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Novel [1_n]-*meta*-Heterophane Frameworks with a Bis-Betaine Nature

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A convergent “5 + 1” and “5 + 3” synthetic strategy allowed the synthesis of the first examples of bis-betaines **2** and **3**, a prototype of phanes that incorporate heterocyclic betaines. The structure of the quadrupolar macrocyclic systems **2** and **3** together with the dicationic [1_6]- and [1_8] *meta*-heterophane precursors **5•2X** and **6•2X** were examined by spectroscopy using ^{1}H and ^{13}C NMR techniques together with ^{1}H-DNMR studies and electrospray ionization mass spectrometry.

Introduction

The molecular diversity of macrocycles permits the design of new molecules with specific physical or biological behavior.[2] Consequently, macrocyclic systems constitute a source of a broad array of molecules and shapes, but none of these systems are related to the macrocyclic bis-betaines **1**−**3**.[3,4] These novel macrocycles are built up from two betaine units and we first examined the quadrupolar [1_4]heterophanes **1** along with the dicationic precursors **4•2X**.[5] For macrocyclic dications **4•2X**, the “3 + 1” convergent synthesis leading to these key [1_4]-heterophanes entails joining a trinuclear protophane with 3,5-bis(chloromethyl)-1,2,4-triazole **7** and the macrocyclization proceeds in >40%.[5] We have recently reported that the “3 + 1” approach is template-controlled by the presence of chloride anions (e.g. TBA•Cl), and moreover, the halide anions, generated in situ during macrocyclization act as self-templates. Thus, the molecular recognition motifs for anion templation involve the interaction of a multicentered chloride ion with the heteroaromatic and aromatic moieties as hydrogen bond donors.[6]

We extend the investigation by considering cyclophanes with bigger cavities leading to the [1_6]- and [1_8]-*meta*-heterophanes **2** and **3**. The present study focuses on the synthesis and structural features of the macrocyclic bis-betaines **2** and **3** together with the key dicationic heterophanes **5•2X** and **6•2X** (see Figure 1).

Synthesis

Using the “5 + 1” and “5 + 3” convergent stepwise approach, the key dicationic macrocycles **5•2X** and **6•2X** were synthesized by coupling a pentanuclear protoheterophane **8** either with a bis-chloromethyl monomer **7**[7] or with the trinucleating protophanes **9** and **10**. However, the synthesis of the advanced protophanes intermediates was complex. Preparation of the open-chain systems **8b**,**c**, **9**, and **10** proceeded for the pentanuclear protophanes **8b**,**c** in seven steps (>35%), whereas the trinuclear systems **9** and **10** were obtained in six steps (29%).[8] For these macrocyclization reactions, the starting protophanes **7**−**9** were analytically pure, and their purity was checked by TLC. In contrast, the best yields were achieved for the “c” series probably due to the increased solubility of dications **5c•2Cl** and **6c•2Br** in organic solvents which improved isolation[9] together with the enhanced reactivity of the bis-bromomethyl protophane **10** instead of the bis-chloromethylanalogue **9**. We also attempted to prepare 3,5-bis(bromomethyl)-1,2,4-triazole.[8a]

As outlined in Scheme 1, dications **5•2X** and **6•2X** were formed in good yields for macrocyclization, e.g., 46% for **5c•2Cl** and 62% for **6c•2Br**. However, purification of these diquaternary macrocycles **5b,c•2X** and **6b,c•2X** was difficult[9a] (see Table 1 and the Experimental Section). The pure quaternary heteroaromatic salts are hard to isolate when the solubility of the ionic species in the

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(8) (a) Alcalde, E.; Ayala, C.; Dinarès, I.; Mesquida, N. *J. Org. Chem.* **2001**, *66*, 2291−2295. (b) The fact that the preparation of protophanes **8a**, **9a**, and dicationic [1_8]-*meta*-heterophane **5a** gave the lowest yields of these series is noteworthy.[8c] (c) Alcalde, E.; Gisbert, M. *Synlett* **1996**, 285−288.

(9) (a) bis-Betaines **2c**, **3c** and dications **6b•2Br** and **6c•2PF$_6$** gave satisfactory elemental analysis. However, the NMR spectra for all compounds lacking CHN analysis are gathered in the Supplementary Information. (b) Alcalde, E. *Adv. Heterocycl. Chem.* **1994**, *60*, 197−259.

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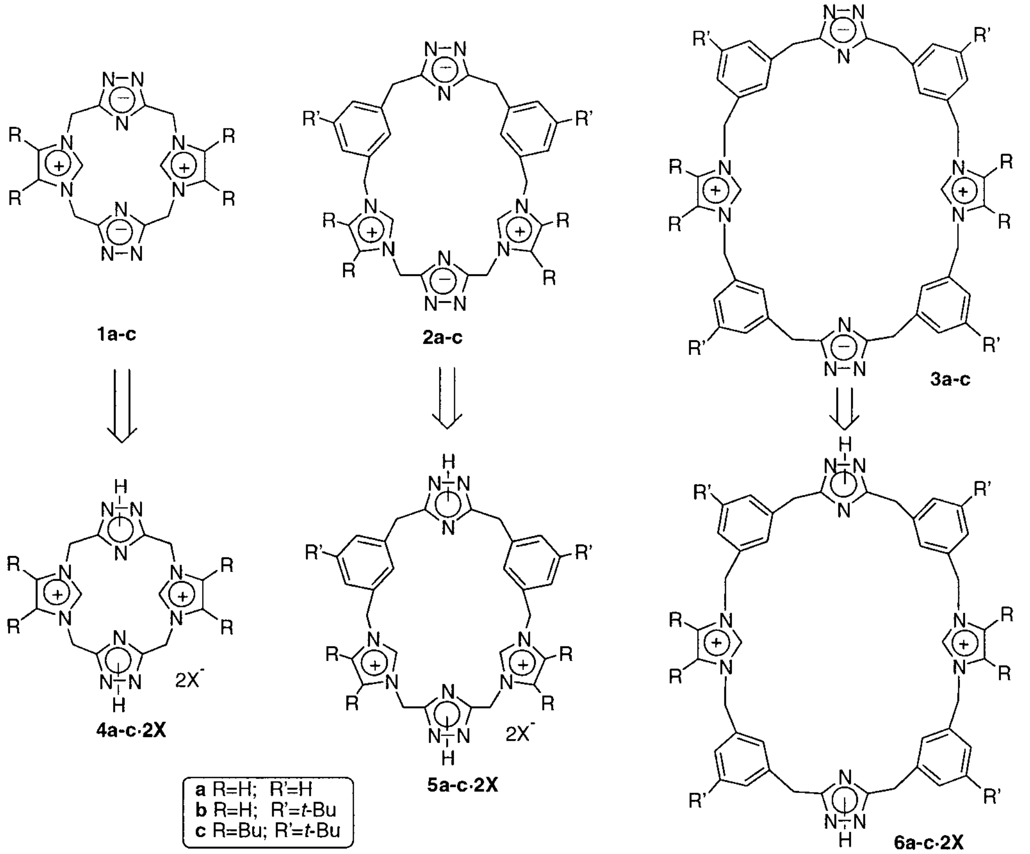

Figure 1.

Table 1. Physical Data of Compounds 2b,c, 3b,c, 5b,c•2X, 6b,c•2X, and 11b•Cl

compd	method	yield[a] (%)	mp (°C)
2b	B	74	218−219
2c[b]	B	95	120−121
3b	B	90	140−141
3c[b]	B	69	182−183
5b•2Cl	A−I; A-II	26	214−215
5b•2PF$_6$	C	98	>300
5c•2Cl	A-II	46	150−151
5c•2PF$_6$	C	98	c
6b•2Cl	A−I	39	176−177
6b•2Br[b]	A-III	52	d
6b•2PF$_6$	C	98	d
6c•2Br	A-III	62	162−163
6c•2PF$_6$[b]	C	88	168−169
11b•Cl	D	95	208−209

[a] Yields were not optimized. [b] Satisfactory analytical data (±0.4% for C, H, N) were obtained (ref 9b). [c] Hygroscopic compound. [d] At ~100 °C was transformed into a gummy material and the mp measurement was precluded.

reaction mixture is similar.[5b,9b,10] As for the "5 + 1" and "3 + 5" macrocyclizations, ^{1}H NMR analysis showed that dications **5b,c•2X** and **6b,c•2X** formed along with the *N*-protonated protophanes **8Hb,c•X** and **8H$_2$b,c•2X**; the similar solubility of the ionic species in the reaction mixture again made the purification of the macrocyclic dications difficult.

Dications **5b,c•2X** and **6b•2X** were transformed into the targeted bis-betaines **2b**,**c** and **3b**,**c**, although the apparent directness of the deprotonation does not imply that it is either simple or trivial. The inorganic counteranion and the acidic NH proton were removed by strongly basic anion-exchange resin (OH^- form). The macrocyclic betaine **11b•Cl** was isolated by acidification of bis-betaine **2b** in a controlled pH range, between 6 and 7, using HCl−H_2O. At pH ca. 3, bis-betaines **2** and **3** gave the corresponding dications **5•2X** and **6•2X**, e.g., **5b•2Cl**, and this is the best way to change the counteranions on these diquaternary imidazolium [1$_n$]heterophanes (see Scheme 2 and the Experimental Section). Physical data of all macrocycles are listed in Table 1.

The anion template effect in the "5 + 1" and "5 + 3" macrocyclizations of targeted dications **5b•2Cl** and **6b•2Cl** was also explored. Under standard reaction conditions with equimolecular amounts of the reagents at 5 mM in dry acetonitrile, the coupling of protophane **8b** with the bis-chloromethyl compound **7** or **9** gave the dications **5b•2Cl** or **6b•2Cl**, respectively (see Scheme 3).[11]

The ESI-MS and ^{1}H NMR analysis of the filtrates from macrocyclization showed that neither linear nor cyclic oligimeric products were detected, whereas in all assays the N-protonated protophanes **8Hb,c•X** and **8H$_2$b,c•2X** were formed. The optimal reaction time for the formation of the dications **5b,c•2X** and **6b,c•2X** was 48 h, after which time the yields were practically invariable. Macrocyclization stopped since unreactive N-protonated protophanes **8Hb,c•X** and **8H$_2$b,c•2X** were formed, and then the dicationic macrocycles were difficult to purify. When 5 molar equiv of tetrabutylammonium chloride was added to the "5 + 1" the macrocyclization, the yield decreased ca. 3%, and similar results were obtained for the "5 + 3" route.[12]

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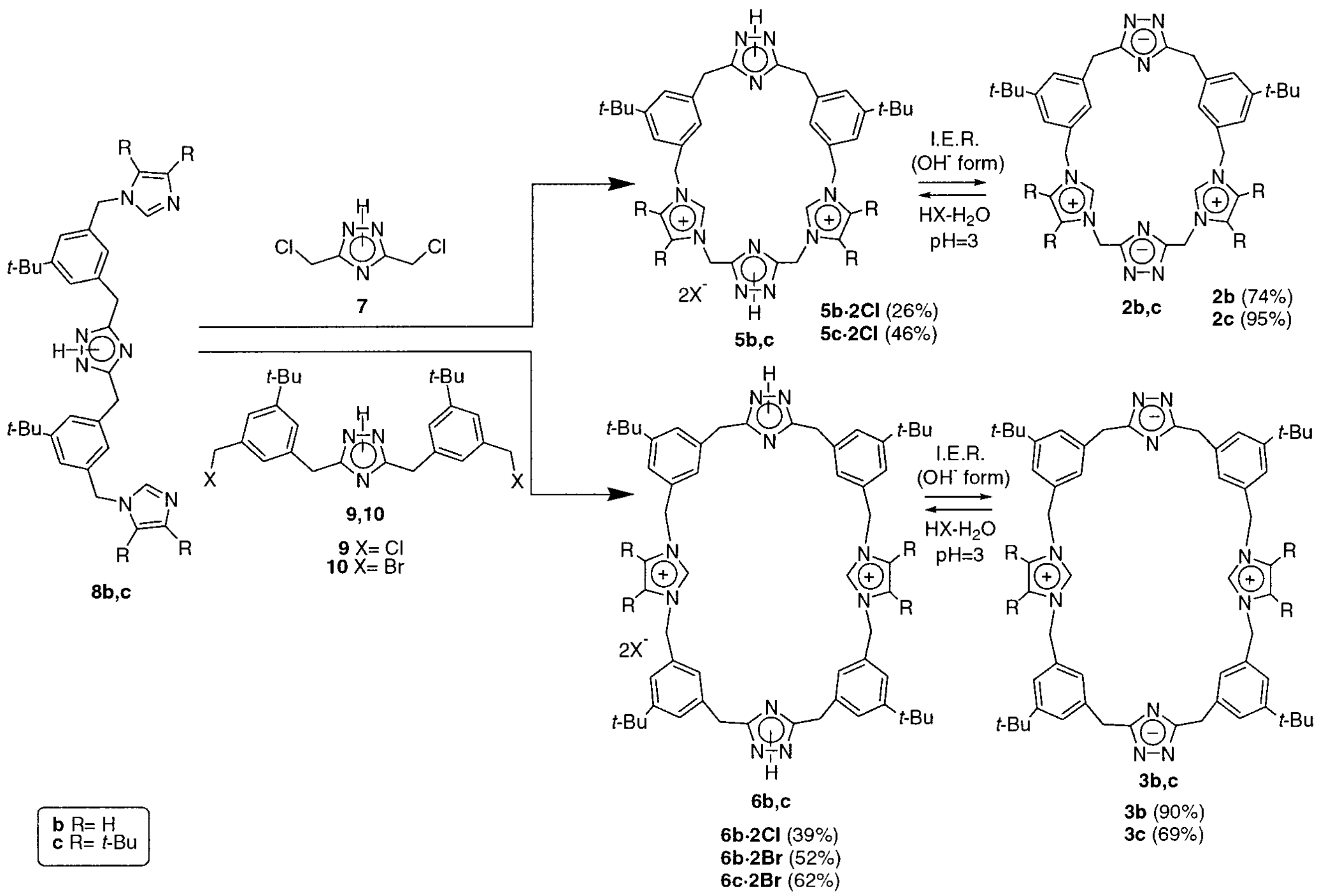
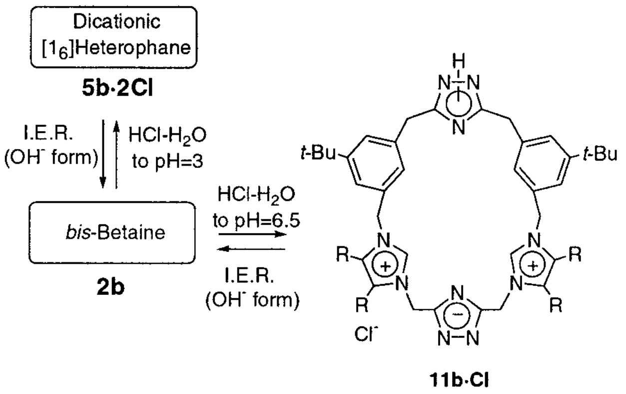
(11) The optimal initial concentration of the *pure* starting materials was also checked and it was found to be 5 mM.

Scheme 1



Scheme 2

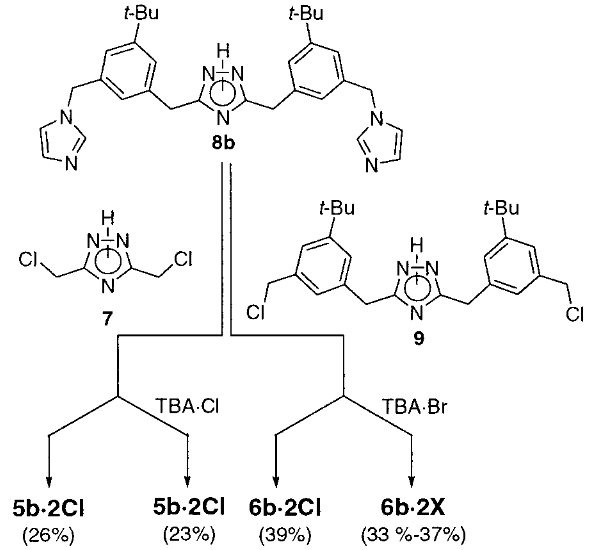


NMR Spectroscopy

The molecular structures of the new macrocycles were identified from spectroscopic data.[9a,13] The IR spectra (KBr) of dications **5•2X** and **6•2X** showed absorption in the range of 3200−3050 cm^{-1} (ν_{NH}) and 2800−2500 cm^{-1} for hydrochlorides or ca.1080 cm^{-1} (ν_{PF6}) for the hexafluorophosphates, while these absorption bands were not seen for the bis-betaines **2** and **3**.

In ^{1}H NMR spectra (298 K) of [1$_6$]heterophanes **2** and **5** the methylene proton atoms[14a] appeared as sharp singlets or broad lines depending on the macrocyclic structure and the solvent used (see below, ^{1}H DNMR). Comparison of the proton chemical shifts of bis-betaine **2b** with those of its precursor **5b•2X** reveals that the δH values of the methylene spacers at positions 7 and 12

Scheme 3



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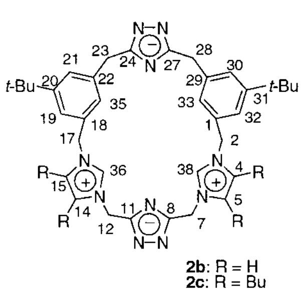
[12] (a) Addition of other anions (**TBA•X)** disfavours the formation of the dicationic [1$_6$]heterophane **5b•2X**, and lower yields resulted in the relative order **TBA•Cl** ≈ **TBA•Br** > **TBA•I** ≫ **TBA•PF$_6$**. (b) For dicationic [1$_8$]heterophane **6b•2X** similar results were observed: **TBA•Cl** ≈ **TBA•Br**.

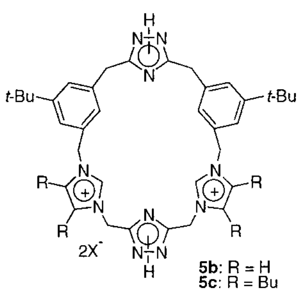
[13] Unfortunately, all efforts to grow single crystals of bis-betaines **2•b**−**c**, **3•b**−**c** and betaine **11•Cl** suitable for X-ray structure analysis failed.

[14] (a) For bis-betaines **1** and dications **4•2X** in solution, the ^{1}H NMR spectra gave a sharp singlet for the four methylene proton atoms, indicating the rapid interconversion of the different possible conformations.[5] (b) In general, the calix[8]arene framework mobility reveals that the *pleated loop* conformations are the more stable and there is a parallelism with the *cone* conformation for calix[4]arenes.[4]

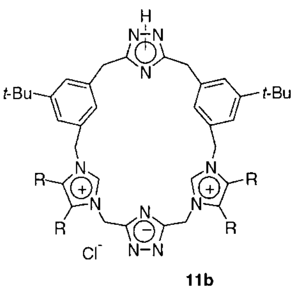
Table 2. Selected ^1H NMR Data of Bis-Betaines 2b,c and Dicationic [1_6]Heterophanes 5b,c•2X and Betaine 11b•Cl[a]



2b: R = H
2c: R = Bu



5b: R = H
5c: R = Bu



11b

Compd	Solvent	CH_2-2	CH_2-7	CH_2-23	H-4	H-5	H-33	H-36
2b	D_2O	5.09	5.16	3.77	7.22	7.16	6.84	*b*
5b·2Cl	D_2O	5.14	5.32	3.86	7.27	7.27	6.86	8.68
11b·Cl	D_2O	5.11	5.18	3.83	7.22	7.16	6.84	*b*
$\Delta\delta^c$		-0.05	-0.16	-0.09	-0.05	-0.11	-0.02	—
$\Delta\delta^d$		-0.03	-0.14	-0.03	-0.05	-0.11	-0.02	—
5b·2PF6	D_2O	5.14	5.36	3.91	7.28	7.28	6.88	8.65
2b[e]	CD_3OD	5.40	5.45	4.05	7.68	7.61	7.18	*b*
5b·2Cl	CD_3OD	5.49	5.69	4.13	7.80	7.80	7.21	9.27
11b·Cl	CD_3OD	5.45	5.46	4.11	7.70	7.63	7.18	*b*
$\Delta\delta^c$		-0.09	-0.24	-0.08	-0.12	-0.19	-0.03	—
$\Delta\delta^d$		-0.04	-0.23	-0.02	-0.10	-0.17	-0.03	—
5b·2PF6	CD_3OD	5.48	5.69	4.13	7.78	7.78	7.21	9.28
5b·2Cl	CD_3OD/TFA[f]	5.56	5.74	4.44	7.82	7.82	7.43	9.47
2b	DMSO-d_6	5.32	5.32	3.89	7.75	7.68	7.08	9.28
5b·2Cl	DMSO-d_6	5.38	5.53	3.93	7.77	7.77	7.14	9.41
$\Delta\delta^c$		-0.06	-0.21	-0.04	-0.03	-0.09	-0.06	-0.13
2b	$CDCl_3$	5.28	5.39	4.05	7.49	7.41	7.11	9.94
2c	$CDCl_3$	5.03	5.26	3.98	—	—	7.02	9.52
5c·2Cl	$CDCl_3$	5.31	5.83	4.35	—	—	7.25	9.88
$\Delta\delta^c$		-0.28	-0.57	-0.37	—	—	-0.23	-0.36
2c	CD_3OD	5.38	5.41	4.10	—	—	7.13	*b*
5c·2PF6	CD_3OD	5.47	5.68	4.23	—	—	7.20	9.25
$\Delta\delta^c$		-0.09	-0.27	-0.13	—	—	-0.7	—

[a] The equivalent proton atoms are abbreviated, i.e., CH_2-2 = CH_2-2,17. [b] Signal not observed due to H/D exchange. [c] $\Delta\delta$: differences in the chemical shifts of bis-betaines **2b**,**c** and the dicationic precursors **5b**,**c•2Cl** ($\delta H_{\text{bis-betaine}} - \delta H_{\text{dication}}$). [d] $\Delta\delta$: differences in the chemical shifts of betaine **11b•Cl** and the dication **5b•2Cl** ($\delta H_{\text{betaine}} - \delta H_{\text{dication}}$). [e] Unambiguous assignments were made by NOESY (see Figure 4). [f] CD_3OD with 10% TFA.

and those of δH-4(15) and δH-5(14) [Im^+] are the most affected; moving to lower frequencies ($\Delta\delta$ in CD_3OD or DMSO-d_6, see Table 2).[15] It was also possible to record the spectra of **2c** and **5c** in $CDCl_3$ because of their solubility in less polar solvents and the shielding effect ($\Delta\delta$H) was indeed pronounced in all the selected positions listed in Table 2. This indicates the presence of strong intermolecular interactions.

In dication **5b•2Cl**, betaine **11b•Cl** and bis-betaine **2b** the methylene protons moved upfield (Figure 2 and Table 2), especially the 1,2,4-triazole spacers flanked by the two quaternary imidazolium rings. Thus, the differences in CD_3OD between bis-betaine **2b** and dication **5b•2Cl** were $\Delta\delta$ CH_2-7,12=−0.24 ppm, and a comparable shielding effect was found for the dipolar macrocycle **11b•Cl** ($\Delta\delta$ CH_2-7,12=−0.23 ppm, see Figure 2). Consequently, the

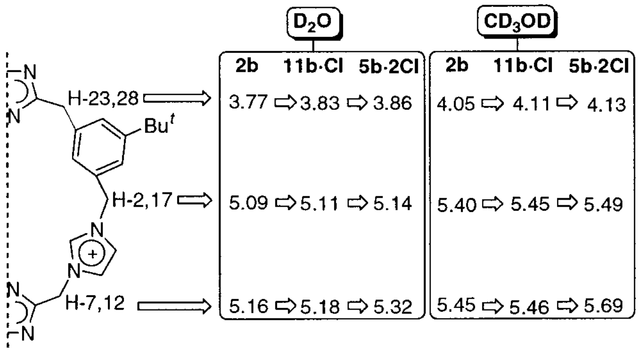
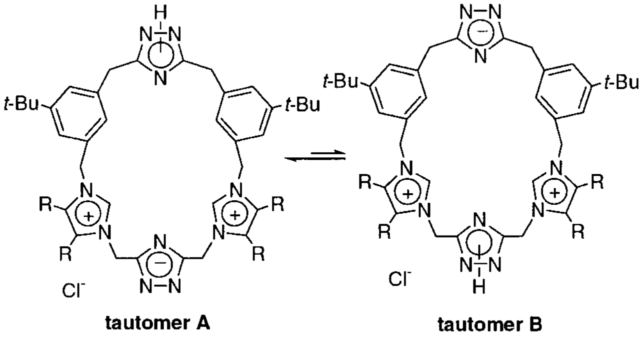


Figure 2. Bis-betaine **2b**, betaine **11b•Cl**, and macrocyclic dication **5b•2Cl**. ^{1}H NMR chemical shift (ppm, D_2O, and CD_3OD) of the methylene bridging proton atoms.

favored tautomer of betaine **11b•Cl** may have the 1,2,4-triazolate ring between the CH_2-7,12 linkers.[13]

The dipolar structure **11b•Cl** should be represented as tautomer A or tautomer B because of the prototropic annular tautomerism (eq 1). This betaine illustrates an unusual case of anion tautomerism:[16a] the *NH* proton migrates between both 1,2,4-triazole rings within the molecule and then only average ^{1}H NMR signals are observed. Moreover, the acidity and basicity of 1,2,4-triazoles,[16b] e.g., triazolocrown ethers,[3,7] have to be taken into account. Comparison of the proton chemical shifts of the compound pair **2b** and **5b•2Cl** with those for betaine **11b•Cl** shows that the δH values of the bridging protons are not average signals for the spacers at position 7 and 12 (see Figure 2). The shielding effect of both betaine **11b•Cl** and the bis-betaine **2b** are similar, and tautomer A should be then favored.[13,16b] Unfortunately, no pK_a values from the macrocyclic set **1**−**6** are available.

Betaine **11b·Cl**: Prototropic Annular of Anion Tautomerism

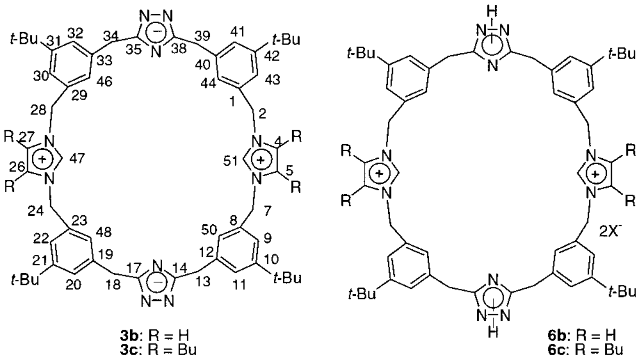


tautomer A **tautomer B**

(eq 1)

In the ^{1}H NMR spectra of [1_8]heterophane pairs **3** and **6•2X**, the shielded effect was especially observed for the methylene spacer within "series c" (Table 3). These differences were $\Delta\delta$ CH_2-2,7,24,28= −0.16 ppm and $\Delta\delta$ CH_2-13,18,34,39=-0.13 ppm in CD_3OD.

Table 3. Selected ^{1}H NMR Data of Bis-Betaines 3b,c and Dicationic [1_8]Heterophanes 6b,c•2X[a]



3b: R = H
3c: R = Bu

6b: R = H
6c: R = Bu

Compd	Solvent	CH_2-2	CH_2-13	H-4	H-44	H-47
3b[b]	CD_3OD	5.38	4.05	7.64	7.12	*c*
6b·2Cl[b]	CD_3OD	5.45	4.13[d]	7.71	7.18	9.20
$\Delta\delta$[e]		-0.07	-0.08	-0.07	-0.06	—
6b·2Br	CD_3OD	5.46	4.17	7.70	7.17	9.20
6b·2PF$_6$	CD_3OD	5.45	4.13	7.71	7.25	8.92
3b	DMSO-d_6	5.33	3.93	7.71	6.76	9.27
6b·2Cl	DMSO-d_6	5.36	3.93[f]	7.81	7.08	9.47
$\Delta\delta$[e]		-0.03	0.0	-0.10	-0.32	—
3c	CD_3OD	5.37	4.06	—	7.02	*c*
6c·2PF$_6$	CD_3OD	5.53	4.19	—	7.05	9.36
$\Delta\delta$[e]		-0.16	-0.13	—	-0.03	—
6c·2Br	$CDCl_3$	5.43	4.19	—	7.15	9.91

[a] The equivalent proton atoms are abbreviated, i.e., CH_2-2= CH_2-2,7,24,28. [b] Unambiguous assignments were made by NOE-SY. [c] Signal not observed. [d] Broad signal. [e] $\Delta\delta$: differences in the chemical shifts of bis-betaines **3b,c** and the dicationic precursors **6b,c•2X** ($\delta H_{\text{bis-betaine}} - \delta H_{\text{dication}}$). [f] At concentration 17 mM (see Figure 5).

The overall ^{1}H NMR parameters at 298 K, therefore, provide evidence of charge distribution within the quadrupolar heterophanes **2** and **3**. Their bis-betaine nature is reflected in the shielding effect of the proton atoms (Figure 3). The proton signals of bis-betaine **2c** were shifted further upfield in the less polar solvent (e.g., $CDCl_3$, see Table 3). The CH protons of the benzene rings showed that the line shapes of the signals corresponded to the expected splitting patterns (see below, ^{1}H DNMR). When the counteranions on dications **5•2X** and **6•2X** were changed, the δCH protons of the imidazolium molecular motifs were shifted downfield in dications **6•2X**, while they were unchanged in dications **5•2X** (see Tables 2 and 3). Hydrogen bond driven anion interactions by the dicatonic [1_8]heterophane framework may be due to the favored pleated looplike conformations.[14b] For the acidic H-47 and H-51 protons of dication **6b•2X**, a deshielding effect of 0.28 ppm was observed in CD_3OD, and the tendency to solvation was partly overcome (see later and Figure 3).

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(15) (a) The macrocyclic [1_n]heterophanes discussed in this paper are identified in abbreviated fashion as bis-betaines (**2** and **3**), betaines (**11b•Cl**), and macrocyclic dications (**5b,c•2X** and **6b,c•2X**),[15b, c] whereas the atom numbering scheme follows the *Chemical Abstracts* numbering system. (b) The nomenclature of cyclophanes and phanes has been simplified and the IUPAC rules are generally avoided[15c] as well as for other molecular systems.[15d] (c) Vögtle, F. *Cyclophane Chemistry*; John Wiley & Sons: Chichester, 1993. (d) Kisakürek, M. V. *Organic Chemistry: Its Language and Its State of the Art*; Verlag Helvetica Chimica Acta: Basel, 1993.

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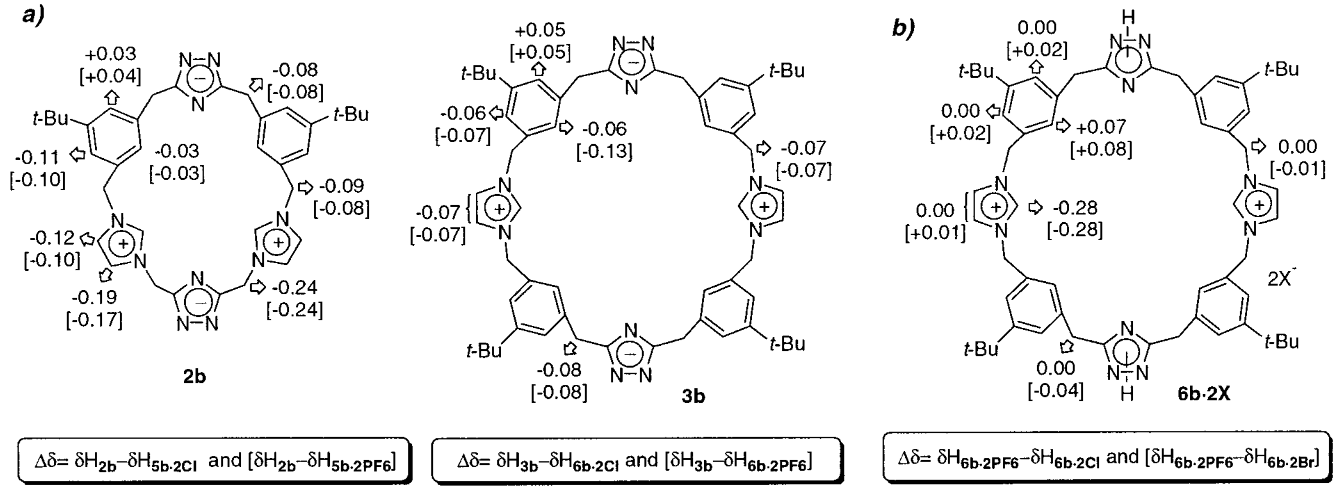

Figure 3. Selected ^{1}H NMR (200 MHz, CD_3OD) chemical shift differences (ΔδH, ppm) between (a) bis-betaines **2b**, **3b** and the corresponding dicationic macrocycles **5b•2Cl** [**5b•2PF$_6$**], **6b•2Cl** [**6b•2PF$_6$**] and (b) dications **6b•2PF$_6$** and **6b•2Cl** [**6b•2Br**].

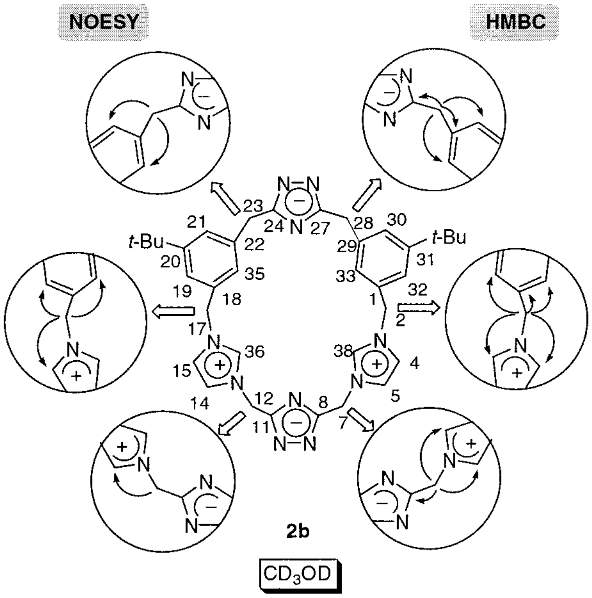

Figure 4. Key NMR responses for bis-betaine **2b**.

Selected ^{13}C NMR chemical shifts for macrocycles **2**, **3**, and **5•2X**, **6•2X** are listed in Table 4. The δC values of the carbon atoms are consistent with data for correlative systems,[5] e.g., [1$_4$]heterophanes **1** and **4•2X** together with their the betainic building blocks.[9b,10] If necessary, individual assignments were made using NMR experiments (ROESY, HMQC, HMBC), except for the NH protons, and key NMR responses for bis-betaine **2b** in CD_3OD are shown in Figure 4.

The propensity to self-aggregation of these multipolar systems (e.g., bis-betaines **1** and dications **4•2X**)[17a,b] is a limitation to the ^{1}H and ^{13}C NMR studies, since the betaine building block presents strong intermolecular forces, mainly due to self-association and hydration.[9b,10] The solubility,[18a] propensity to hydration and solvation,[18b] and aggregation of macrocycles of "series b" were examined by qualitative interpretation of the ^{1}H NMR data at 298 K. The proton chemical shifts were dependent on concentration only for the dication **6b•2Cl** in CD_3OD and DMSO-d_6 (see Figure 5 and Experimental Section). Curiously, a slight modification of their molecular shapes alters their solution aggregation behavior. As the concentration changed from 2.0 to 37.9 mM, the^{1}H NMR (200 Mz) spectra of **6b•2Cl** in CD_3OD showed that the δH-44,46,48,50, δH-47,51, and δCH_2-13,18,34,39 were deshielded 0.13 and 0.19 ppm, respectively.

The chemical shifts in DMSO-d_6 of the bridging proton atoms at positions 13,18,34,39 remained unchanged, whereas signal varied from a broad band to two fairly resolved peaks, as shown in Figure 5. Dication **6b•2Cl** was also studied by dynamic ^{1}H NMR[19a] (see later, Figure 6).

Dynamic ^{1}H NMR Study

Macrocyclic systems show a variety of conformations, for example, [1$_n$]calixarenes whose structural and dynamic features have been extensively investigated in solution and solid state.[4] Among the new compounds reported, dications **6b•2Cl**, **6b•2Br** in CD_3OD, and **6c•2Br**, **6c•2PF$_6$** together with protophane **8b** in acetone-d_6 revealed line broadening at 298 K, and ^{1}H NMR spectral measurements were carried out at the temperatures ranging from 300 to 200 K.[19] Dynamic ^{1}H NMR studies with bis-betaines **2** and **3** were precluded due to either the low solubility in low melting point solvents of series "a" and "b" or the absence of line broadening for

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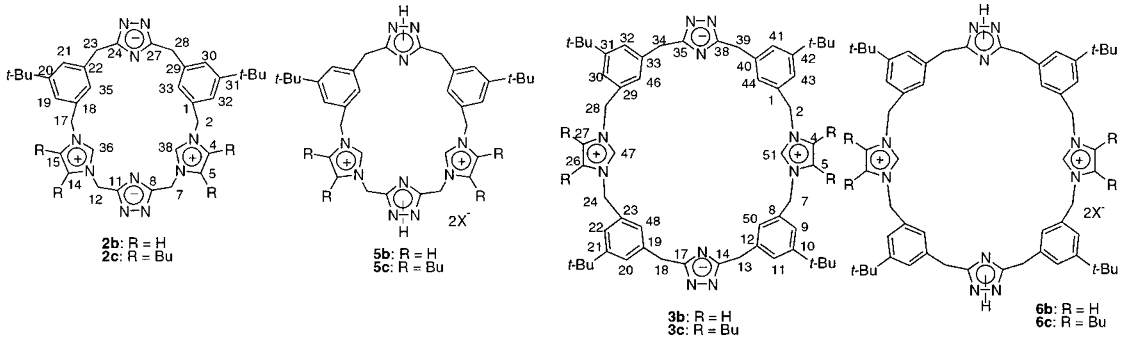
(17) (a) Bis-betaines **1a**,**c** and dications **4a**,**c•2X** could not be analyzed by ^{1}H NMR data because they are insoluble in organic solvents.[5, 17b] In the gas phase, their associative behavior was studied by electrospray ionization mass spectrometry[1] and the formation of stable nonconvalent polymolecular self-assembled structures was observed, e.g., at a cone voltage of 100V, *bis*-betaine **1c** generated the self-assembled species $[2M + H]^+$ (50%) and $[3M + 2H]^+$ (2%), (see Table 5 and the Supporting Information). (b) The ^{1}H NMR spectra in D_2O of bis-betaines **1** reveal a shielding effect for the δCH and δCH_2 proton atoms ($\Delta\delta CH_2$ ca. -0.24 ppm).[5] This is the first time that the tendency for hydration has been overcome, in contrast to the corresponding betainic building blocks.[9b, 10]

(18) (a) The macrocycles of "series b" were all soluble in methanol and in DMSO, at concentrations ranging from 5 to 68 mM. The following compounds were fairly soluble in the solvents shown in parentheses: **5b•2Cl**, **5b•2PF$_6$**, **11b•Cl** (water); **2b** (acetonitrile); **2b** and **3b** (chloroform). (b) From the ^{1}H NMR data in Tables 2 and 3, there was still a shielding effect of several protons within the macrocyclic frameworks **2** and **3**, but less pronounced than in the above-mentioned bis-betaines **1**.[5,17b]

(19) (a) Using a Bruker ARX 400 spectrometer in nonaggregating concentration conditions. (b) At a concentration of 6.5 mM. (c) The energy-minimized conformations were calculated by AM1 (MOPAC included in the package Insight II, 97.0).

Table 4. Selected ^{13}C NMR Data of Bis-Betaines 2b,c, 3b,c, and Dicationic [1_n]Heterophanes 5b,c•2X and 6b,c•2X



2b: R = H
2c: R = Bu

5b: R = H
5c: R = Bu

3b: R = H
3c: R = Bu

6b: R = H
6c: R = Bu

Compd[a]	Solvent	C-4	C-5	C-8	C-22	C-24	C-33	C-36	C-2	C-7	C-23
2b[b]	CD_3OD	124.1	124.0	158.1	140.0	161.2	127.6	*c*	54.5	47.8	34.5
5b·2Cl	CD_3OD	124.1	124.0	156.3	137.3	160.0	128.1	*c*	54.4	46.5	35.8
11b·Cl	CD_3OD	123.9	123.9	158.0	139.1	160.6	128.1	*c*	54.4	47.8	35.7
$\Delta\delta$[d]		0	0	+1.8	+2.7	+1.2	-0.5	—	+0.1	+1.3	-0.7
$\Delta\delta$[e]		-0.2	-0.1	+1.7	+1.8	+0.6	0	—	0	+1.3	-0.1
5b·2Cl	CD_3OD[f]	124.1	124.6	156.0	137.8	160.1	127.7	*c*	59.6	54.4	46.5
2c	CD_3OD	133.5	133.0	158.1	140.0	160.8	127.0	*c*	59.8	52.0	45.9
5c·2PF$_6$	CD_3OD	133.4	133.1	156.1	138.4	159.2	126.9	135.2	59.8	52.0	44.1
$\Delta\delta$[d]		+0.1	-0.1	+2.0	+1.6	+1.6	+0.1	—	0	0	+1.8
5c·2Cl	$CDCl_3$	131.9	131.0	153.3	134.9	153.6	126.5	136.7	58.9	51.4	42.1

Compd[g]	Solvent	C-4	C-8	C-12	C-14	C-44	C-47		C-2	C-13
3b[b]	CD_3OD	124.8	135.4	142.5	162.6	128.0	*c*		55.4	35.9
6b·2Cl[b]	CD_3OD	123.9	138.1	135.7	*c*	127.4	137.5		53.8	33.7
$\Delta\delta$[d]		+0.9	-2.7	+6.8	—	+0.6	—		+1.6	+2.2
3c	CD_3OD	133.9	134.1	141.8	161.8	126.6	*c*		52.2	34.9
6c·2PF6	CD_3OD	133.3	139.0	139.0	*c*	126.8	137.7		51.9	33.6
$\Delta\delta$[d]		+0.6	-4.9	+2.8	—	-0.2	—		+0.3	+1.3

[a] The equivalent carbon atoms are abbreviated, i.e., C-4 = C-4,15. [b] Assignation of signals by HMBC and HMQC. [c] No signal observed. [d] $\Delta\delta$: differences in the chemical shifts of bis-betaines **2b**,**c** and **3b**,**c** and the dicationic precursors **5b,c•2X** and **6b,c•2X** ($\delta H_{\text{bis-betaine}} - \delta H_{\text{dication}}$). [e] $\Delta\delta$: differences in chemical shifts of betaine **11b•Cl** and dication **5b•2Cl** ($\delta H_{\text{betaine}}$ - $\delta H_{\text{dication}}$). [f] CD_3OD with 10% TFA. [g] The equivalent carbon atoms are abbreviated, i.e., C-4 = C-4,5,26,27.

series “c”. Moreover, the instability of macrocycles of “series c” precluded recording clean ^{1}H NMR spectra since products of alteration appeared along with the broad signals of the corresponding dications at 200 K. There was no variation in the ^{1}H NMR spectral pattern of protophane **8b** throughout the temperature range.

For the dicationic macrocycle **6b•2Cl**, the proton DNMR study in CD_3OD[19b] was performed at 400 MHz (300−200 K, see Figure 6). For dication **6b•2Br**, the conformational mobility increased and still showed unresolved broad bands at 200 K. Accordingly, chloride anions can suppress the macrocyclic ring motions of dication **6b•2X** through intermolecular interactions mainly driven by hydrogen bonds.

Upon cooling, the signal due to the imidazolium protons H-4(26) and H-5(27) at $\delta = 7.70$ ppm remained as a singlet, although somewhat broader, while the band of the methylene protons H-2(7,24,28) at $\delta = 5.45$ ppm broadened considerably (Figure 6).

The methylene protons H-13(18,34,39) appeared as a very broad singlet around $\delta = 4.15$ ppm at 300 K and gave rise at 200−240 K to two well-resolved singlets at 4.07 and 4.19 ppm. These two signals may belong to two different methylene bridging pairs or to the H_A and H_B proton atoms of each methylene. In the last case, it may be an AB system, with a geminal J_{AB}. Unfortunately, further cooling to resolve this was impossible. As mentioned above, the conformations of flexible calix[*n*]arenes in solution have been studied in detail,[4a,b] and Gutsche et al. have recently reported a comparative conformational study of *p-tert*-calix[4−16]arenes[4c] showing that the $ArCH_2Ar$ protons from 20 to −55 °C for *p-tert*-butylcalix[8]arene in $CDCl_3$ appear as a well-resolved AB system.

The greatest changes were observed for the benzene ring protons H-9, H-11, and H-44. At 300 K, protons H-44 appeared as a singlet at 7.17 ppm, while the remaining benzene protons H-9/H-11 appeared as an ill-resolved multiplet at 7.43−7.45 ppm. Upon cooling, both signals

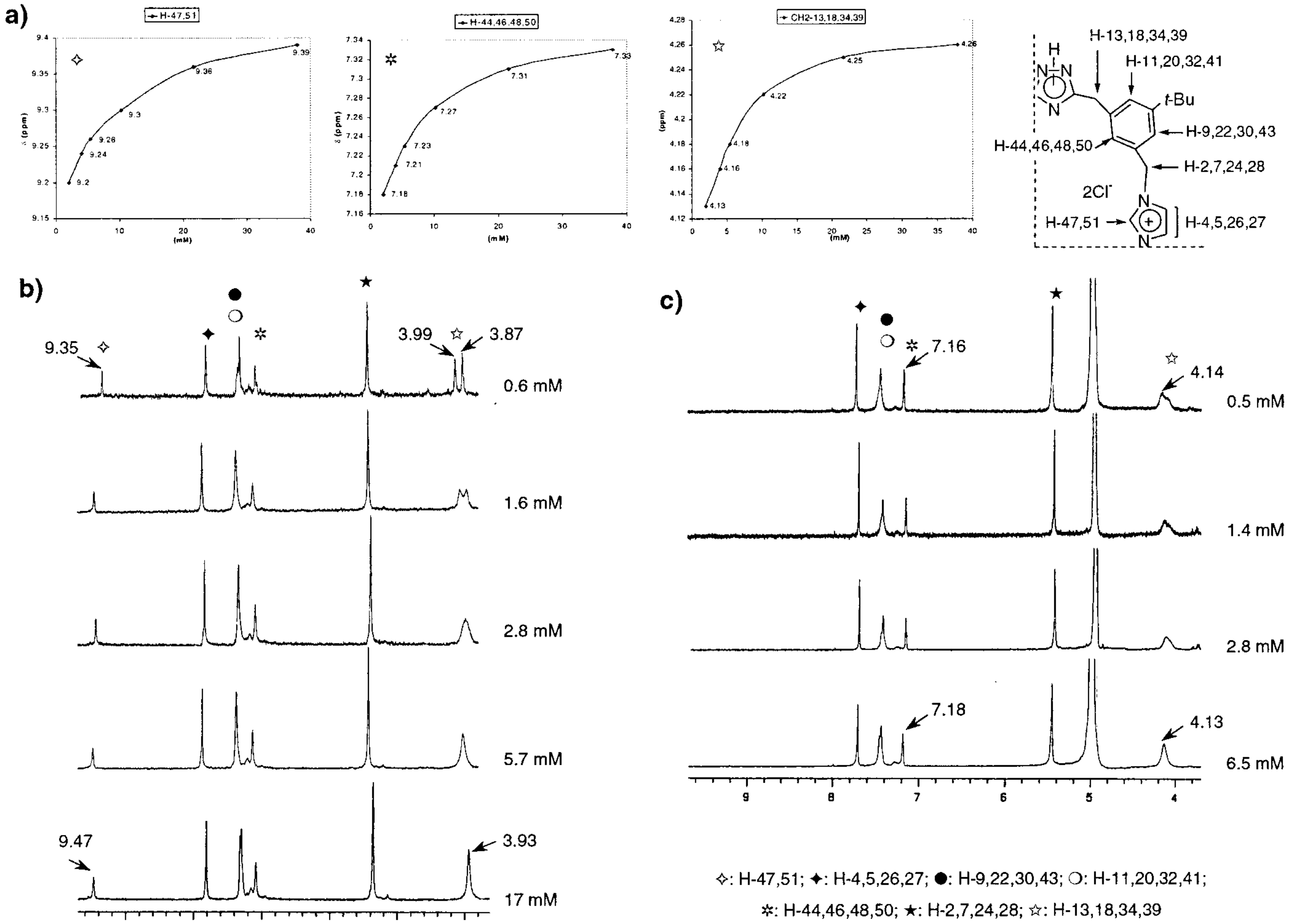


Figure 5. Concentration dependence of ^{1}H NMR chemical shifts of **6b•2Cl** at 298 K (a) for imidazolium H-47,51, aromatic H-44,46,48,50, and methylene spacer H-13,18,34,39 proton atoms in CD_3OD at 200 MHz; (b) in DMSO-d_6 at 300 MHz; and (c) nonaggregating concentrations in CD_3OD at 300 MHz.

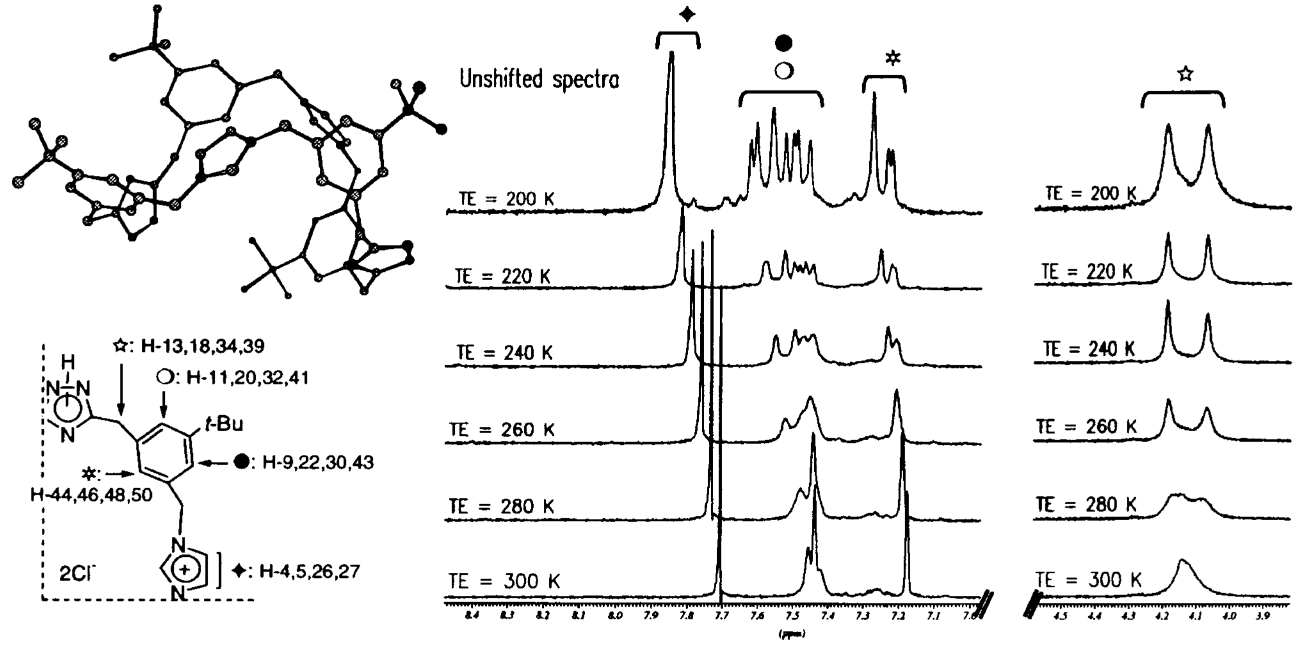


Figure 6. Partial ^{1}H DNMR spectra of **6b•2Cl** (6.5 mM) in CD_3OD.

began to broaden and resolve into additional signals. At 200 K, the eight protons of types H-41/H-43 gave rise to seven signals (one of them of double intensity) between 7.45 and 7.62 ppm. Analogously, the four protons of type H-44 appeared at 200 K as three signals (one of them of double intensity) between 7.22 and 7.27 ppm. Accord-

Table 5. Summary of Data Obtained from Positive-Ion ESI-MS of 2b,c, 3b,c, 5b,c•2X, and 6b,c•2X[a]

		ions, *m/z* ratio relative abundance (%)				ions, *m/z* ratio relative abundance (%)	
V$_c$ (V)	compd (mol wt)	MH_2]$^{2+}$	MH]$^+$	MH+2CH_3CN]$^+$	compd (mol wt)	MH_2]$^{2+}$	MH]$^+$
	1a[b] (322.2)	162.2	323.3		**4a•2PF$_6$**[b] (614.3)	162.2	323.3
50		100	14			100	10
100		36	100			100	55
	2b (614.8)	308.4	615.8		**2c** (839.2)	420.6	840.3
55		8	100			100	92
120		c	100			80	100
	5b•2Cl (687.7)	308.4	615.8		**5c•2PF$_6$** (1131.2)	420.6	840.3
55		17	100			100	8
120		1	100			100	11
	3b (907.3)	454.7	908.3	990.4	**3c**[e] (1131.7)	566.9	1132.7
55		100	1	30		100	c
120		100	2	12		100	c
	6b•2Cl[d,e] (980.2)	454.7	908.3	990.4	**6c•2PF$_6$**[e] (1423.6)	566.9	1132.7
55		100	c	3		100	2
120		100	2	7		100	5
	6b•2Br[e,f] (1069.1)	454.7	908.3	990.4	**6c•2Br**[e] (1293.5)	566.9	1132.7
55		100	1	8		100	c
120		100	8	42		100	c

[a] Molecular weight and ion *m/z* values apply to the lowest mass component of any isotope distribution and are based on a scale in which $^{12}C = 12.000$. [b] $[2M + H]^+$ at *m/z* 645.7: **1a** 50 V (2%), 100 V (32%) and **4a•2PF$_6$** 50V (<1%), 100 V (8%); see ref 1. [c] No signal observed. [d] $[MH_2 + Cl]^+$ at *m/z* 943.8 (~5%). [e] Fragment ion at *m/z* 386.6: **3b** 55 V (1%), 120 V (2%); **6b•2Cl** 55 V (2%), 120 V (2%); **6b•2Br** 55 V (4%), 120 V (28%); **3c** 55 V (72%), 120 V (53%); **6c•2PF$_6$** 55 V (98%), 120 V (65%) and **6c•2Br** 55 V (58%), 120 V (45%). [f] $[MH_2 + Br]^+$ at *m/z* 988.2 and 990.2: at 55 V (5%) and at 120 V (28%).

ingly, the conformation of **6b•2Cl** at 200 K does not have any symmetry and a plausible conformation of the macrocyclic framework is depicted in Figure 6. The computer-generated structure[19c] adopted a pleated loop-like conformation; the hydrogen atoms together with the chloride anions have been omitted for clarity. Dication **6b•2Cl** may adopt a pleated loop-like conformation, and the nonsymmetrical conformation shown in Figure 6 may describe the ^1H DNMR results.

Electrospay Mass Spectrometry Analysis

ESI-MS is the method of choice for the characterization of tetracationic catenanes[20] together with a variety of multicationic systems.[2]

We used electrospray ionization to examine macrocyclic bis-betaines **1a**,**c** and dications **4a**,**c•2X** in the gas phase.[1] All produced clean positive-ion ESI mass spectra at a cone voltage of 50V; the same major peaks were formed and the base peak in each case corresponded to the doubly charged ion $[MH_2]^{2+}$, irrespective of the structural pattern of the π-rich heteroaromatic rings *s*-triazolate or *s*-triazole. Moreover, at a cone voltage of 100V, bis-betaines **1a**,**c** generated the self-assembled species $[2M + H]^+$ with a relative abundance of ≤50%, although the base peak was the singly charged ion $[MH]^+$.[17a]

Positive-ion ESI-MS were performed following the same experimental protocol as for macrocyclic compound pair **1** and **4•2X**.[1] Samples were dissolved in a 1:1 mixture of H_2O/CH_3CN at 250 pmol μL^{-1}, and the cone voltage was varied between 55 and 120 V. The positive-ion ESI response of bis-betaines **2**, **3**, and the dicationic heterophanes **5•2X**, **6•2X** within "series b and c" gave the two common characteristic doubly charged and single charged species $[MH_2]^{2+}$ and $[MH]^+$, along with several peaks due to molecular fragmentation, especially in heterophanes "c" (see the Supporting Information).

Both [1$_4$]heterophanes[1] and [1$_6$]heterophanes of "series b" gave clean ESI spectra (see Table 5 and the Supporting Information). In contrast, [1$_8$]heterophanes produced a variety of peaks arising from the fragmentation of the molecular species, although the base peak was the doubly charged ions $[MH_2]^{2+}$. Moreover, [1$_8$]heterophane pair **3b** and **6b•2X** generated the singly charged $[MH + 2CH_3CN]^+$ resulting from the association of $[MH]^+$ with two solvent molecules.

Conclusions

"5 + 1" and "5 + 3" synthetic strategy allowed an entrance to the unconventional cyclophanes **3** and **4**, illustrating the first examples of [1$_6$]- and [1$_8$]-*meta*-heterophanes containing both highly π-rich and highly π-deficient heteroaromatic moieties: two 1,2,4-triazolate and two imidazolium rings. The ^1H NMR studies provided evidence of charge distribution in the novel macrocycles with a bis-betaine nature. The title heterophanes underwent proton-mediated ion−molecule reactions in the gas phase. Further studies are now pursuing the use of the betainic building blocks for the construction of supramolecular scaffolds by passing from quadrupolar to multipolar systems.

Experimental Section

General Methods. Melting point: CTP-MP 300 hot-plate apparatus with ASTM 2C thermometer (given in Table 1). IR (NaCl or KBr disks): Nicolet 205 FT spectrophotometer. ^1H NMR: Varian Gemini 200 and Varian Gemini 300 spectrometers (200 and 300 MHz) at 298 K. Chemical shifts were referenced and expressed in ppm (δ) relative to the central peak of deuterium oxide (4.63 ppm), methanol-d_4 (3.40 ppm), dimethyl-d_6 sulfoxide (2.49 ppm), acetonitrile-d_3 (1.93 ppm), and TMS for chloroform-*d*. ^{13}C NMR: Varian Gemini 200 and Varian Gemini 300 spectrometers (50.3 and 75.4 MHz) at 298 K. Chemical shifts were referenced and expressed in ppm (δ) relative to the central peak of methanol-d_4 (49.0 ppm), dimethyl-d_6 sulfoxide (39.7 ppm) and chloroform-*d* (77.0 ppm). HMQC, HMBC ,and NOESY experiments: Varian VXR-500 spectrometer (500 MHz). DNMR: Bruker ARX400 spectrometer (400 MHz) at temperatures ranging from 300 to 200 K. Chemical shifts at all temperatures were referred to the methanol signal at $\delta = 3.40$ ppm or the acetone signal at $\delta =$

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(20) Ashton, P. R.; Brown, C. L.; Chapman, J. R.; Gallagher, R. T.; Stoddart, F. S. *Tetrahedron Lett.* **1992**, *35*, 1154−1157.

2.09 ppm. Positive ion ESI-MS: VG-Quattro (Micromass Instruments) spectrometer. TLC: Merck precoated silica gel 60 F_{254} plates or Panreac aluminum oxide 60−200 UV_{254} Polyester CCM plates using UV light (254 nm) as visualizing agent and/or H_2PtCl_2 3% aq/KI 10% aq (1:1) or $KMnO_4$ ethanolic solution. Column chromatography was performed on neutral aluminum oxide 90 activity II−III (Merck).

Materials. Solvents were distilled prior to use and dried according to the methods described in the literature. Protophanes **8b**,**c**[8a] and ion-exchange III resin (OH $^-$ form) were prepared as described in the literature.[5b,10] ***Caution***: 3,5-Bis(chloromethyl)-1,2,4-triazole (**7**)[3c,7] and the trinuclear protophanes **9**[8a] and **10**[8a] are strong *blistering agents*.

Method A. General Procedure for Macrocyclization Reaction. To a stirred suspension of **8b**,**c** (0.375 mmol) in dry acetonitrile (50 mL) was added dropwise 0.375 mmol of **7**, **9**, or **10** in dry acetonitrile (25 mL) under argon atmosphere at room temperature. The reaction mixture was then refluxed for 48 h. After evaporation of the solvent in a vacuum the residue was purified.

Purification. Method I. A suspension of the residue was sonicated with dry ethyl ether (3 × 15 mL) and dry acetone (3 × 15 mL) for macrocycle **5b•2Cl** or ethyl acetate and dry acetone 1:1 (2 × 15 mL) for macrocycle **6b•2Cl**. Then dissolved in ethanol (50 mL) and passed through an anion-exchange resin (OH^- form). The neutral eluates were evaporated to dryness and the residues were triturated with dry acetone (3 × 10 mL). The filtrates were dissolved in methanol (50 mL) and acidified to pH 3 with 5% aqueous HCl, and the solvent was removed to give the solid compounds, which were dried in a vacuum oven at 40 °C.

Method II. The crude material was purified by column chromatography on neutral aluminum oxide [**5b•2Cl**: 2-propanol/methanol 19:1, 2-propanol/water 4:1] [**5c•2Cl**: ethyl acetate/methanol 19:1 to 1:1]. The eluates were evaporated to dryness and the residue was treated with absolute ethanol (3 × 10 mL). The alcoholic solutions were collected, passed through an anion-exchange resin (OH^- form) and then acidified to pH 3 with 5% aqueous HCl. The solvent was removed and the remaining solids were dried in a vacuum oven at 40 °C.

Method III. A suspension of the residue was sonicated successively with a 3:1 mixture of Cl_4C/acetone (4 × 20 mL) and 9:1 of Cl_4C/Cl_3CH (1 × 10 mL) for macrocycle **6b•2Br** or acetone (3 × 15 mL) and then Cl_4C (5 × 15 mL) for macrocycle **6c•2Br**. The solid compounds were filtered and dried in a vacuum oven at 40 °C.

Method B: Preparation of Bis-Betaines 2b,c and 3b,c. A column (0.5 in. diameter) was packed with ion-exchange III resin (OH $^-$ form) to a height of 5 in., and the column bed was equilibrated with the following eluants: H_2O (20 mL), 20% ethanol (20 mL), 60% ethanol (20 mL), 80% ethanol (20 mL), 96% ethanol (20 mL). A solution of dicationic macrocycles **5b,c•2X** and **6b,c•2X** (100 mg) in 96% ethanol (50 mL) was passed through the column. The neutral eluates were evaporated to dryness to give the corresponding bis-betaines **2b**,**c** and **3b**,**c**.

Method C: Preparation of Macrocycles 5b,c•2PF$_6$ and 6b,c•2PF$_6$. A solution of bis-betaines **2b**,**c** and **3b**,**c** (50 mg) in methanol (50 mL) was acidified to pH 3 with 1% aqueous hexafluorophosphoric acid, and the solvent was evaporated to dryness to give the corresponding dications **5b,c•2PF$_6$** and **6b,c•2PF$_6$.**

Method D: Preparation of Betaine 11b•Cl. A solution of bis-betaine **2b** (50 mg) in methanol (50 mL) was acidified to pH 6.5 with 5% hydrochloric acid, and the solvent was then evaporated to dryness to afford **11b•Cl**.

Table 6. Concentration Dependence of ^{1}H NMR Spectra of 6b•2Cl in CD_3OD (200 MHz) or DMSO-d_6 (300 MHz) at 298 K[a]

concn (mM)	CD_3OD	H-4	H-47	CH_2−2	CH_2−13	H-15(16)
2.0		7.18	9.20	5.45	4.13	b
4.0		7.21	9.24	5.46	4.16	b
	$\Delta\delta^c$	−0.03	−0.04	−0.01	−0.03	b
5.4		7.23	9.26	5.46	4.18	b
	$\Delta\delta^c$	−0.05	−0.06	−0.01	−0.05	b
10.25		7.27	9.30	5.47	4.22	b
	$\Delta\delta^c$	−0.09	−0.10	−0.02	−0.09	b
21.65		7.31	9.36	5.50	4.25	b
	$\Delta\delta^c$	−0.13	−0.16	−0.05	−0.12	b
37.9		7.33	9.39	5.50	4.26	b
	$\Delta\delta^c$	−0.15	−0.19	−0.05	−0.13	b

conc (mM)	DMSO-d_6	H-4	H-47	CH_2−2	CH_2−13	H-15(16)
0.3		7.04	9.35	5.34	3.93^d	13.55
0.6		7.04	9.36	5.34	3.93^d	13.55
	$\Delta\delta^c$	0	−0.01	0	0	0
1.6		7.05	9.39	5.34	3.93^d	13.60
	$\Delta\delta^c$	−0.01	−0.03	0	0	−0.05
2.8		7.05	9.40	5.34	3.93^d	13.58
	$\Delta\delta^c$	−0.01	−0.05	0	0	−0.03
5.7		7.06	9.41	5.35	3.93^e	13.60
	$\Delta\delta^c$	−0.02	−0.06	−0.01	0	−0.05
8.5		7.06	9.44	5.35	3.93^e	13.62
	$\Delta\delta^c$	−0.02	−0.09	−0.01	0	−0.07
17.0		7.08	9.47	5.36	3.93^e	13.66
	$\Delta\delta^c$	−0.04	−0.12	−0.02	0	−0.11

[a] The equivalent proton atoms are abbreviated. For the 1,2,4-triazole H-15(16) = H-15(16), 36(37); the imidazolium H-4 = H-4,5,26,27; H-47 = H-47,51; methylene spacers CH_2-2 = CH_2-2,7,24,28; CH_2-13 = CH_2-13,18,34,39). [b] Signal not observed due to H/D exchange. [c] $\Delta\delta = \delta_{[\min]} - \delta_{[X]}$. [d] See Figure 5. [e] Broad signal (see Figure 5).

Qualitative Aggregation Studies of Dication 6b•2Cl. At higher concentration, the ^{1}H NMR chemical shifts of the imidazolium H-4,5,26,27 and H-47,51 together with the methylene spacers CH_2-13,18,34,39 were shifted downfield in CD_3OD, and a less sensitive concentration dependence was observed in DMSO-d_6 (see Table 6). No significant chemical shift changes were observed for the other protons.

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Supporting Information Available: Listing of complete ^{1}H and ^{13}C NMR spectral data and ^{1}H NMR spectra for all compounds lacking CHN analyses. Positive ion ESI mass spectra of **1a**[1]and **2b** (Figure 7). ESI-MS spectra of bis-betaines **2c**, **3b**, and **3c** and dicationic macrocycle **5b•2Cl**. Computer-generated pleated looplike conformation of **6b•2Cl** (Figure 8). This material is available free of charge via the Internet at http://pubs.acs.org.

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