-4,4′-(1*H*-1,2,4-triazole-3,5-diyldicarbonyl)dipyridinium diiodide (**21·2I**). A solution of the mixture in dry acetonitrile (40 mL) was heated to 60 °C and dry oxygen was bubbled through for 6 h. The resulting solvents were evaporated to dryness to afford **21·2I** as a thick oil (Table 4). ^{1}H NMR (200 MHz, [D$_6$]DMSO) of **19·2I**: δ = 4.56 (s, 4 H; CH_2), 8.05 (d, J = 7.4 Hz, 2 H; 3′-,5′-H), 9.02 (d, J = 7.4 Hz, 2 H; 2′-,6′-H).

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