Selection of Betaine Building Blocks for the Construction of Quadrupolar Heterophane Frameworks[‡]

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Keywords: Betaines / Cyclophanes / Dipole moments / Mass spectrometry / NMR spectroscopy

The synthesis of a set of [(azolio)methyl]azolate betaines **3**–**6** designed by combination of a variety of heterocyclic fragments based on pyrazole, 1,2,4-triazole, and benzimidazole is reported. The dipolar nature of the betaines is discussed on the basis of ^{1}H and ^{13}C NMR spectroscopic data and dipole moment values, which range between 13.4 and 16.5 D. By exploitation of the sensitivity of electrospray ionization mass spectrometry in both the positive and negative modes, several informative peaks and stable noncovalent polymolecular self-assembled structures in the gas phase were observed. From these results, the [(imidazolio)methyl]-1,2,4-triazolate betaine subunits **1** were chosen as the most suitable building blocks for the construction of quadrupolar [1$_n$]heterophanes.

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Introduction

A survey of possible novel heterocyclic structures demonstrates that betaines form an ensemble of highly dipolar chemical entities of low molecular weight.[2] Accordingly, imidazolium (pyridinium) azolate betaines with a range of spacers represent a pool of versatile dipolar molecular platforms, the incorporation of which in a variety of frameworks permits the development of applications in organic advanced materials[3] and supramolecular scaffolds.[4] [(Imidazolio)methyl]-1,2,4-triazolate inner salts,[5] for example, are building blocks for nonclassical quadrupolar [1$_4$] and [1$_6$]metaheterophanes[4] (Figure 1), while several betaines of this pool have found an application in second-order nonlinear optical (NLO) materials.[3,6−8]

The design of novel macrocyclic systems built up from betaines is hindered by the difficulty in choosing appropriate betaine subunits. We chose [(imidazolio)methyl]-1,2,4-triazolate betaines after rigorous examination both of their physical properties and of their chemical stabilities.[3a] The C−CH$_2$−N′ spacer was considered appropriate, and the [(imidazolio)- and (pyridinio)methyl]-1,2,4-triazolate betaines **1a**, **1b**, **2c**, and **2d** (Figure 2) were studied.[5] Related compounds were devised by changing the nature of the π-rich and/or π-deficient heteroaromatic moieties.[9] Kauffmann's areno-analogy principle permits heteroaromatic fragments to be related with classical functional groups.[9a] In this context, the electronic effects of heterocyclic fragments as substituents have been examined,[9b−9d] and the basicity and acidity of the azoles have been reviewed.[9e] In the current study, several examples of betaines **3**−**6** − especially those (**3** and **4**) with a pyrazolate nucleus (Figure 2) − have been examined and their physical and chemical properties tested. From previously reported findings[5] and the results described in this work, we have concluded that [(imidazolio)methyl]-1,2,4-triazolate betaines **1a** and **1b** constitute the best building blocks for the construction of quadrupolar [1$_n$]heterophanes,[4] due both to their synthetic accessibility and to their chemical stability.

Results and Discussion

Synthesis

The precursors of the target betaines **1**,[5] **2**,[5] and **3**−**6** are the *N*-[(azolyl)methyl]imidazolium, -pyridinium and -triazolium salts **7·X**,[5] **8·Cl**,[5] and **9·X**−**12·X** (Scheme 1). The imidazolium, pyridinium and triazolium quaternary salts **9a·X**, **9b·X**, **10d·Cl**, **11b·Cl**, **11e·Cl**, **12b·Cl**, and **12e·Cl** were prepared by treatment of (chloromethyl)azoles **13**−**15** with a 1-alkylimidazole, a pyridine, or a 1-alkyl-1,2,4-triazole. The yields were variable, depending on the success of purification and stability in solution. As one example, compound **9b·X** was isolated as its tetrafluoroborate salt

[‡] Heterocyclic Betaines, 48. Part 47: Ref.[1]

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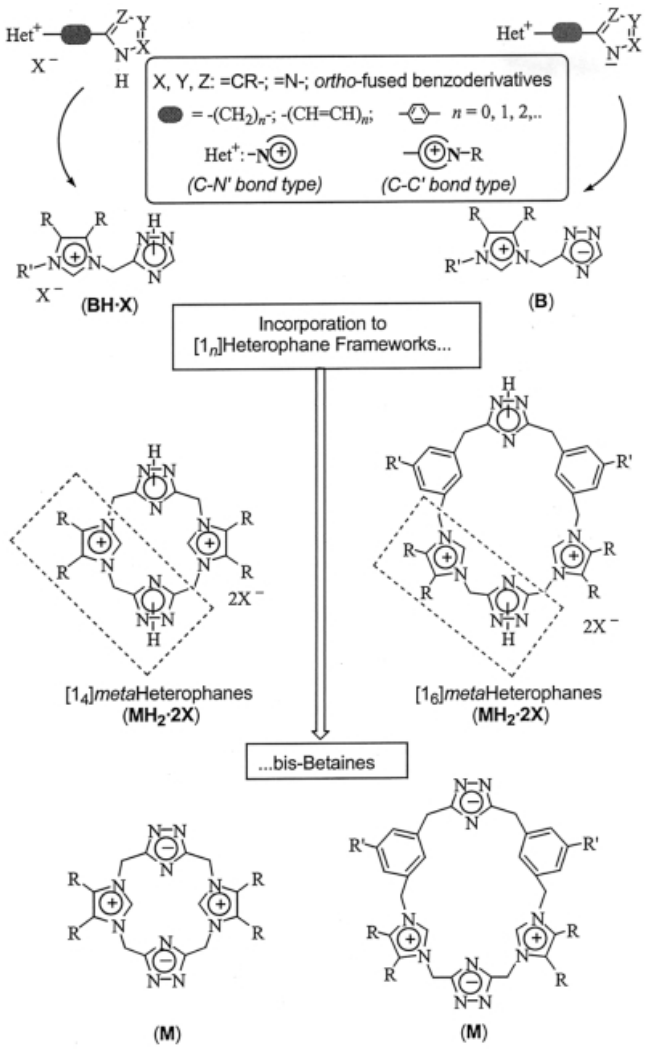


Figure 1. Incorporation of [(imidazolio)methyl]-1,2,4-triazolate betaine moieties into quadrupolar [1*n*]metaheterophanes

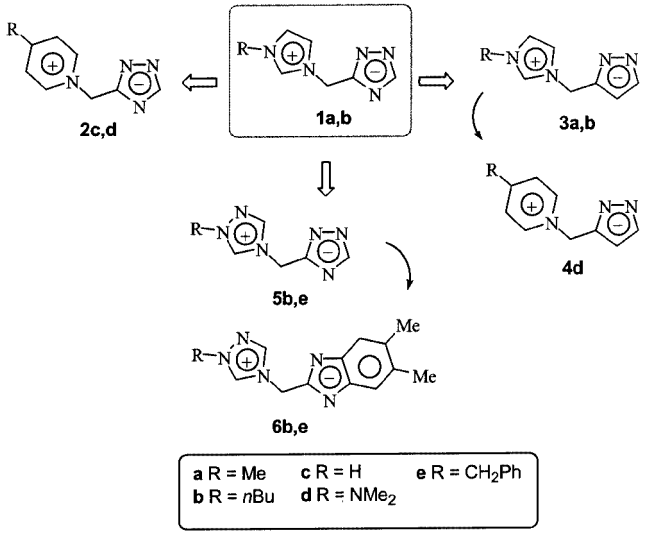
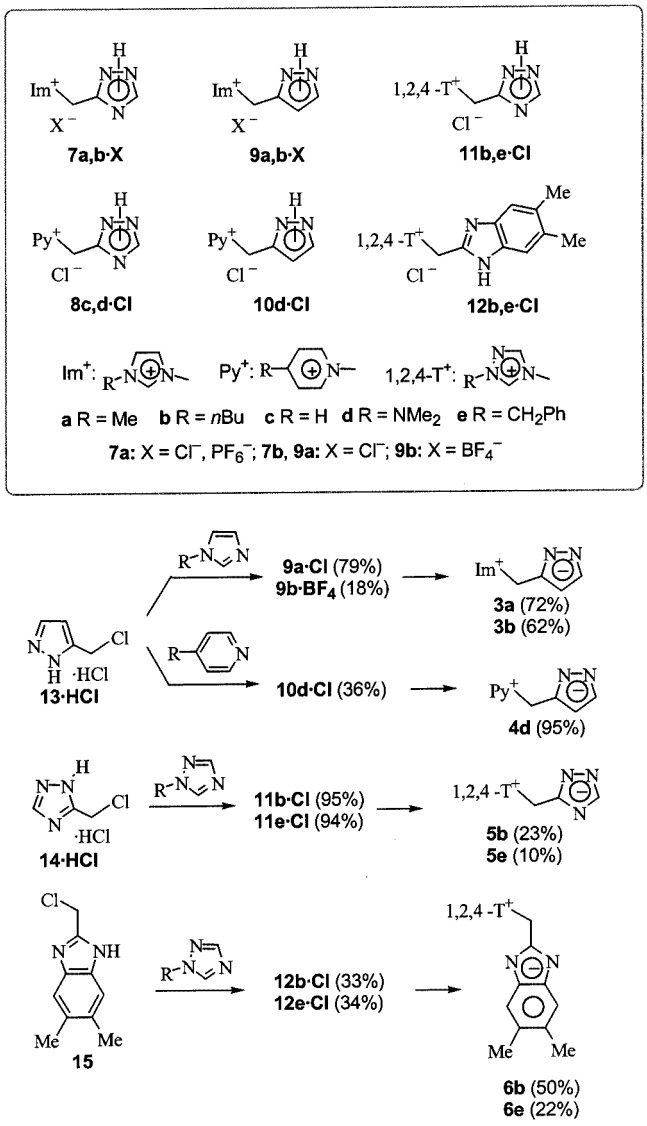


Figure 2. Construction of heterocyclic betaines by combining azole subunits



Scheme 1. Synthesis of [(azolio)methyl]azolate betaines **3**−**6**

(Scheme 1 and Exp. Sect.). The [(pyrazolyl)methyl]imidazolium and -pyridinium salts **9·X** and **10·Cl** were fairly unstable and difficult to isolate both in solution and in the solid state, which partially explains the moderate reported yields for their preparation, especially in comparison to benzimidazolyl or triazolyl analogues.[5] For the same reason, preparation of the unsubstituted pyridinium derivative was not attempted, since we predicted[5] that it would be less stable than the 4-(dimethylamino)pyridinium derivative **10d·Cl**.

Deprotonation of azolylimidazolium and -pyridinium salts with different spacers has usually proceeded in > 80% yield.[3a,5] However, by use of a basic ion-exchange resin (OH^- form),[5] the key precursors **9a·X**, **9b·X**, **10d·Cl**, **11b·Cl**, **11e·Cl**, **12b·Cl**, and **12e·Cl** were transformed into the corresponding betaines **3a**, **3b**, **4d**, **5b**, **5e**, **6b**, and **6e** in yields that varied from 10 to 95%. Unfortunately, the heterocyclic betaines reported here were unstable, which explains the low yields obtained, and products of alteration

and decomposition were detected both in solution and in the solid state. In particular, the [(triazolio)methyl]benzimidazolate inner salts **6b** and **6e** were among the least stable, as were especially those containing a benzyl group, such as the betaines **5e** and **6e**. This low chemical stability of the [(triazolio)methyl]azolate inner salts limited some aspects of their study in solution, such as the recording of their NMR spectra.

Structural Studies

The structural properties of [(imidazolio)- and (pyridinio)methyl]azolate betaine had previously been examined both in solution and in the solid state by spectroscopic methods (IR, ^{1}H and ^{13}C NMR), by their experimental dipole moment values (which were in the range of 12.34 to 15.34 D in dioxane), and by single-crystal X-ray diffraction analysis.[5] Theoretical studies are based on experimental molecular geometry and dipole moments, and the method of choice to predict experimentally observable trends of these betaines is AM1 SCF-MO. The dipole moment values of betaines **1b**, **2c**, **2d**, and **3b** are: **1b**: μ_{exp} = 15.34 D, $\mu_{calcd(AM1)}$ = 15.39 D; **2c**: $\mu_{calcd(AM1)}$ = 13.43 D; **2d**: μ_{exp} = 14.82 D, $\mu_{calcd(AM1)}$ = 16.52 D; **3b**: $\mu_{calcd(AM1)}$ = 14.34 D.

The dipole moment values evaluated from AM1 SCF-MO[10] calculations compare well with the experimental values,[5] especially for the [(butylimidazolio)methyl]triazolate inner salt **1b** (see Supporting Information).

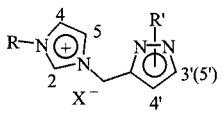
Spectroscopic Methods

The IR spectra of the quaternary salt precursors **9a·Cl**, **10d·Cl**, **11b·Cl**, **11d·Cl**, **12b·Cl**, and **12e·Cl** showed absorptions in the 3400−3200 cm^{-1} (ν_{NH}) and 2800−2500 cm^{-1} ranges (hydrochlorides), while compound **9b·BF$_4$** showed absorption in the 1200−1000 cm^{-1} range (tetrafluoroborate). For the corresponding betaines **3**−**6**, these bands were absent.

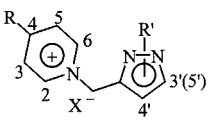
The NMR spectra and the experimental and the calculated (AM1 SCF-MO) dipole moments contribute to deeper understanding of the dipolar nature, as for that of the previously reported azolate analogues **1** and **2**. The NMR results provide evidence of the charge distribution within the betaines **1**−**6**, the choice of the solvent being dictated by the product's solubility. For reliable interpretation of data measured in solution, however, intermolecular forces and hydration have to be taken into consideration. To reduce the perturbing dominance of these effects, anhydrous samples were used at high dilution, and the water content of the solvent was reduced as much as possible, by experimental procedures similar to those described previously.[5]

Selected ^{1}H chemical shifts are given in Tables 1 and 2, and ^{13}C NMR parameters are listed in the Supporting Information. The results obtained from these spectroscopic data were compared with those described for related anionic species in the azole series,[5] and unambiguous assignments were performed by use of NOESY, HMBC, and HMQC techniques. For the less studied 1,2,4-triazolium moiety, the model compound 1,4-dibutyl-1,2,4-triazolium iodide was prepared, and the ^{1}H and ^{13}C NMR spectroscopic data were compared with the NMR spectroscopic data of bis(triazolium) salts previously reported[11] (see Supporting Information). The aggregation of the model pair **1a** and **7a·X** (X = Cl$^-$, PF_6^-), was examined by ^{1}H NMR in [D$_6$]DMSO. Hydrogen bonding and electrostatic interactions were weakened by solvation, and no significant chemical shift changes were observed at concentrations ranging from 17.5 to 61.3 mM for **1a** and 35.8 to 170 mM for **7a·X** (see below, Electrospray Mass Spectrometry).

Table 1. ^{1}H NMR data of [(imidazolio)methyl]pyrazolate **3a** and **3b** and [(pyridinio)methyl]pyrazolate **4d** inner salts and their corresponding *N*-(pyrazolylmethyl)imidazolium salts **9a·X** and **9b·X** and *N*-(pyrazolylmethyl)pyridinium salt **10d·Cl**



3a, **3b**, **9a·Cl**, **9b·BF$_4$**



4d, **10d·Cl**

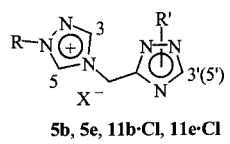
3a: R = Me R' = – X = –
3b: R = *n*Bu R' = – X = –
4d: R = NMe$_2$ R' = – X = –
9a: R = Me R' = H X = Cl
9b: R = *n*Bu R' = H X = BF$_4$
10d: R = NMe$_2$ R' = H X = Cl

Compd.[a][b]	H-2	H-4	H-5	−CH$_2$−	H-3′(5′)	H-4′	R
3a	[c]	7.62	7.69	5.28	7.46	6.03	3.81
9a·Cl	9.26	7.71	7.76	5.42	7.76	6.36	3.85
Δδ[d]	–	−0.09	−0.07	−0.14	−0.30	−0.33	−0.04
3b	[c]	7.55	7.58	5.36	7.50	6.19	4.15
9b·BF$_4$	9.23	7.76	7.76	5.40	7.77	6.35	4.16
Δδ[d]	–	−0.21	−0.18	−0.04	−0.27	−0.16	−0.01
	H-2,6	H-3,5	H-4				
4d	8.31	6.69	–	5.28	7.36	6.00	3.13
10d·Cl	8.35	7.03	–	5.40	7.73	6.33	3.13
Δδ[d]	−0.04	−0.07	–	−0.12	−0.37	−0.33	−0.03

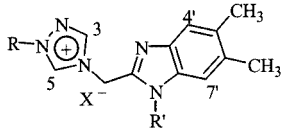
[a] ^{1}H NMR spectroscopic data in [D$_6$]DMSO. [b] All compounds were very unstable in [D$_6$]DMSO. [c] No signal observed, due to H/D exchange. [d] Δδ: difference in the chemical shift of inner salts **3a**, **3b**, and **4d**, and their corresponding salts **9a·Cl**, **9b·BF$_4$**, and **10d·Cl**.

The CH protons of the azole ring were more shielded in the anion than in the neutral molecule. Figure 3 in the Supporting Information shows selected ^{1}H NMR chemical shift differences [Δδ(H) (ppm) at 200 MHz in [D$_6$]DMSO] between betaines **3a**, **4d**, **5b**, and **6b** and their quaternary cationic salts **9a·Cl**, **10d·Cl**, **11b·Cl**, and **12b·Cl**, respectively. As can be seen from the ΔδH values between pyrazolate betaines **3** and **4** and the pyrazolyl salts **9·X** and **10·Cl**, the most strongly affected values were, notably, those of the pyrazolate/pyrazole ring, followed by the methylene spacer. For compound **3a**, for example, Δδ[H-3(5)] = −0.30 ppm, Δδ(H-4) = −0.33 ppm, and Δδ(CH$_2$) = −0.14 ppm. For the **3b/9b·BF$_4$** pair, anomalous chemical shifts were observed, and these are mainly attributed to the instability of

Table 2. ^{1}H and ^{13}C NMR spectroscopic data of [(triazolio)methyl]azolate inner salts **5b**, **5e**, and **6b**, and their corresponding *N*-(azolylmethyl)triazolium salts **11b·Cl**, **11e·Cl, 12b·Cl**, and **12e·Cl**.



5b, **5e**, **11b·Cl**, **11e·Cl**



6b, **12b·Cl**, **12e·Cl**

5b: R = *n*Bu R' = – X = –
5e: R = CH_2Ph R' = – X = –
11b: R = *n*Bu R' = H X = Cl
11e: R = CH_2Ph R' = H X = Cl

6b: R = *n*Bu R' = – X = –
12b: R = *n*Bu R' = H X = Cl
12e: R = CH_2Ph R' = H X = Cl

Compd.[a]	H-3	H-5	$-CH_2-$	H-3′(5′)		R
5b	9.30	[b]	5.45	7.64		4.39[c]
11b·Cl	9.39[d]	10.46[d]	5.71	8.63		4.26[c]
Δδ[e]	−0.09	–	−0.26	−0.99		−0.13
5e	9.26	[b]	5.44	7.63		5.63, 7.38−7.40
11e·Cl	9.36	10.53	5.70	8.62[f]		5.70, 7.40−7.47
Δδ[e]	−0.10	–	−0.26	−0.99		−0.07, −0.02, −0.07
				H-4′,7′	$-CH_3$	
6b	9.33	[b]	5.58	7.11	2.22	4.35[c]
12b·Cl	9.45	10.49	5.86	7.32	2.28	4.45[c]
Δδ[e]	−0.12	–	−0.28	−0.21	−0.06	−0.10
12e·Cl	9.50	10.58	5.72	7.55	2.37	6.19, 7.40−7.51

[a] In [D_6]DMSO; betaine **6e** is extremely unstable in [D_6]DMSO. [b] No signal observed. [c] Chemical shift quoted for the methylene group α to the triazolium ring. [d] Unambiguous assignment by NOESY. [e] Δδ: difference in the chemical shift of inner salts **5b**, **5e**, **6b**, and their corresponding salts **11b·Cl**, **11e·Cl**, and **12b·Cl**. [f] Weak signal.

betaine **3b** in solution, especially in dimethyl sulfoxide (Table 1).

In the case of the 1,2,4-triazole series, the most strongly affected chemical shift differences between the *s*-triazolate betaines **5b** and **5e** and the *s*-triazolyl salts **11b·Cl** and **11e·Cl** were those of the *s*-triazolate/*s*-triazole ring, followed by the methylene spacer: for compound **5b**, for instance, $\Delta\delta$[H-3(5)] = −0.99 ppm and $\Delta\delta(CH_2)$ = −0.26 ppm (Table 2). These values were in good agreement with those of previously described betaines containing 1,2,4-triazolate rings.[5]

Finally, for the benzimidazole series, the methylene interannular linkages were less shielded than those of previously reported [(imidazolio)methyl]benzimidazolate betaines:[5] for **6b** $\Delta\delta(CH_2)$ = −0.28 ppm (Table 2). In this case the benzimidazolate/benzimidazole protons were also quite strongly affected; shielding for the betaine **6b**, for instance {$\Delta\delta$[H-4(7)] = −0.21 ppm}, was in accordance with previous reports.[5]

The high instability of pyrazolate derivatives, especially betaines **3** and **4**, in solution obliged us to record the ^{13}C NMR spectra in CD_3OD (see Supporting Information), although it is not the solvent of choice for observation of the chemical differences between betaines and their corresponding salts, due to solvation. The benzimidazolate betaines **6b** and **6e** were unfortunately too unstable in solution for their ^{13}C NMR spectra to be recorded.

Electrospray Ionization Mass Spectrometry

Over recent years, ESI-MS has consolidated itself as an innovative analytical technique, normally involving the use of positive-ion ESI experiments.[12] However, recent negative-ion ESI-MS studies by Cole et al.[13] have expanded the current capabilities of the negative-ion mode work. On the other hand, we have exploited the sensitivity of the electrospray ionization technique to examine the gas-phase behavior of multicharged [1_4]metaheterophanes containing either proton-ionizable 1,2,4-triazole or betaine units, the dications (**MH_2·2X**) and bis(betaines) (**M**) shown in Figure 1.[14]

For macrocyclic bis(betaines) (**M**) and dicationic [1_4]metaheterophanes (**MH_2·2X**) (see Figure 1), the positive-ion ESI-MS data at 50 V showed the same major peaks, the base peak in both cases corresponding to the doubly charged ions $[MH_2]^{2+}$. At higher cone voltage the base peak was the ion $[M + H]^+$. The formation of self-assembled aggregates for bis(betaines), however, included the species $[2 M + H]^+$ and $[3 M + 2 H]^{2+}$ with relative abundances of ≤ 50%. ESI responses were not observed in the negative-ion mode experiments, with the exception of **MH_2·2PF_6**, which displayed a peak of a PF_6^- anion at m/z = 145.[14]

Here we utilized the sensitivity of electrospray ionization mass spectrometry to examine the betaine building blocks **1a**, **2c**, **4d**, **5b**, **5e**, **6b**, and **6e** (**B**), together with their cationic

counterparts **7a·Cl**, **7a·PF$_6$**, **8c·Cl**, **10d·Cl**, **11b·Cl**, **11e·Cl**, **12b·Cl**, and **12e·Cl** (**BH·X**). Experiments were carried out in both the positive- and negative-ion modes and all fifteen neutral analytes underwent proton-mediated ion-molecule reactions at low cone voltage (Vc = 55 V) while molecular fragmentation produced the most abundant species at 120 V (Tables 3 and 4, see Supporting Information).

Positive-Ion ESI-MS

In the positive-ion mode experiments, the base peak corresponded in each case to the ion $[BH]^+$. This common peak is the result of protonation of the betaines, such as **1a**, **2c** and **5b**, while in their precursors, such as **7a·Cl**, **7a·PF$_6$**, **8c·Cl** and **11b·Cl**, this peak corresponds to the loss of the counterion. The ESI$^+$ response at 120 V resulted in the appearance of several peaks arising from molecular fragmentation (Table 3). There was one exception: the base peak of betaine **5e** was the doubly charged dimeric species $[2\ BH + H_2O]^{2+}$ at m/z = 250.1 whereas the ion $[BH]^+$ was produced in a relative abundance of ≤ 14% at 55 V and even at 120 V (see Supporting Information).

Negative-Ion ESI-MS

The novel neutral analytes were examined and the comparative negative-ion ESI$^-$ response showed that betaines (**B**) and their corresponding salts (**BH·X**) produced distinct major peaks. The different ionic species arose from proton-mediated ion-molecule reactions and noncovalent interactions, which produced a variety of polymolecular self-assemblies (Table 4). For betaines **1a** and **5b**, the base peak was the negatively charged ion $[B-H]^-$ and for betaine **2c** it was either $[B-H]^-$ or $[B-H + H_2O]^-$. At a cone voltage of 120 V, betaines **2c** and **5b** gave rise to the appearance of several peaks due to molecular fragmentation. Similar ESI$^-$ response was observed for both betaines **6b** and **6e**. Dimeric and trimeric ionic self-aggregates $[2\ B-H + H_2O]^-$ and $[3\ B-H]^-$ were also formed (≤ 22%).

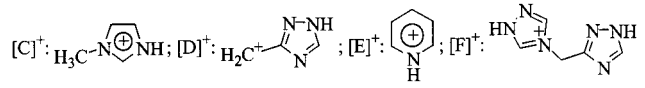
For the *N*-[(azolyl)methyl]azolium and -pyridinium salts examined (such as **7a·Cl**, **8c·Cl**, and **11b·Cl**), the ESI$^-$ response was remarkable for ions $[B + Cl]^-$ and $[BH + 2Cl]^-$ at a cone voltage of 55 V; less abundant ions (≤ 42%) correspond to the self-assembled species $[B + BH + 2\ Cl]^-$, and $[2\ BH + 3\ Cl]^-$.

The lack of hydrogen bonding between the PF_6^- counteranions with either dicationic protophanes[1] or [1$_4$]heterophanes[4] has been observed both in solution (^{1}H NMR) and in the solid state (X-ray diffraction analysis). Here, different ESI$^-$ responses for cations **7a·Cl** and **7a·PF$_6$** were observed, indicating weak noncovalent interactions with the PF_6^- anions in the gas phase. At a cone voltage of 55V, for example, the model building block pair **1a** and **7a·Cl/7a·PF$_6$** produced distinct ionic species, as shown in Figure 4 (see Supporting Information). Noncovalent self-aggregates were formed as a consequence of the hydrogen-bonded complexes with chloride anions, but further study to confirm this was impracticable because of instrument limitations in

Table 3. Summary of data obtained for **1a**, **2c**, **5b**, **7a·Cl**, **7a·PF$_6$**, **8c·Cl**, and **11b·Cl** by positive-ion ESI-MS

Vc [V]	Compd. (MW)[a]	Ions[b], m/z ratio Relative abundance (%)					Vc [V]	Compd. (MW)[a]	Ions[b], m/z ratio Relative abundance (%)				
		$[BH]^+$	$[C]^+$	$[D]^+$	$[E]^+$	$[F]^+$			$[BH]^+$	$[C]^+$	$[D]^+$	$[E]^+$	$[F]^+$
	7a·Cl (199.6)	164.1	83.1	82.1	80.1	151.2		**1a** (163.1)	164.1	83.1	82.1	80.1	151.2
55		**100**	2	[c]			55		**100**	1	[c]		
80		**100**	8	2			80		**100**	8	1		
120		25	**100**	44			120		30	**100**	38		
	7a·PF$_6$ (309.1)												
55		**100**	[c]	[c]									
80		**100**	22	5									
120		34	**100**	42									
	8c·Cl (196.6)	161.2						**2c** (160.1)	161.1				
55		**100**		[c]	1		55		**100**		[c]	[c]	
80		**100**		15	27		80		**100**		10	17	
120		28		67	**100**		120		43		77	**100**	
	11b·Cl (242.7)	207.3						**5b** (206.1)	207.1				
55		**100**		[c]		[c]	55		**100**		[c]		[c]
80[e]		**100**		1		12	80[d]		**100**		3		24
120[e]		13		82		52	120[d]		12		79		44

[a] Molecular weight (MW) of betaines (**B**) and cations (**BH·X**);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 ions:



[c] No signal observed. [d] Fragment ion at m/z = 70.1 (**5b**): 80 V (5%), 120 V (100%). [e] Fragment ion at m/z = 70.1 (**11b·Cl**): 80 V (4%), 120 V (100%).

Table 4. Selected data obtained for **1a**, **2c**, **5b**, **7a·Cl**, **7a·PF_6**, **8c·Cl**, and **11b·Cl** by negative-ion ESI-MS

Vc [V]	Compd. (MW.)[a]	Ions, *m/z* ratio Relative abundance (%)						
		$[B-H]^-$	$[B-H+H_2O]^-$	$[B-H+EtOH]^-$	$[2\,B-H]^-$	$[2\,B-H+H_2O]^-$	$[2\,B-H+EtOH]^-$	$[3\,B-H]^-$
	1a[b] (163.1)	162.1		208.1	325.2		371.2	488.3
55		**100**		13	22		9	10
80		**100**		3	13		4	6
120		**100**		2	15		1	6
	2c[b] (160.1)	159.1	177.1	205.1	319.2	337.2	365.2	479.3
55		38	**100**	62	18	15	29	5
80		**100**	74	29	15	5	8	1
120[d]		78	12	12	5	[c]	[c]	[c]
	5b[b] (206.1)	205.1		251.1	411.2			617.3
55		**100**		4	6			1
80		**100**		[c]	5			[c]
120[d]		39		[c]	2			[c]
		$[B+Cl]^-$	$[BH+2\,Cl]^-$	$[2\,B+Cl]^-$	$[B+BH+2\,Cl]^-$	$[2\,BH+3\,Cl]^-$	$[B+2\,BH+3\,Cl]^-$	$[3\,BH+4\,Cl]^-$
	7a·Cl (199.1)	198.1	234.1	361.2	397.1	433.1	596.1	632.2
55		**100**	72	15	42	22	3	2
80		**100**	48	5	18	20	1	3
120[d]		42	19	4	10	5	[c]	[c]
	7a·PF_6 (309.1)	$[PF_6]^-$ 145.0						
55		**100**						
80		**100**						
120		**100**						
	8c·Cl (196.1)	$[B+Cl]^-$ 195.0	231.0	355.2	391.1	427.1	587.2	623.2
55[d]		72	98	9	39	46	15	32
80[d]		80	74	23	32	30	4	12
120[d]		54	55	15	12	5	[c]	[c]
	11b·Cl (242.1)	241.1	277.0		483.1	519.1		761.2
55		**100**	55		2	17		22
80[d]		25	18		1	4		[c]
120[d]		8	7		[c]	[c]		[c]

[a] Molecular weight (MW) of betaines (**B**) and cations (**BH·X**); 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] Only betaine **1a** was dried at 80 °C in a vacuum oven for 5 h. [c] No signal observed. [d] Fragment ion (100%): **2c** (120 V) at *m/z* = 81.4; **5b** (120 V) at *m/z* = 97.2; **7a·Cl** (120 V) at *m/z* = 144.8; **8c·Cl** (55 V) at *m/z* = 116.2, (80 V) at *m/z* = 116.2, (120 V) at *m/z* = 160.8; **11b·Cl** (80 V) at *m/z* = 69.5, (120 V) at *m/z* = 97.3.

lowering the cone voltage below 55 V to carry out appropriate negative-ion ESI-MS/MS experiments.

Conclusion

The information obtained from the experimental data for the examined heterocyclic betaines reveals a dipolar molecular construction set that could be used to build up new molecular systems and materials. The structural properties of betaines have been examined and their ^1H NMR spectroscopic data provided evidence of the charge distribution in these betaines in solution. Electrospray ionization mass spectrometry revealed the formation of several informative ionic species in the gas phase. Moreover, this ESI mass spectral analysis, in both the positive and negative modes, illustrates an example of the very mild ionization conditions under which ions are transferred from solution to the gas phase, which allows the observation of stable self-assembled aggregates. Further studies are currently pursuing the use of betaine building blocks for the construction of supramolecular scaffolds ranging from quadrupolar to multipolar systems.

Experimental Section

Materials: 1-Butyl-1*H*-imidazole, butyl iodide, 4-(dimethylamino)-pyridine, and 1-methyl-1*H*-imidazole were purchased from commercial sources. 1-Benzyl-1*H*-1,2,4-triazole,[15,16] 1-butyl-1*H*-1,2,4-triazole,[15–17] 3(5)-(chloromethyl)-1*H*-pyrazole (**13**),[18] 3(5)-(chlor-

omethyl)-1*H*-1,2,4-triazole (**14**),[5,19] 2-(chloromethyl)-5,6-dimethyl-1*H*-benzimidazole (**15**),[5,20] 1-methyl-3-[1*H*-1,2,4-triazol-3(5)-ylmethyl]imidazolium salt **7a·Cl**[5] and the corresponding betaine **1a**[5] were prepared as described in the literature. ***Caution:*** The (chloromethyl)azoles **13**−**15** are blistering agents, especially 3(5)-(chloromethyl)-1,2,4-triazole **14**. Physical data for compounds **3a**, **3b**, **4d**, **5b**, **5e**, **6b**, **6e**, **9a·Cl**, **9b·BF$_4$**, **10d·Cl**, **11b·Cl**, **11e·Cl**, **12b·Cl** and **12e·Cl** are listed in Table 5 in the Supporting Information.

1-Methyl-3-[1*H*-1,2,4-triazol-3(5)-ylmethyl]imidazolium Hexafluorophosphate [(7a)·PF$_6$]: Betaine **1a**[5] (50 mg) was dissolved in 96% ethanol (50 mL) and the solution was passed through a column packed with a strongly basic anion-exchange resin (ion exchanger III, hydroxide form). The neutral eluates were acidified to pH = 6 with HPF_6/H_2O, and the resulting solution was concentrated to dryness at room temperature to give **7a·PF$_6$** as a white solid, yield 95%, m.p. 111−112 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 3.86 (s, 3 H, CH_3), 5.55 (s, 2 H, CH_2), 7.70 (dd, *J* = 1.8, 2.0 Hz, 1 H, H-4), 7.76 (dd, *J* = 1.8, 1.9 Hz, 1 H, H-5), 8.57 [s, 1 H, H-3′(5′)], 9.21 (br s, 1 H, H-2) ppm.

1-Alkyl-3-(1*H*-pyrazol-3(5)-ylmethyl)imidazolium Salts 9a·Cl and 9b·BF$_4$. Method A: A solution of 3(5)-(chloromethyl)pyrazole hydrochloride (**13**,[18] 1.7 g, 11.3 mmol) and 1-alkylimidazole (33.3 mmol) was heated to 125 °C under nitrogen for 0.66 and 0.5 h, respectively.

1-Methyl-3-[1*H*-pyrazol-3(5)-ylmethyl]imidazolium Chloride [(9a)·Cl]: The reaction mixture was allowed to cool to room temperature and washed in dry diethyl ether (2 × 20 mL). The residue obtained was dissolved in 96% ethanol (40 mL), and the solution was passed through a column packed with a strongly basic anion-exchange resin (Amberlite IRA 401, hydroxide form). The neutral eluates were acidified to pH = 6 with an ethanolic hydrochloric acid solution, and the resulting solution was concentrated to dryness at room temperature. The residue was washed with acetone (2 × 5 mL) to afford the chloride **9a·Cl** as a viscous oil.

1-Butyl-3-[1*H*-pyrazol-3(5)-ylmethyl]imidazolium Tetrafluoroborate [(9b)·BF$_4$]: The reaction mixture was allowed to cool to room temperature and washed with hexane (3 × 30 mL). The residue obtained was dissolved in 96% ethanol (40 mL), and the solution was passed through a column packed with a strongly basic anion-exchange resin (Amberlite IRA 401, hydroxide form). The neutral eluates were acidified to pH = 6 with an ethereal tetrafluoroboric acid solution, and the resulting solution was concentrated to dryness at room temperature to give the tetrafluoroborate **9b·BF$_4$** as an oil.

4-(Dimethylamino)-1-[1*H*-pyrazol-3(5)-ylmethyl]pyridinium Chloride [(10d)·Cl]. Method B: A solution of 3(5)-(chloromethyl)pyrazole hydrochloride (**13**)[18] (1.1 g, 7.2 mmol) and 4-(dimethylamino)pyridine (1.8 g, 14.8 mmol) in dry dimethylformamide was heated to 120 °C under nitrogen for 0.4 h. The reaction mixture was allowed to cool to room temperature and the residue was filtered and washed in DMF (3 × 10 mL) under nitrogen. The residue obtained was suspended in dichloromethane (100 mL) and heated under reflux for 48 h. The resulting solid was filtered, washed in dichloromethane (2 × 5 mL), and dried to yield the chloride **10d·Cl**.

1-Alkyl-4-[1*H*-1,2,4-triazol-3(5)-ylmethyl]-1,2,4-triazolium Chlorides (11b)·Cl and (11e)·Cl. Method C: A solution of 3(5)-(chloromethyl)-1,2,4-triazole hydrochloride (**14**)[19] (1.0 g, 6.5 mmol) and either 1-butyl-1,2,4-triazole[15] (2.4 g, 19.5 mmol) or 1-benzyl-1,2,4-triazole[16] (4.65 g, 19.5 mmol) in dry DMF (10 mL) was heated to 130 °C under nitrogen for 2.75 and 4 h, respectively. The reaction mixture was allowed to cool to room temperature and the solvents were evaporated to dryness. The oily residue was washed in dry diethyl ether (3 × 5 mL) and the solid obtained was filtered and dried to give the chlorides **11b·Cl** and **11e·Cl** as hygroscope solids.

1-Alkyl-4-[(5,6-dimethyl-1*H*-benzimidazol-2-yl)methyl]-1,2,4-triazolium Chlorides 12b·Cl and 12e·Cl. Method D: A solution of 2-(chloromethyl)-5,6-dimethylbenzimidazole (**15**)[20] (1.0 g, 5.1 mmol) and either 1-butyl-1,2,4-triazole[16] (1.9 g, 15.4 mmol) or 1-benzyl-1,2,4-triazole[16] (2.45 g, 15.4 mmol) in dry DMF was heated to 130 °C under nitrogen for 1 and 1.75 h, respectively.

1-Butyl-4-[(5,6-dimethyl-1*H*-benzimidazol-2-yl)methyl]-1,2,4-triazolium Chloride [(12b)·Cl]: The reaction mixture was allowed to cool to room temperature, and the suspension was filtered. The solution was concentrated in a rotary evaporator and the solid was filtered. The combined solids were dissolved in hot DMF, and the insoluble residue was removed by filtration. The solution was concentrated to dryness and the residue was washed with diethyl ether (3 × 20 mL), filtered, and dried to afford the chloride **12b·Cl**.

1-Benzyl-4-[(5,6-dimethyl-1*H*-benzimidazol-2-yl)methyl]-1,2,4-triazolium Chloride [(12e)·Cl]: The reaction mixture was allowed to cool to room temperature and the suspension was filtered. The solid was dissolved in dry hot DMF, and the insoluble residue was removed by filtration. The solution was concentrated to dryness to yield chloride **12e·Cl**.

[(Pyridinio)methyl]pyrazolate 4d and [(Azolio)methyl]azolate Inner Salts 3a, 3b, 5b, 5e, 6b, and 6e. Method E: A solution of a [(pyrazolyl)methyl]pyridinium chloride (**10d**) or [(azolyl)methyl]azolium salt (**9a·Cl**, **9b·BF$_4$**, **11b·Cl**, **11e·Cl**, **12b·Cl**, or **12e·Cl**, 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 inner salts **3a**, **3b**, **4d**, **5b**, **5e**, **6b**, or **6e**. Yields are given in Table 5 of the Supporting Information.

1,4-Dibutyl-1,2,4-triazolium Iodide (Supporting Information): A solution of 1-butyl-1,2,4-triazole (1.5 g, 12 mmol) and butyl iodide (4.5 mL, 39.5 mmol) in dry acetonitrile (15 mL) was heated to reflux under nitrogen for 7 h. The reaction mixture was allowed to cool to room temperature and the solvents were evaporated to dryness. The resulting residue was washed in diethyl ether (5 × 50 mL), filtered, and dried to afford 1,4-dibutyl-1,2,4-triazolium iodide.

Electrospray Ionization Mass Spectrometry: The positive and negative ESI-MS experiments on compound pairs **1a**, **2c**, **4d**, **5b**, **5e**, **6b**, and **6e** (**B**) and **7a·Cl**, **7a·PF$_6$**, **8c·Cl**, **10d·Cl**, **11b·Cl**, **11e·Cl**, **12b·Cl**, and **12e·Cl** (**BH·X**) were performed as described elsewhere.[14] Identical samples of betaines were used in the ESI$^+$ and ESI$^-$ experiments, and betaine **1a** (**B**) was dried in a vacuum oven at 80 °C for 5 h. The ESI-MS data of selected compound pairs are listed in Tables 3 and 4. ESI$^+$ and ESI$^-$ data for all the fifteen neutral analytes examined are included in the Supporting Information. All mass spectrometry experiments were performed with a VG-Quattro mass spectrometer from Micromass Instruments, equipped with a pneumatically assisted electrospray ionization (ESI) source working at a cone voltage ≥ 55 V. For the positive-ion ESI-MS, the electrospray source operated under the following conditions: the nebulizing nitrogen gas flow was 10 L h^{-1} and the drying nitrogen flow 450 L h^{-1}, the source was heated to 80 °C with a capillary voltage of 3.5 kV and a cone voltage ranging between 55 and 120 V, depending on the experiment. Samples were dissolved in a 1:1 mixture of H_2O/CH_3CN and introduced directly into the mass spectrometer at a flow rate of 20 μL min^{-1}. Negative-ion ESI-MS experiments

were obtained under the same conditions as the positive-ion ESI-MS experiments with a capillary voltage of −3.5 kV.

Acknowledgments

We thank the Dirección General de Investigación (MCYT, Spain) for financial support, through grant PB 98-1164. Additional support came from the Comissionat per a Universitats i Recerca de la Generalitat de Catalunya through grant 2001SGR00082.

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Received February 26, 2002
[O02105]