Open-Chain Dications and Betaines with Imidazolium Molecular Motifs: Synthesis and Structural Aspects[‡]

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The synthesis of trinuclear open-chain prototypes gave variable yields: > 53% for dications **1·2X** and **2·2X** and > 80% for proton-ionizable dications **3·2X**–**5·2X** incorporating 1*H*-1,2,4-triazole moieties. Deprotonation of the latter compounds resulted in the formation of the betaine counterparts **13·X**–**15·X**. The courses of the dequaternization reactions of compounds **4·2X** and **5·2X** were also studied. The structural properties of dicationic protophanes **1·2X** and **2·2X**, containing bis(imidazolium) motifs, were examined by ^{1}H and ^{13}C NMR spectroscopy, electrospray mass spectrometry and by single-crystal X-ray diffraction analysis of the dication **1b·2PF$_6$**. Weak noncovalent interactions between the dications and the hexafluorophosphate ions bias the protophane conformation both in solution and in the solid state. X-ray diffraction reveals that the PF_6^- counterions are located in a channel formed by the dications (**1b^{2+}**).
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Introduction

The design of substrates for the ultimate preparation of supramolecular species is an area of considerable interest in organic chemistry. Acyclic polydentate building blocks containing heteroaromatic units are of interest for the construction of a broad array of molecules ranging from crown ethers and macrocycles[2,3] to a variety of supramolecular entities[4] and self-assembled helices,[5a] together with metallo-supramolecular systems.[2,5b] In this context, the syntheses and properties of a number of different 1,2,4-triazole-containing macrocycles have been reported.[1,3a,3b] At the same time, the chemistry of isolable N-heterocyclic carbenes derived from azolium quaternary salts precursors has been developed in recent years.[6]

In the context of our research concerning the design of molecular scaffolds for supramolecular entities, we have become engaged in the study of an ensemble of trinuclear dicationic protoheterophanes **1·2X**, **2·2X**, and **3·2X**−**5·2X**, formed by two imidazolium rings linked either by 1,3-dimethylbenzene or by proton-ionizable 3,5-bis(dimethyl-1,2,4-triazole) subunits (Figure 1). It is noticeable that dicationic protophanes **1·2X** and **2·2X** contain the trinuclear component of [1$_4$]imidazoliophanes,[7] while dications **3·2X**−**5·2X** are related to [1$_4$]azolophanes with proton-ionizable 1,2,4-triazole subunits[1a] (Figure 1). Thus, the trinuclear protoheterophanes with two imidazole rings are advanced intermediates in the "3+1" convergent, stepwise synthesis of dicationic [1$_4$]metaheterophanes,[1,7] and the "3+1" approach is template-controlled by chloride anions (e.g., TBA·Cl),[8] especially for [1$_4$]imidazoliophanes.

The potential of the molecular and supramolecular behaviour of these compounds[9] prompted us to explore their synthesis as well as to look for further insight into their structural properties, both in solution and the solid state. Understanding of the noncovalent interactions governing the conformational pattern of the protophanes, as well as their crystal packing, is a crucial issue regarding knowledge of the bis(imidazolium)-based protoheterophanes. These interactions are responsible for the location of the counterions relative to the dication and are manifested not only in the solid state but also in solution, as discussed in this paper. Therefore, the implications of their presence go beyond the chemical structure itself, and result in consequences in chemical behaviour. On these premises, we report here the synthesis of open-chain prototypes containing two imidazolium rings as common structural motifs: the dicationic protophanes **1·2X**−**5·2X** and the betaine counterparts of the proton-ionizable dications **3·2X**−**5·2X**. We also describe results from the structural study of dicationic protophanes

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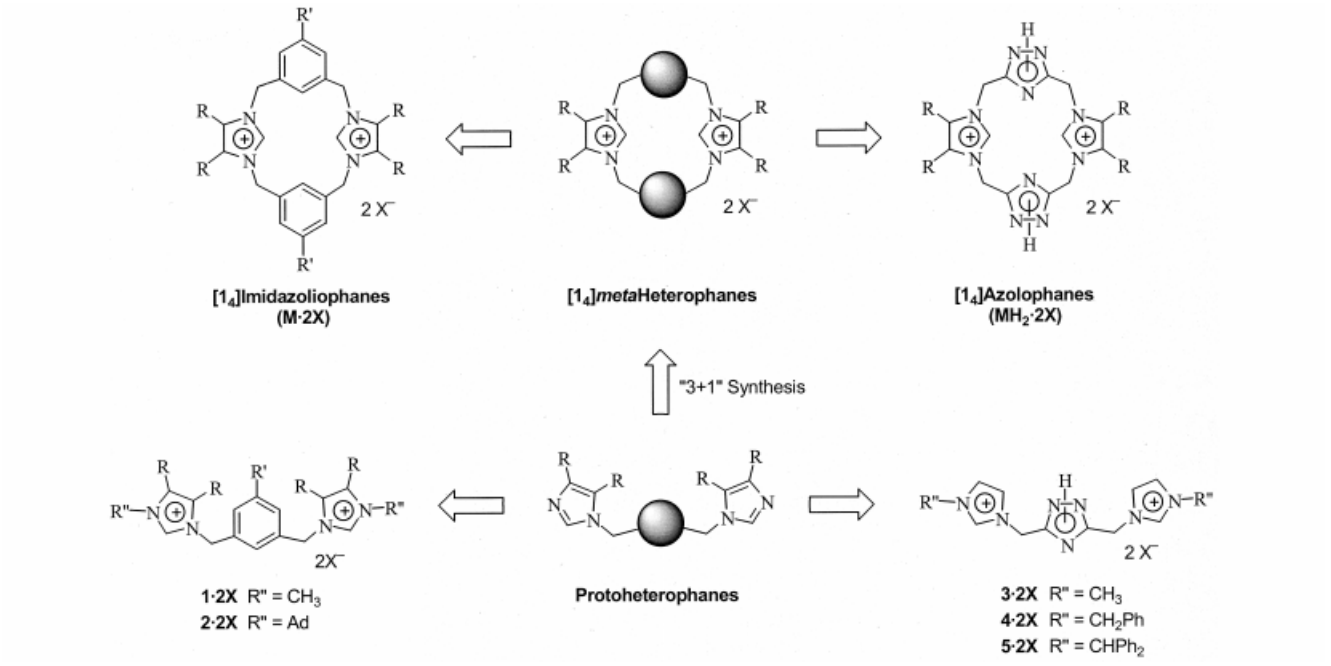


Figure 1 From protoheterophanes to dicationic protoheterophanes and their incorporation into [1₄]metaheterophanes

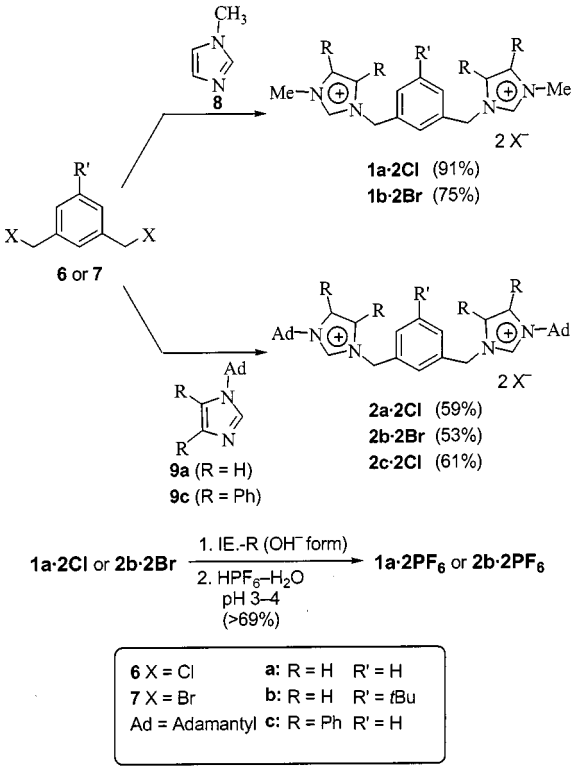
1·2X and **2·2X** gained by NMR spectroscopy, mass spectrometry and X-ray diffraction analysis.

Results and Discussion

Dicationic Protophanes 1·2X and 2·2X[1b]

Synthesis

The quaternization reaction providing dications **1·2X** and **2·2X** under neutral conditions gave yields that depended on the *N*-substituted imidazole used. Protophanes **1a·2Cl** and **1b·2Br** were obtained in > 75% yield on treatment of 1,3-bis(chloromethyl)benzene (**6**) or 1,3-bis(bromomethyl)-5-*tert*-butylbenzene (**7**) with *N*-methylimidazole (**8**), whereas quaternization of *N*-adamantylimidazoles **9a** and **9c** proceeded in lower yields (> 53%) (Scheme 1). For protophanes **2a·2Cl**, **2b·2Br**, and **2c·2Cl**, different reaction conditions in neutral media were investigated, and the best results are described. The counterions of these dicationic protophanes were changed by use of an ion-exchange resin (OH^- form) and the eluates were immediately treated with HX/H_2O in a pH range between 3 and 4 − see, for example, **1a·2PF$_6$** or **2b·2PF$_6$** in Scheme 1 (see Exp. Sect.). The structural properties of the new protophanes were examined by ^{1}H NMR and ^{13}C NMR spectroscopy and electrospray mass spectrometry, and the structure of dication **1b·2PF$_6$** was confirmed by a single-crystal X-ray analysis.

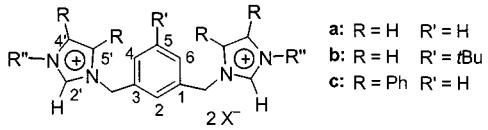


Scheme 1. Synthesis of dicationic protophanes **1·2X** and **2·2X**

NMR Spectroscopy

The ^{1}H NMR spectra of dications **1a·2X**, **1b·2X**, and **2a−c·2X** (X = Cl^-, Br^-, PF_6^-) in [D$_6$]DMSO showed sharp singlets for the methylene protons, which indicates conformational mobility; this flexibility was also observed in the [1$_4$]metaheterophane frameworks.[1a,10] The proton chemical shifts shown in Table 1 showed that the δH values of the acidic C(2′)-H, flanked by the two heteroatoms, and 2-H from the aromatic ring were the most affected, and a deshielding effect due to structural factors and the anion

Table 1. Selected ^{1}H NMR spectroscopic data of dicationic protoheterophanes **1a,b·2X** and **2a−c·2X**



1a,b·2X (R" = CH_3)
2a-c·2X (R" = Ad)

Compd.[a]	2′-H	4′-H	5′-H	$-CH_2-$	2-H	4,6-H
1a·2Cl	9.64	7.76	7.92	5.48	7.68	7.44
1a·2Br	9.39	7.75	7.84	5.47	7.60	7.44
1a·2PF$_6$	9.21	7.72	7.74	5.41	7.48	7.40
1b·2Cl	9.57	7.74	7.90	5.42	7.43	7.54
1b·2Br[b]	9.30	7.74	7.83	5.41	7.31	7.52
1b·2PF$_6$[c]	9.15	7.71	7.75	5.37	7.20	7.49
2a·2Cl[c]	10.10	8.13	8.04	5.51	7.95	7.53
2b·2Br[c]	9.57	8.07	7.87	5.39	7.28	7.50
2b·2PF$_6$	10.02	7.96	7.96	5.41	7.94	7.56
2c·2Cl[c]	9.94	−	−	5.30	6.82	6.79

[a] In [D$_6$]DMSO (300 MHz) at a concentration range between 30 and 80 mM. [b] Assignment by NOE. [c] ^{1}H NMR spectra recorded at 200 MHz.

Table 2. Concentration dependence of ^{1}H NMR chemical shifts of dication **1b·2X** [**X** = **Cl$^-$**, **Br$^-$**, **PF$_6^-$**] in CD_3CN, [D$_6$]DMSO and CD_3OD (300 MHz) at 298 K

Compd.	Conc. [mM]	CD_3CN			Conc. [mM]	[D$_6$]DMSO			Conc. [mM]	CD_3OD		
		2-H′[a]	5′-H	2-H		2′-H	5′-H	2-H		2′-H	5′-H	2-H
1b·2Cl	2.8	9.74	7.57	7.66								
	6.3	9.79	7.58	7.67	6.3	9.36	7.81	7.31	6.3	9.05	7.64	7.36
Δδ≅[b]		−0.05	−0.01	−0.01								
	12.6	9.84	7.61	7.69	12.6	9.38	7.82	7.33	13.0	9.07	7.64	7.38
Δδ[b]		−0.10	−0.04	−0.03		−0.02	−0.01	−0.02		−0.02	0	−0.02
	78.0	9.96	7.72	7.72	75.8	9.59	7.91	7.44	78.0	9.12	7.66	7.40
Δδ[b]		−0.22	−0.15	−0.06		−0.23	−0.10	−0.13		−0.07	−0.02	−0.04
1b·2Br	2.9	9.24	7.52	7.50	2.9	9.19	7.76	7.23	2.9	9.05	7.64	7.38
	14.7	9.45	7.55	7.60	14.7	9.25	7.78	7.27	14.7	9.09	7.64	7.42
Δδ[b]		−0.21	−0.05	−0.10		−0.06	−0.02	−0.04		−0.04	0	−0.04
	35.4	9.54	7.62	7.64	35.4	9.29	7.81	7.30	35.4	9.11	7.66	7.42
Δδ[b]		−0.30	−0.10	−0.14		−0.10	−0.05	−0.07		−0.06	−0.02	−0.04
1b·2PF$_6$	2.3	[c]	7.46	7.14	2.3	9.15[d]	7.74	7.20	2.3	[c]	7.57	7.27
	11.6	8.45[d]	7.47	7.14	11.6	9.15[d]	7.74	7.20	11.6	8.84	7.57	7.25
Δδ[b]		−	−0.01	0		0	0	0		−	0	+0.02
	27.9	8.43	7.47	7.14	27.9	9.14	7.74	7.20	27.9	8.81	7.57	7.25
Δδ[b]		+0.02	−0.01	0		+0.01	0	0		+0.03	0	+0.02

[a] H numbering scheme see Table 1. [b] $\Delta\delta = \delta_{[min]} - \delta_{[x]}$. [c] No signal observed due to H/D exchange. [d] Broad signal.

effect was observed. Comparison of the δ(2′-H) and δ(2-H) values of the *N*-adamantyl dication **2b·2PF$_6$** showed that they were more deshielded than those of the *N*-methyl dication **1b·2PF$_6$** (Table 1). For the protophane pair **1b·2Cl** and **1b·2PF$_6$**, the deshielding effect was examined at nonaggregating concentrations (see below, Table 2). The ^{13}C NMR chemical shifts for dications **1a·2X**, **1b·2X**, and **2a−c·2X** were consistent with data from correlative systems,[1a,10] and individual assignments were made by HMQC (Supporting Information available; see also footnote on the first page of this article).

Qualitative ^{1}H NMR Observations

Dicationic protophane **1b·2X** (X = Cl$^-$, Br$^-$, PF$_6^-$) was further examined by ^{1}H NMR in various solvents. The solution aggregation behaviour depended on the nature of the counterion and the solvent polarity. In CD_3CN and

[D_6]DMSO, the proton chemical shifts for **1b·2Cl** and **1b·Br** depended on concentration, while they were unchanged for **1b·PF$_6$**.[11] In a more polar solvent such as [D_4]methanol, hydrogen bond and electrostatic interactions were weakened by solvation and no aggregation was detected for dications **1b·2X** (Table 2 and Supporting Information).

The anion effect and solvent polarity[9,12] had a strong influence on the chemical shift changes observed for **1b·2X**, especially for δ(2′-H), δ(5′-H), and δ(2-H), as a consequence of hydrogen bonding with the counterions; this result is similar to those found with [1_4]imidazoliophanes (M·2X, see below). At nonaggregating concentrations,[11] the greatest deshielding effect corresponded to the acidic 2′-H protons of the imidazolium rings in dication **1b·2Cl**. Comparison of the δ(2′-H) values in compound pair **1b·2Cl** and **1b·2PF$_6$** showed that the deshielding was up to 1.29 ppm in CD_3CN, and ca. 0.21 ppm in [D_6]DMSO and [D_4]methanol. According to the ^{1}H NMR spectroscopic data summarized in Table 2, the open-chain trinuclear dication (**1b^{2+}**) showed weak noncovalent interactions with the hexafluorophosphate counterions in solution, which were also confirmed in the solid state by the X-ray diffraction analysis of the model protophane **1b·2PF$_6$** (see below).

Electrospray Mass Spectrometry Analysis

Electrospray ionization has been used to examine an ensemble of dicationic [1_4]imidazoliophanes (M·2X)[13a] and multicharged [1_n]azolophanes with proton-ionizable 1*H*-1,2,4-triazole or/and 1,2,4-triazolate subunits[13] {dicationic [1_4]azolophanes (MH_2·2X), for example,[13b] see Figure 1}. Several informative peaks were the result of proton-transfer reactions and the ring components in these macrocyclic systems modulated their ionization behaviour. Direct electrospray mass spectrometric evidence was obtained for singly charged imidazolylidene ions $[M - H]^+$, which were generated by simple systems with two imidazolium rings, such as [1_4]imidazoliophanes (M·2X). Electrosprayed macrocyclic dications thus produced loss of the counterions and fission of the labile imidazolium C−H bond, the three common ions being $[M]^{2+}$ and $[M + X]^+$, together with the carbene species $[M - H]^+$. This representative peak appeared in the ESI mass spectra of the regiospecific deuterated counterparts as the singly charged ion $[M - D]^+$, which validates the positive ion ESI-MS study.[13a]

The positive ion ESI-MS of dications **1a·2X**, **1b·2X**, **2a·2X**, and **2b·2X** was performed as described elsewhere:[13a] Samples were dissolved in a 1:1 mixture of H_2O/CH_3CN at 100 pmol·μL^{-1} and the cone voltage was varied between 50 and 120 V. The positive ESI response of the open-chain imidazolium dications **1·2X** and **2·2X** resulted in the formation of the three characteristic ions $[M]^{2+}$, $[M + X]^+$, and $[M - H]^+$ mentioned above. Several peaks arising from molecular fragmentation were also produced, especially in the *N*-adamantyl series (Table 3). At 80 and 120 V, the singly charged imidazolylidene species $[M - H]^+$ was more abundant in the *N*-methyl series; this result is similar to those found with [1_4]imidazoliophanes (M·2X).[13a] As for the *N*-adamantyl series, the base peak corresponded to the doubly charged ions $[M]^{2+}$ at low cone voltage while molecular fragmentation produced the singly charged fragment ions at m/z = 135.5 $[Ad]^+$ and at m/z = 429.7 $[M - Ad]^+$ as the most abundant species, at both 80 and 120V.

Table 3. Summary of data obtained from positive ion ESI-MS of **1a,b·2X** and **2a−c·2X**

Vc [V]	Compd. (mol. mass)[a]	Ions, m/z ratio, relative abundance (%)[a] $[M]^{2+}$	$[M - H]^+$	$[M + X]^+$	Compd. (mol. mass)[a]	Ions, m/z ratio, relative abundance (%)[a] $[M]^{2+}$	$[M - H]^+$	$[M + X]^+$	$[Ad]^+$	$[M - Ad]^+$
	1a·2Cl[b] (339.3)	134.2	267.4	303.8	**2a·2Cl** (579.7)	254.5	507.9	544.3	135.2	373.7
50		**100**	5	1		**100**	1	12	4	6
80		**100**	50	15		2	5	44	**100**	72
120		[c]	18	20		[c]	11	4	**100**	14
	1a·2Br[d] (428.2)	134.2	267.4	348.3	**2b·2Br** (724.7)	282.5	563.9	644.8	135.2	429.7
50		**100**	1	10		**100**	[c]	14	3	4
80		10	90	20		**100**	[c]	36	32	28
120		−	−	−		[c]	5	20	**100**	25
	1b·2Cl[e] (395.4)	162.2	323.5	359.9	**2c·2Cl** (884.1)	406.6	812.1	848.6	135.2	677.9
50		**100**	[c]	5		**100**	[c]	3	2	5
80		20	**100**	20		3	2	40	90	**100**
120		90	20	15		[c]	5	5	**100**	30
	1b·2Br[f] (484.3)	162.2	323.5	404.4						
50		**100**	[c]	5						
80		[c]	35	50						
120		[c]	20	10						
	1b·2PF$_6$ (614.4)	162.2	323.5	469.4						
50		**100**	[c]	10						
80		20	20	**100**						
120		10	**100**	10						

[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 ^{12}C = 12.000. [b] Fragment ion at m/z = 185.1 and at 120 V (100%). [c] No signal observed. [d] Fragment ion at m/z = 92.8 and at 80 V (100%). [e] Fragment ion at m/z = 175.8 and at 120 V (100%). [f] Fragment ion at m/z = 243.5 and at 80 V (100%) and fragment ion at m/z = 161.0 and at 120 V (100%).

X-ray Analysis

The molecular structure of **1b·2PF$_6$** is depicted in Figure 2.[14] Both the *tert*-butyl group and the PF_6^- ions display thermal disorder, as reported for the hexafluorophosphate counterions.[15] Although the crystal structure seems to be mainly dominated by Coulombic forces, a series of noncovalent C−H···F interactions is also observed and reveals association of the PF_6^- anions and the dication **1b** through a combination of electrostatic and minimal hydrogen bonding. In particular, the shortest distances observed are: [H3···F4] = 2.33 Å and [C3−H3···F4] = 151°; [H1A···F2] = 2.47 Å and [C1−H1A···F2] = 147°, and [H5B···F5] = 2.55 Å and [C5−H5B···F5] = 168°. For other C−H···F contacts, the distances are rather long to be considered hydrogen bonds.[16] The weak character of these interactions is consistent with the poor complexing ability of anions such as PF_6^-.

The dications **1b** are ordered in continuous stacks along the *b* crystallographic axis, with the PF_6^- counterions arranged in a channel (Figure 3). Indeed, each molecule is stacked almost directly above its neighbour in adjacent unit cells along the crystallographic *b* axis, with the imidazolium rings 13.4 Å apart. The benzene ring is aligned nearly perpendicular to the plane of the axis, whereas the imidazolium rings stack almost parallel to this plane, and therefore perpendicularly to the benzene ring [N(4)−C(5)−C(6)−C(10) torsion angle: 75.1°]. Furthermore, the solid-state structure shows nonequidistant intercalation of one imidazolium ring of one molecule between two imidazolium rings of two different molecules of the neighbouring parallel stack. The interplanar separations between these imidazolium rings and the sandwiched one are of the order of 4.8 Å and 8.9 Å, respectively. The region between dications is occupied by PF_6^- counterions, also aligned along the *b* axis, filling the cavities between dications, and forming channels that extend through the crystal. The results obtained from the solid structure of **1b·2PF$_6$** reflect the lack of hydrogen bonding as well as π-π stacking.

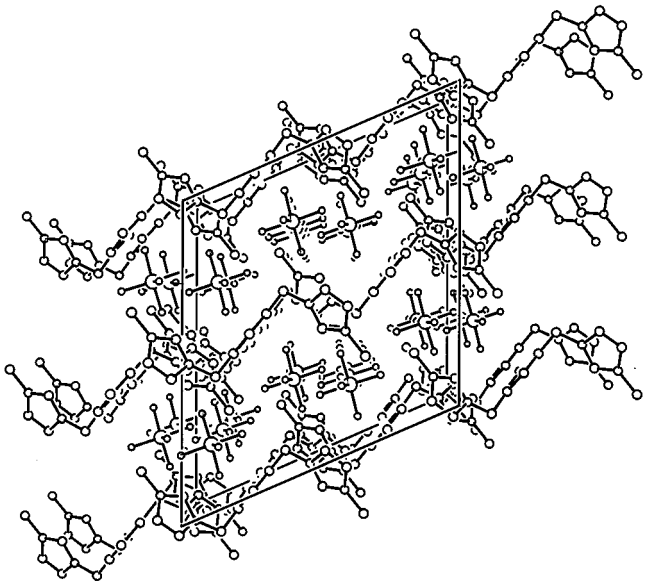


Figure 3. Packing of dicationic protophane **1b·2PF$_6$** viewed along the crystallographic *b* axis

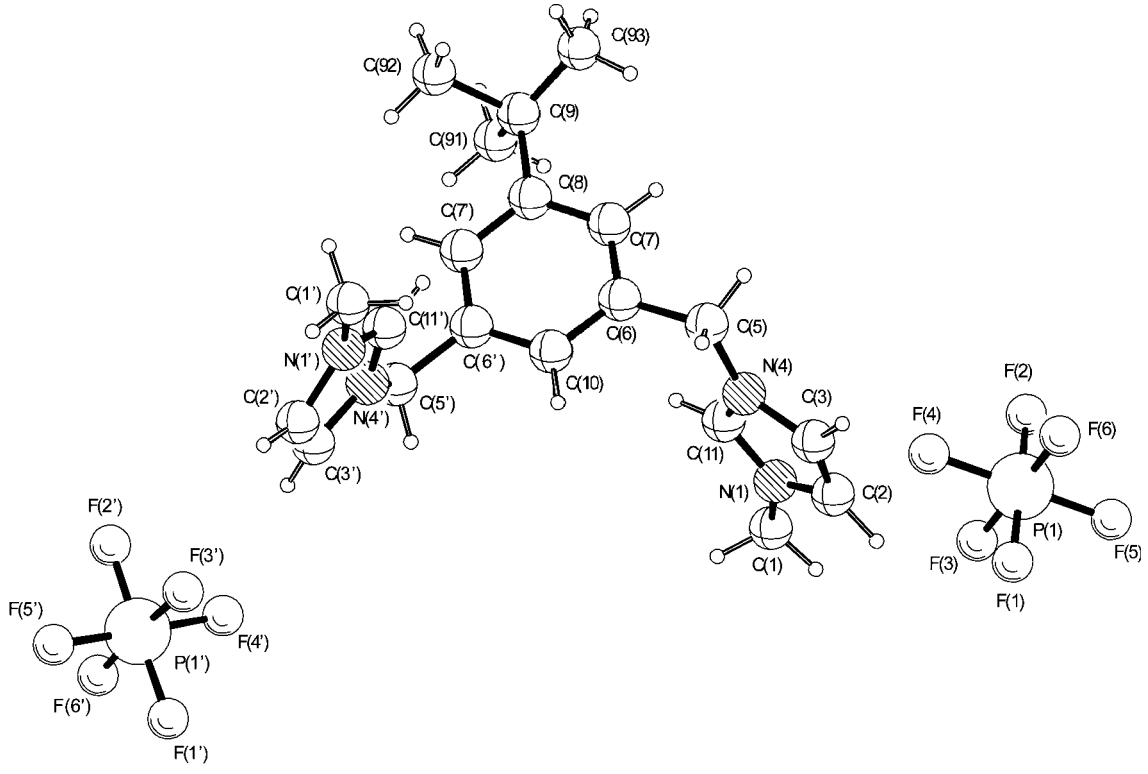
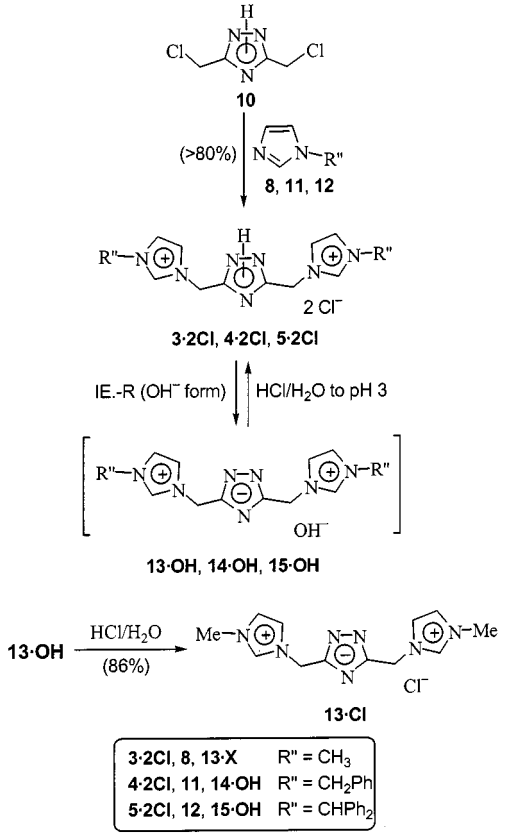


Figure 2. Molecular structure of **1b·2PF$_6$**

Dicationic Protophanes with a Proton-Ionizable 1,2,4-Triazole Ring, 3·2X−5·2X[1c]

Synthesis

Quaternization of *N*-alkylimidazoles **8**, **11**, and **12** with 3,5-bis(chloromethyl)-1,2,4-triazole (**10**)[3c] under neutral conditions gave the corresponding dicationic protophanes **3·2Cl−5·2Cl** (> 80%). However, purification of these diquaternary heteroaromatic salts was difficult, due to the similar solubilities of the ionic species present in the reaction mixtures, especially for protophanes **4·2Cl** and **5·2Cl**. The pure dicationic protophanes were treated with an ion-exchange resin (OH^- form) and transformed into the betaine intermediates **13·OH−15·OH**, which are unstable, although it was possible to record their ^1H NMR spectra (Scheme 2). The intermediate **13·OH** was then acidified by carefully controlled addition of HCl/H_2O and the stable betaine **13·Cl** was isolated.



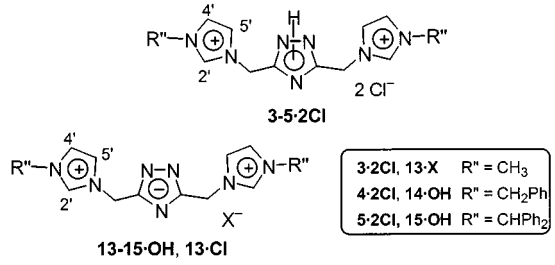
Scheme 2. Synthesis of proton-ionizable dicationic protophanes **3·2X−5·2X** and their corresponding betaines **13·X-15·X**

Spectroscopic Study

The dicationic protophanes **3·2Cl−5·2Cl**, the betaine **13·Cl** and the betaine intermediates **13·OH−15·OH** were characterized by their spectroscopic data (IR, ^1H and ^{13}C NMR). It was not possible, however, to obtain single crystals of these protophanes for X-ray analysis. Both the ^1H and the ^{13}C NMR of the protophanes with 1,2,4-triazole or 1,2,4-triazolate units provided relevant information on these dicationic or betaine trinucleating systems, and was well in accordance with the nature of the π-rich and π-deficient heteroaromatic fragments. The chemical shift values were similar to those seen in the building blocks[17] and in [1_n]azolophanes.[1a,18]

Selected ^1H NMR spectroscopic data in [D_6]DMSO are given in Table 4, and the ^{13}C NMR parameters are listed in the Supporting Information. Comparison of the proton chemical shifts of betaine **13·Cl** with those of the corresponding dication **3·2Cl** precursor shows that the δH values of both the methylene spacers and 2-H′ protons of the imidazolium rings are shifted upfield by −0.20 ppm. In the compound pair **13·OH** and **3·2Cl**, the shielding effect was up to −0.40 ppm (see Δδ in Table 4).

Table 4. Selected ^1H NMR spectroscopic data of dicationic protoheterophanes **3−5·2Cl** and the betaines **13−15·OH** and **13·Cl**

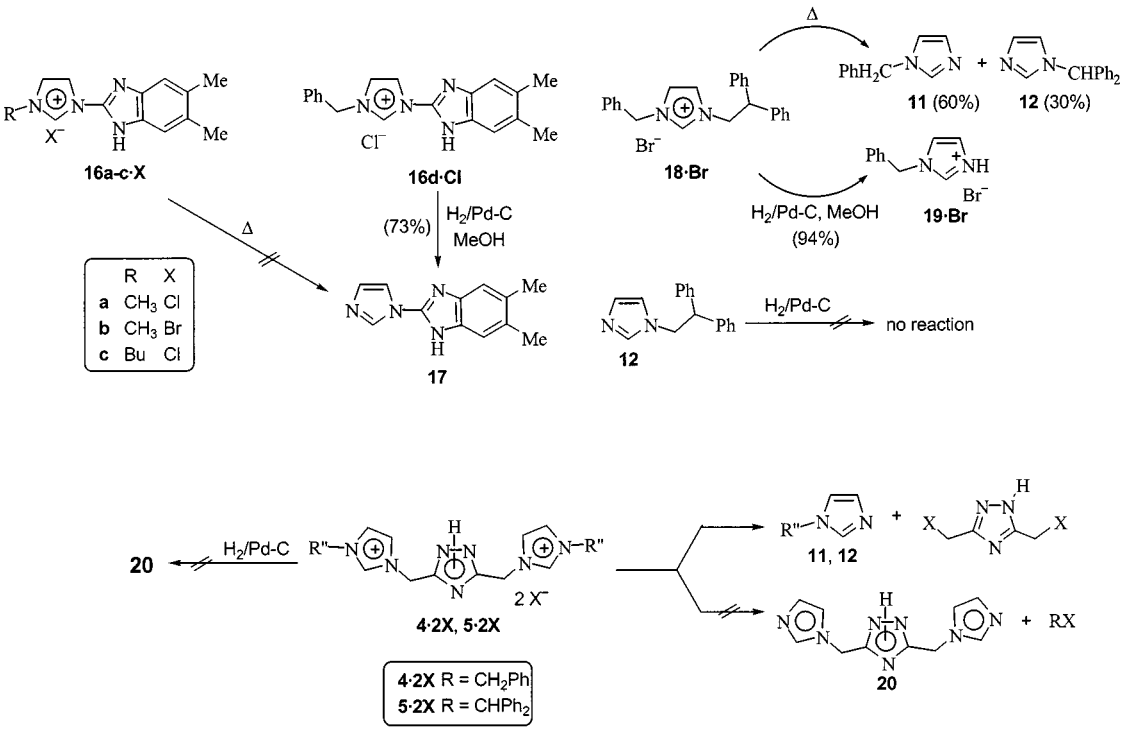


Compound[a]	2′-H	4′-H	5′-H	−CH_2−
13·Cl	9.29	7.71	7.76	5.46
3·2Cl	9.49	7.80	7.87	5.66
Δδ [b]	−0.20	−0.09	−0.11	−0.20
13·OH[c][d]	9.12	7.63	7.68	5.26
Δδ [e]	−0.37	−0.17	−0.19	−0.40
14·OH	9.38	7.70	7.77	5.29
4·2Cl	9.61	7.85	7.88	5.60
Δδ [e]	−0.23	−0.15	−0.11	−0.31
15·OH	9.24	7.71	7.75	5.31
5·2Cl	9.42	7.83	7.91	5.64
Δδ [e]	−0.18	−0.12	−0.16	−0.33

[a] In [D_6]DMSO (300 MHz). [b] Δδ: Difference in the chemical shift of betaine **13·Cl** and its corresponding dication **3·2Cl**. [c] Unstable compound in [D_6]DMSO. [d] Value obtained from different experiments, the spectra being recorded at a constant concentration of 10 mg/3 mL in [D_6]DMSO. [e] Difference in the chemical shift of betaines **13−15·OH** and their corresponding dications **3−5·2Cl**.

Dequaternization Reactions

Dequaternization of several examples of *N*-azolylazolium salts has been reported. Examples include compounds **16·X**, and debenzylation of the *N*-benzimidazolylimidazolium salt **16d·Cl** produced **17** in good yield (73%) (Scheme 3); this was the first example of an imidazolium salt in which dequaternization proceeded through hydrogenolysis.[19] In this context, the model quaternary imidazolium salt **18·Br** was next examined. Thermal dequaternization produced *N*-benzylimidazole **11** (60%) and *N*-benzhydrylimidazole **12** (30%) along with alteration products (10%) (Table S1 and

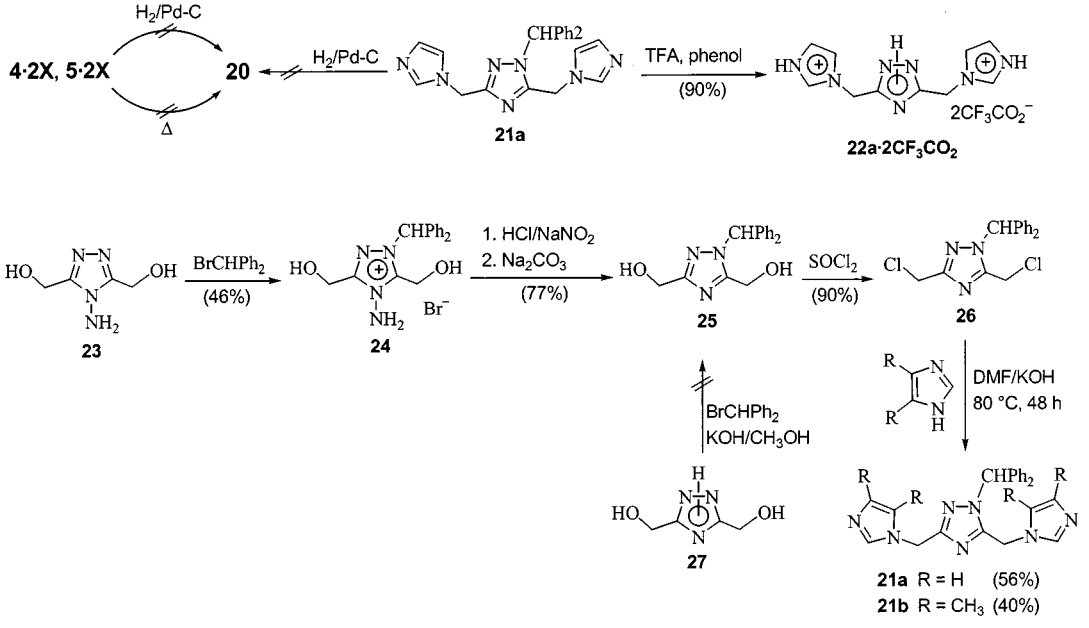


Scheme 3. Dequaternization reactions of azolium salts **16·X**, **18·Br** and dicationic protoheterophanes **4·2X**, **5·2X**

Exp. Sect. in the Supporting Information; see also footnote on the first page of this article). In contrast, hydrogenolysis of **18·Br** resulted in the formation of *N*-benzylimidazolium salt **19·Br** in 94% yield. Moreover, catalytic hydrogenation of *N*-benzhydrylimidazole **12** gave no reaction (Scheme 3, and Table S2 and Exp. Sect. in the Supporting Information; see also footnote on the first page of this article).

With these results in mind, dequaternization reactions of the dicationic protophanes **4·2X** and **5·2X** were examined, but the uncharged protophane **20** was not formed either by thermolysis or hydrogenolysis (Scheme 3). Several attempts at this dequaternization were made; selected assays are listed in Tables S1 and S2 (see Supporting Information).

Alternatively, removal of the *N*-benzhydryl group of 1-benzhydryl-3,5-bis(1-imidazolylmethyl)-1,2,4-triazole (**21a**) with trifluoroacetic acid gave the *N*-unprotected dication **22a·2CF$_3$CO$_2$**, the ditrifluoroacetate dication counterpart of the uncharged protophane **20**, whereas catalytic hydro-



Scheme 4. Synthesis and dequaternization of *N*-benzhydrylprotophanes **21**

genation gave no reaction (Scheme 4 and Supporting Information). However, 3,5-bis(1-imidazolylmethyl)-1*H*-1,2,4-triazole (**20**) has been prepared by an alternative route starting from *N*-cyanomethylimidazole, which proceeded in two steps (70%).[1a]

Preparation of the multitopic building blocks[1a] **21a** and **21b** started with 4-amino-3,5-bis(hydroxymethyl)triazole (**23**)[3c] and followed a four-step sequence as shown in Scheme 4. 1-Benzhydryl-3,5-bis(hydroxymethyl)-1,2,4-triazole (**25**) was prepared by a procedure similar to those described by Scriven et al.:[20] The quaternization of 4-amino-3,5-bis(hydroxymethyl)triazole (**23**)[3c] with benzhydryl bromide gave the *N*-benzhydryl-protected cation **24·Br**, which was then transformed into compound **25**. Subsequent halogenation gave the 1-benzhydryl-3,5-bis(chloromethyl)triazole (**26**), which reacted with the appropriate imidazoles to produce the multitopic molecules **21a** and **21b**. Finally, *N*-alkylation of bis(hydroxymethyl)-1,2,4-triazole **27**[3c] with benzhydryl bromide failed (see Exp. Sect.).

Conclusion

The syntheses of dicationic open-chain prototypes **1·2X−5·2X**, multitopic scaffolds based on two imidazolium units as their common structural motifs, are reported. The proton-ionizable dications **3·2X−5·2X** were transformed into the unstable betaines **13·OH-15·OH** and also into the stable betaine **13·Cl**. Dequaternization reactions of dications **4·2X** and **5·2X** by thermolysis and hydrogenolysis were studied. The structural properties of dications **1·2X** and **2·2X** were examined in detail by ^{1}H NMR and positive ion ESI-MS, and by the single-crystal X-ray diffraction analysis of dication **1b·2PF$_6$**. Both in solution and in the solid state, the bis(hexafluorophosphate) dications showed weak noncovalent intermolecular interactions and, moreover, the crystal packing of **1b·2PF$_6$** indicated that the hexafluorophosphate counterions are located between the dications (**1b^{2+}**) in a channel. Further studies are now investigating the use of dicatonic and betaine building blocks for the construction of supramolecular scaffolds from dicationic and dipolar to multipolar systems.

Experimental Section

General Remarks: Melting points: CTP−MP 300 hot-plate apparatus with ASTM 2C thermometer. IR (KBr disks or thin film): Perkin−Elmer 1430 and Nicolet 205 FT spectrophotometers. ^{1}H NMR: Varian Gemini 200, Varian Gemini 300 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 and HMBC: Varian Gemini 300 and VXR-500 spectrometers (300 MHz and 500 MHz). NMR spectra were determined in [D$_6$]dimethyl sulfoxide, [D$_3$]acetonitrile, and [D$_4$]methanol, and chemical shifts were referenced and expressed in parts per million (δ) relative to the central peak of [D$_6$]dimethyl sulfoxide or [D$_3$]acetonitrile or [D$_4$]methanol. ESI-MS:[13] VG-Quattro mass spectrometer (Micromass Instruments). EIMS: Hewlett−Packard HP-5988A. The pH was monitored with a CRISON micro-pH 2001 apparatus. Pyrolysis was performed with a Büchi GKR-50 Kugelrohr apparatus. TLC: Merck precoated 60 F$_{254}$ silica gel plates; detection by UV light, and spots developed with a 10% aqueous solution of potassium iodide or 3% aqueous solution of hexachloroplatinic acid. Chromatography: SDS silicium oxide 60 ACC (30−75 μm). Ion-exchange resin[1a] (I-E.R.): A column (0.5 inch diameter) was packed with ion exchanger III resin or Amberlite IRA 401 (OH$^-$ form) to a height of 5 inches. 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 with a Carlo Erba 1106 Analyzer.

Materials: Benzhydryl bromide, 1-bromoadamantane, 4,5-dimethylimidazole hydrochloride, 4,5-diphenyl-1*H*-imidazole, 1*H*-imidazole, 1,3-bis(chloromethyl)benzene (**6**), 1-methyl-1*H*-imidazole (**8**), and 1-benzyl-1*H*-imidazole (**11**) were purchased from commercial sources. 1,3-Bis(bromomethyl)-5-*tert*-butylbenzene (**7**),[21] 1-(1-adamantyl)-1*H*-imidazole (**9a**),[22] 3,5-bis(chloromethyl)-1*H*-1,2,4-triazole (**10**),[3c] 1-benzhydryl-1*H*-imidazole (**12**),[23] 4-amino-3,5-bis(hydroxymethyl)-1*H*-1,2,4-triazole (**23**)[3c] and 3,5-bis(hydroxymethyl)-1*H*-1,2,4-triazole (**27**)[3c] were prepared as described in the literature.

3,3′-Dimethyl-1,1′-[1,3-phenylenebis(methylene)]bis(imidazolium) Dichloride (1a·2Cl): See Table 5. A mixture of 1,3-bis(chloromethyl)benzene (**6**, 1.75 g, 10 mmol) and 1-methylimidazole (**8**; 2.2 mL, 27.5 mmol) was heated to 135 °C under nitrogen for 10 min. The reaction mixture was allowed to cool to room temperature and the solid obtained was triturated with dry hot acetone (3 × 5 mL). The resulting solid was filtered to give **1a·2Cl**.

Counterion Exchange. − Dications 1a·2Br and 1a·2PF$_6$: See Table 5. A solution of dicationic protophane **1a·2Cl** (0.23 g, 0.68 mmol or 0.13 g, 0.4 mmol) in 96% ethanol (50 mL) was passed through a column packed with a strongly basic anion-exchange resin (Ion exchanger III, Merck, hydroxide form). The neutral eluates were acidified to pH = 3 either with 47% HBr solution or with a hexa-

Table 5. Physical data of dicationic protoheterophanes **1a,b·2X**, **2a−c·2X**, and **3·2X−5·2X** and betaines **13·OH−15·OH** and **13·Cl**

Compd.	Reaction time [h]	Yield (%)[a]	M.p. [°C]
1a·2Cl	0.16	91	170−172
1a·2Br	−	99	[b]
1a·2PF$_6$	−	99	118−120
1b·2Cl	−	99	[b]
1b·2Br	17	75	200−2
1b·2PF$_6$	−	69	160−162[c]
2a·2Cl	96	59	115−116
2b·2Br	3.5	53	>300[c]
2b·2PF$_6$	−	66	211−212
2c·2Cl	168	61	272[c]
3·2Cl	0.11	80	[d]
4·2Cl	10.5	83	159−161
5·2Cl	49	89	150−153
5·2Br	0.75	88	[d]
13·OH	−	73	[d]
14·OH	−	67	[d]
15·OH	−	72	145−146
13·Cl	−	86	[d]

[a] Yields were not optimized. [b] Foamy compound. [c] Recrystallization solvent: **1b·2PF$_6$** (ethanol), **2b·2Br** (acetonitrile), **2c·2Cl** (acetone). [d] Hygroscopic compound.

fluorophosphoric acid solution, and the resulting solution was concentrated to dryness to afford the bromide **1a·2Br** or the hexafluorophosphate **1a·2PF$_6$**, respectively.

3,3′-Dimethyl-1,1′-[5-*tert*-butyl-1,3-phenylenebis(methylene)]-bis(imidazolium) Dibromide (1b·2Br): See Table 5. − **Experiment 1:** A mixture of 1,3-bis(bromomethyl)-5-*tert*-butylbenzene (**7**;[21] 1.6 g, 5 mmol) and 1-methylimidazole (**8**; 1.1 mL, 13.8 mmol) was heated to 135 °C under nitrogen for 10 min. The reaction mixture was allowed to cool to room temperature and the slurry was triturated with ethyl acetate (20 mL). The resulting solid was filtered to give **1a·2Br** (22% yield). **Experiment 2:** A solution of **7**[21] (1.6 g, 5 mmol) and **8** (1.1 mL, 13.8 mmol) in dry acetonitrile (15 mL) was heated to reflux temperature under nitrogen for 5 h. The reaction solvents were evaporated to dryness and the foamy solid was triturated with ethyl acetate (20 mL). The resulting solid was filtered to give **1a·2Br** (42% yield). **Experiment 3:** A solution of **7**[21] (1.6 g, 5 mmol) and **8** (1.1 mL, 13.8 mmol) in dry dioxane (20 mL) was heated to reflux temperature under nitrogen for 17 h. The reaction solvents were evaporated to dryness and the foamy solid was triturated with ethyl acetate (20 mL). The resulting solid was filtered to give **1a·2Br** (75% yield).

Counterion Exchange with Dication 1b·2Br. − Dication 1b·2Cl: See Table 5. A solution of dicationic protophane **1b·2Br** (0.25 g, 0.52 mmol) in 96% ethanol (50 mL) was passed through a column packed with a strongly basic anion-exchange resin (Ion exchanger III, Merck, hydroxide form). The neutral eluates were acidified to pH = 3 with a concentrated hydrochloric acid solution, and the resulting solution was concentrated to dryness to afford the bromide **1b·2Cl**. − **Dication 1b·2PF$_6$:** See Table 5. A solution of ammonium hexafluorophosphate (0.5 g) in water (5 mL) was added to a solution of dicationic protophane **1b·2Br** (0.14 g, 0.3 mmol) in water (5 mL), and the mixture was stirred overnight. The resulting solid was filtered and triturated in water (2 × 5 mL) and diethyl ether (3 × 5 mL). The solid was filtered to afford the hexafluorophosphate **1b·2PF$_6$**.

3,3′-Diadamantyl-1,1′-[1,3-phenylenebis(methylene)]bis(imidazolium) Dichloride (2a·2Cl): See Table 5. A solution of 1,3-bis(chloromethyl)benzene (**6**; 0.44 g, 2.5 mmol) in dry acetonitrile (10 mL) was added under nitrogen to a solution of 1-adamantylimidazole (**9a**;[22] 1 g, 5 mmol) in dry acetonitrile (20 mL), and the mixture was heated to reflux temperature for 4 d. The reaction mixture was allowed to cool to room temperature and filtered, and the obtained solid was dried to give **2a·2Cl**.

3,3′-Diadamantyl-1,1′-[5-*tert*-butyl-1,3-phenylenebis(methylene)]-bis(imidazolium) Dichloride (2b·2Br): See Table 5. A solution of 1,3-bis(bromomethyl)-5-*tert*-butylbenzene (**7**;[21] 0.64 g, 2 mmol) and 1-adamantylimidazole (**9a**;[22] 0.83 g, 4.1 mmol) was heated to reflux temperature under argon for 3.5 h. The reaction mixture was allowed to cool to room temperature and filtered, and the solid was triturated with dry acetonitrile (20 mL). The resulting solid was filtered to afford **2b·2Br**.

Counterion Exchange. − Dication 2b·2PF$_6$: See Table 5. A solution of dicationic protophane **2b·2Br** (0.1 g, 0.14 mmol) in 96% ethanol (50 mL) was passed through a column packed with a strongly basic anion-exchange resin (Ion exchanger III, Merck, hydroxide form). The neutral eluates were acidified to pH = 3 with concentrated hexafluorophosphoric acid solution, and the resulting solution was concentrated to dryness to afford the hexafluorophosphate **2b·2PF$_6$**.

1-(1-Adamantyl)-4,5-diphenyl-1*H*-imidazole (9c): See Table 5. A mixture of 4,5-diphenylimidazole (4.4 g, 20 mmol) and 1-bromoadamantane (2.2 g, 10 mmol) was heated to 200 °C for 4 d. The reaction mixture was allowed to cool to room temperature, and chromatographed on silica gel (SiO_2; CH_2Cl_2/EtOH, 98:2, v/v). The fractions containing the product were chromatographed on silica gel (SiO_2; hexane/EtOAc, 50:50, v/v) to give **9c**.

3,3′-Diadamantyl-4,4′,5,5′-tetraphenyl-1,1′-[1,3-phenylenebis-(methylene)]bis(imidazolium) Dichloride (2c·2Cl): See Table 5. A solution of 1,3-bis(chloromethyl)benzene (**6**; 0.18 g, 1 mmol) in dry dioxane (4 mL) was added under nitrogen to a solution of 1-adamantyl-4,5-diphenylimidazole (**9c**; 0.74 g, 2.1 mmol) in dry dioxane (10 mL), and the mixture was heated to reflux temperature for 7 d. The reaction mixture was allowed to cool to room temperature and filtered, and the obtained solid was triturated with dry ethyl ether (3 × 2 mL) and dried to give **2c·2Cl**.

3,3′-Dimethyl-1,1′-[3,5-(1*H*-1,2,4-triazolylene)bis(methylene)]-bis(imidazolium) Dichloride (3·2Cl): See Table 5. **Method A:** A solution of 3,5-bis(chloromethyl)-1*H*-1,2,4-triazole (**10**;[3c] 1.6 g, 9.6 mmol) and 1-methylimidazole (**8**; 3.8 g, 24.0 mmol) was heated to 135 °C under nitrogen for 7 min. The reaction mixture was cooled and triturated with dry acetone. The resulting solid was filtered and dried to afford **3·2Cl**. An analytical sample was obtained by recrystallization with 2-propanol.

Dicationic Protophane 4·2Cl: See Table 5. **Method B:** A mixture of 3,5-bis(chloromethyl)-1*H*-1,2,4-triazole (**10**;[3c] 1.0 g, 6.0 mmol) and 1-benzyl-1*H*-imidazole (**11**; 3.8 g, 24.0 mmol) was heated to 140 °C in a sealed tube for 10.5 h. The reaction mixture was cooled and triturated with dry acetone (4 × 100 mL). The resulting solid was filtered, dissolved in water (100 mL) and washed in dichloromethane (6 × 100 mL). The aqueous layer was concentrated to dryness to give **4·2Cl**.

Dicationic Protophane 5·2Cl: See Table 5. **Method C:** *N*-Benzhydrylimidazole (**12**;[23] 1.4 g, 6.0 mmol) was added to a solution of 3,5-bis(chloromethyl)-1,2,4-triazole (**10**;[3c] 0.5 g, 3.0 mmol) in dry acetonitrile (25 mL), and the mixture was heated to 105 °C in a sealed tube for 49 h. The reaction solvents were evaporated to dryness, and the residue was dissolved in water (60 mL) and washed with dichloromethane (8 × 20 mL). The aqueous layer was concentrated to dryness to give **5·2Cl**.

Dicationic Protophanes 4·2Br and 5·2Br: See Table 5. **Method D:** An anion-exchange resin (Amberlist A-26, bromide form, 0.8 mmol of bromide anion) was added to a solution of protophanes **4·2Cl** or **5·2Cl** (0.1 mmol) in 96% ethanol (10 mL), and the suspension was stirred at room temperature for 45 min. The suspension was then filtered, the resin was washed with ethanol (2 × 5 mL), and the solution was concentrated to dryness to afford **4·2Br** and **5·2Br**, respectively. Alternatively, a solution of protophane **5·2Cl** (50 mg, 0.08 mmol) in 96% ethanol (20 mL) was passed through a column packed with a strongly basic anion-exchange resin (Amberlite IRA-401, hydroxide form). The neutral eluates were acidified with 47% HBr solution, and the solution was concentrated to dryness to afford the bromide **5·2Br**.

Betaines 13·OH−15·OH: See Table 5. **Method E:** A solution of a dicationic protophane **3·2Cl−5·2Cl** (0.1 g) in 96% ethanol (30 mL) was passed through a column packed with a strongly basic anion-exchange resin (Amberlite IRA 401, hydroxide form). The neutral eluates were concentrated to dryness at room temperature to afford the corresponding hydroxides **13·OH−15·OH**.

3,5-Bis(3-methyl-1-imidazoliomethyl)-1*H*-1,2,4-triazolate (13·Cl): See Table 5. **Method F:** A solution of the dicationic protophane **3·2Cl** (0.06 g, 0.2 mmol) in 96% ethanol (20 mL) was passed through a column packed with a strongly basic anion-exchange

resin (Amberlite IRA 401, hydroxide form). Hydrochloric acid solution (0.12 M, 1.5 mL, 0.2 mmol) was carefully added to the neutral eluates. The solution was concentrated to dryness to give an oil, which was washed in dry acetonitrile (2 × 5 mL) and dried to afford **13·Cl**.

1-Benzhydryl-3-benzylimidazolium Bromide (18·Br): See Table 5. Benzhydryl bromide (1.55 g, 6.3 mmol) was added to a solution of 1-benzylimidazole (**11**; 1 g, 6.3 mmol) in dry acetonitrile (25 mL), and the mixture was heated to reflux temperature for 12.5 h. Benzhydryl bromide (0.4 g, 1.6 mmol) was then added and the mixture was further refluxed for 73 h. The reaction mixture was washed in diethyl ether (5 × 100 mL), and the residue was dried to give **18·Br**.

Protophanes 21a and 21b: See Table 5. A suspension of 1*H*-imidazole (686 mg, 10.1 mmol) or 4,5-dimethylimidazole hydrochloride (1.33 g, 10.1 mmol) and finely powdered 85% potassium hydroxide (668 mg, 10.1 mmol and 1.34 g, 20.2 mmol, respectively) in dry dimethylformamide (200 mL) was vigorously stirred under nitrogen at room temperature for 1.5 h. A solution of 1-benzhydryl-3,5-bis(chloromethyl)-1*H*-1,2,4-triazole (**26**; 1.67 g, 5.0 mmol) in dry dimethylformamide (40 mL) was then added dropwise, and the mixture was stirred at 80 °C for 47 h. The reaction mixture was cooled, and the solvent was removed to dryness. The resulting oil was extracted with dichloromethane (3 × 50 mL) and brine. The organic layers were collected, dried (Na_2SO_4) and filtered, and the solvents were evaporated. The oily residue was purified by flash chromatography (SiO_2) with chloroform or chloroform/methanol mixtures of increasing polarity. Compound **21a** was further purified by trituration with hexane (2 × 10 mL) to afford **21a** as a solid. For compound **21b**, the fractions containing the product were collected, the solvent was removed, and the residue was dissolved in dichloromethane and water, neutralized to pH = 7 with a saturated aqueous solution of sodium carbonate and extracted with dichloromethane (3 × 30 mL). The organic layers were dried (Na_2SO_4) and filtered, and the solvents were evaporated to afford **21b**.

Preparation of Dicationic Protophane 22a·CF_3CO_2: See Table 5. A stirred solution of protophane **21a** (5.1 g, 12.9 mmol) and phenol (5.1 g, 54.2 mmol) in trifluoroacetic acid (10 mL) was refluxed for 1 h. The reaction mixture was cooled, the solvent was removed to dryness, and the resulting oil was triturated with dry diethyl ether (4 × 20 mL) and filtered to give the corresponding trifluoroacetate **22a·2CF_3CO_2**.

4-Amino-1-benzhydryl-3,5-bis(hydroxymethyl)-1,2,4-triazolium Bromide (24·Br): See Table 5. A suspension of 4-amino-3,5-bis(hydroxymethyl)-1,2,4-triazole (**23**;[3c] 0.5 g, 3.5 mmol) and benzhydryl bromide (0.9 g, 3.5 mmol) in dry dimethylformamide (40 mL) was stirred in a sealed tube at 90 °C for 48 h. The reaction mixture was cooled, the solvent was evaporated to dryness, and the resulting oil was triturated with diethyl ether (3 × 100 mL), dichloromethane (3 × 20 mL) and methanol (3 × 20 mL) to yield the bromide **24·Br**.

1-Benzhydryl-3,5-bis(hydroxymethyl)-1*H*-1,2,4-triazole (25): See Table 5. **Method 1:** A solution of sodium nitrite (9.4 mg, 13.7 mmol) in water (50 mL) was added dropwise to a suspension of the bromide **24·Br** (2.7 g, 6.8 mmol) in water (200 mL) and 35% HCl aqueous solution (7.2 mL, 68.4 mmol) at a temperature between 0 and 10 °C. The suspension was stirred at room temperature for 22 h. The resulting solution was neutralized to pH = 7 with solid sodium carbonate and the solid formed was filtered and identified as **25**. **Method 2:** A suspension of 4-amino-3,5-bis(hydroxymethyl)-1,2,4-triazole (**23**;[3c] 0.5 g, 3.5 mmol) and benzhydryl bromide (0.9 g, 3.5 mmol) in dry dimethylformamide (40 mL) was stirred in a sealed tube at 90 °C for 48 h. The reaction mixture was cooled, the solvent was evaporated to dryness, and the remaining oil was triturated with diethyl ether (3 × 100 mL) and dichloromethane (3 × 10 mL). The resulting solid was suspended in water (100 mL) and 35% HCl aqueous solution (3.7 mL, 35 mmol), and a solution of sodium nitrite (0.5 g, 6.9 mmol) in water (40 mL) was then added at a temperature between 0 and 10 °C. The solution was neutralized to pH = 7 with solid sodium carbonate, and the solid was filtered to give **25**.

Attempted Formation of 25 from Hydroxy Derivative 27: 3,5-Bis(hydroxymethyl)-1*H*-1,2,4-triazole (**27**;[3c] 0.5 g, 4.0 mmol) was added to a solution of 85% potassium hydroxide (0.26 g, 4.0 mmol) in dry methanol (50 mL), and the mixture was stirred under nitrogen at room temperature for 1 h. Benzhydryl bromide (1.08 g, 4.4 mmol) was then added and the mixture was heated at 60 °C for 27 h. The reaction solvents were evaporated to dryness and the residue was dissolved in dry dimethylformamide. The solution was heated at 110 °C for 19 h and 125 °C for 22 h. The reaction progress was monitored by TLC, which indicated the recovery of the starting material **27**.

1-Benzhydryl-3,5-bis(chloromethyl)-1*H*-1,2,4-triazole (26): See Table 5. Derivative **25** (0.7 g, 2.4 mmol) was added portionwise to thionyl chloride (2.4 mL, 3.7 mmol) externally cooled with an ice bath. The suspension was refluxed to 5 h. The mixture was cooled and the excess of thionyl chloride was removed in a rotary evaporator, and the residue was dissolved in dichloromethane (10 mL), basified to pH = 8 with a 2 N sodium carbonate aqueous solution and extracted with dichloromethane (3 × 50 mL). The organic extracts were dried (Na_2SO_4) and filtered, and the solvents were evaporated to afford **26**.

General X-ray Crystallographic Procedures. – Dication 1b·2PF_6: Single crystals of **1b·2PF_6**, suitable for X-ray crystallography, were grown by recrystallization of the salt from ethanol. The unit cell parameters were obtained from the least-squares fit of 25 reflections (with θ between 10° and 13°). Data were collected at 293 K with the ω-2θ scan technique and a variable scan rate, with a maximum scan time of 60 s per reflection. The final drift correction factors were between 0.97 and 1.00. Profile analysis[24,25] was performed on all reflections. Lorentz and polarization corrections were applied and the data were reduced to F_o^2 values. Semiempirical absorption correction was applied using ψ-scans,[26] resulting in maximum and minimum correction factors of 1.00 and 0.57, respectively. The structure was solved by Patterson methods and phase extension with DIRDIF-96.[27] Isotropic full-matrix, least-squares refinement on F^2 was carried out with SHELXL-97.[28] Crystallographic symmetry was carefully checked and found to be *C*2/*c*. The carbon atoms of the *tert*-butyl group were refined with an occupancy factor of 0.5 in order to make them compatible with the twofold axis that runs through C9. Hydrogen atoms were located by Fourier difference synthesis, except those of the CH_2 and CH_3 groups, which were placed geometrically. In this case, the coordinates were refined riding on their parent atom. During the final stages of the refinement, the positional parameters and the anisotropic thermal parameters of the non-H atoms were refined. The carbon atoms of the *tert*-butyl group were refined isotropically. All hydrogen atoms not placed geometrically were refined isotropically using a common thermal parameter. Hydrogen atoms in CH_2 and CH_3 groups were refined with a thermal parameter dependent on the correspondent carbon atom. The function minimized was $[\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$, $w = 1/[\sigma^2(F_o^2) + (0.1490 \cdot P)^2 + 2.0543 \cdot P]$, where $P = [\max(F_o^2,0) + 2 \cdot F_c^2]/3$ with $\sigma^2(F_o^2)$ from counting statist-

ics. The maximum shift to e.s.d. ratio in the last full-matrix, least-squares cycle was less than 0.001. The final difference Fourier map showed no peak higher than 0.552 e·Å^{-3} nor any deeper than −0.455 e·Å^{-3}. Atomic scattering factors were taken from International Tables for X-ray Crystallography.[29] Geometrical calculations were made with PARST.[30] The crystallographic plots were made with EUCLID[31] and ORTEP-3.[32] All calculations were made at the University of Oviedo on the Scientific Computer Center and X-ray group VAX/AXP computers.

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