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Anion Template-Directed Synthesis of Dicationic [1_4]Imidazoliophanes

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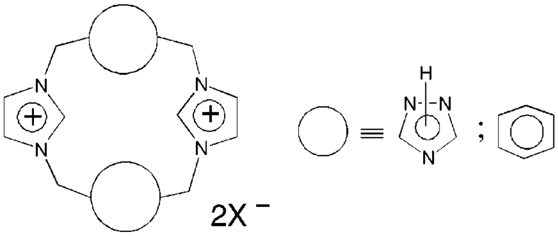
ABSTRACT



The “3 + 1” synthesis of the title macrocycle frameworks containing two imidazolium moieties linked in a 1,3-alternating manner can be controlled by the presence of chloride anions—*e.g.* TBA·Cl. Moreover, the halide anions generated in situ during macrocyclization act as self-templates. Competitive experiments indicate the relevance of both the condensation step and the halide-template ring closure step in the “3 + 1” approach.

Among the different facets of synthetic supramolecular chemistry, template-directed synthesis is a fertile area of investigation.[1] Development of efficient templated macrocyclization normally involves the use of cations or neutral molecules as templates.[2,3] However, anions have been employed in only a few examples.[4] As part of our research in the quest for novel macrocyclic systems built up from heterocyclic betaine subunits, an ensemble of quadrupolar [1_n]heterophanes have been reported[5,6]—*e.g.* **1** and its alkyl-substituted derivatives. In the “3 + 1” convergent stepwise synthesis of the key [1_4]azoliophane precursors, *e.g.* dication **2·2X** and its alkyl-substituted derivatives, the macrocyclization proceeded in fairly good yield (>40%).[5] Similar results were obtained for the model dications—*e.g.* **3·2X** and its alkyl-substituted derivatives—and these dications revealed hydrogen bond driven anion binding.[7,8] Here we report a demonstration of the template-controlled “3 + 1” macrocyclization reactions in the presence of anions, leading to the targeted [1_4]imidazoliophanes (Figure 1).

The coupling (Scheme 1) of protophanes **5** or **6**[9] with 3,5-bis(chloromethyl)-1,2,4-triazole **7** or 1,3-bis(chloromethyl)-benzene **8**, in standard reaction conditions with equimolecular

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(1) Fyfe, M. C. T.; Stoddart, J. F. *Acc. Chem. Res.* **1997**, *30*, 393−401.

(2) For reviews, see: (a) Chapman, R. G.; Sherman, J. C. *Tetrahedron* **1997**, *53*, 15911−15945. (b) Busch, D. H.; Vance, A. L.; Kolchinksi, A. G. *Comprehensive Supramolecular Chemistry*; Atwood, J. L.; Davies, J. E. D.; Macnicol, D. D.; Vögtle, F.; Sauvage, J.-P.; Wais Hosseini, M., Eds.; Pergamon Press: Oxford, 1996; Vol. 9, pp 1−42. (c) Hoss, R.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 375−384. (d) Anderson, S.; Anderson, H. L.; Sanders, J. K. M. *Acc. Chem. Res.* **1993**, *26*, 469−475.

(3) (a) As for *neutral templates*, prime examples are Stoddart’s synthesis of tetracationic [2]catenanes, which involved the use of macrocyclic polyether templates (refs 1 and 2). Both competitive self-assembly experiments (ref 3b) and kinetic studies (ref 3c) have shown that the selectivity for catenane formation is under kinetic control. (b) Amabilino, D. B.; Ashton, P. R.; Pérez-García, L.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2378−2380. (c) Capobianchi, S.; Doddi, G.; Ercolani, G.; Mencarelli, P. *J. Org. Chem.* **1998**, *63*, 8088−8089.

(4) For some examples of anion templates in the synthesis of organic molecules and supramolecules, see: (a) Fyfe, M. C. T.; Glink, P. T.; Menzer, S.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2068−2070. (b) Li, F.; Yang, K.; Tyhonas, J. S.; MacCrum, K. A.; Lindsey, J. S. *Tetrahedron* **1997**, *53*, 12239−12360. (c) Kim, Y. H.; Calabrese, J.; McEwen, C. *J. Am. Chem. Soc.* **1996**, *118*, 1545−1546. (d) Sánchez-Quesada, J.; Seel, C.; Prados, P.; de Mendoza, J.; Dalcol, I.; Giralt, E. *J. Am. Chem. Soc.* **1996**, *118*, 277−278. (e) Fujita, M.; Nagao, S.; Ogura, K. *J. Am. Chem. Soc.* **1995**, *117*, 1649−1650. (f) Sessler, J. L.; Mody, T. D.; Lynch, V. *J. Am. Chem. Soc.* **1993**, *115*, 3346−3347, and references therein.

(5) (a) Alcalde, E.; Alemany, M.; Gisbert, M.; Pérez-García, L. *Synlett.* **1995**, 757−760. (b) Alcalde, E.; Alemany, M.; Gisbert, M. *Tetrahedron* **1996**, *52*, 15171−15188, and references therein.

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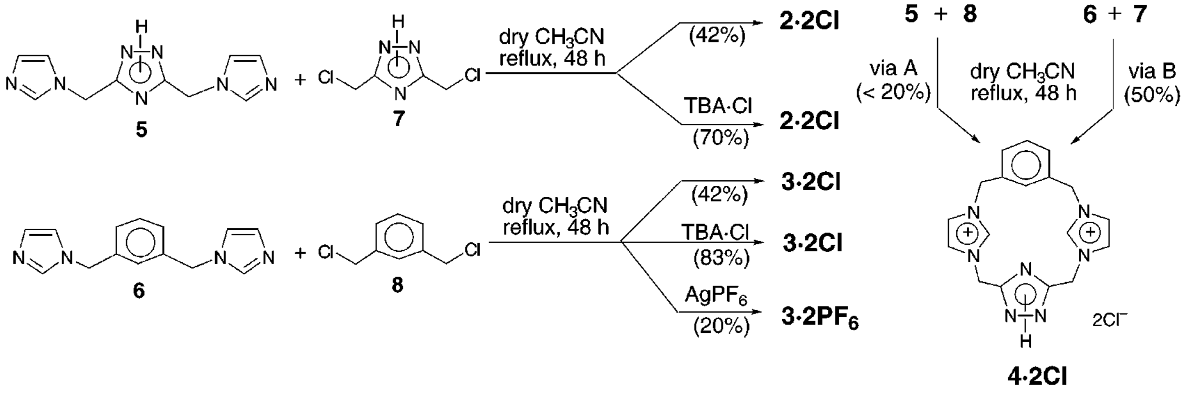
Scheme 1. "3 + 1" Convergent Synthesis of Dicationic [1_4]Imidazoliophanes Driven by Anion Template Effect



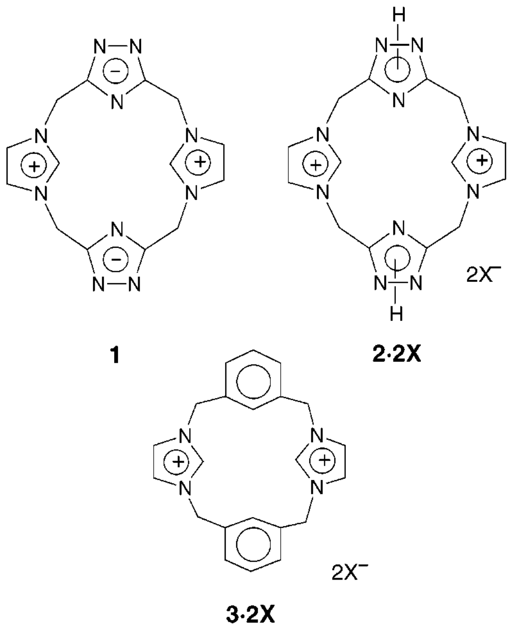


Figure 1. Dicationic [1_4]imidazoliophanes **1**−**3**.

amounts of the reagents at 2.3 mM in dry CH_3CN,[10] proceeded through a remarkably clean macrocyclization reaction,[11] producing the title phanes **2·2X**[5] and **3·2X**[7b] together with **4·2X**.

The ability of several anions to act as a template for the "3 + 1" stepwise approach was then evaluated. When 5 molar equiv of tetrabutylammonium chloride (TBA·Cl) was added to the reaction, the yield was improved to 83% for the model **3·2Cl**[12] and to 70% for the azoliophane **2·2Cl** (Scheme 1). These reaction conditions using **TBA·Cl** were applied to a set of several tetrabutylammonium salts, and the results are gathered in Table 1.[12,13]

Table 1. Survey of Anion Effects on Yields in the Standard Reaction for the Formation of [1_4]Imidazoliophanes **2·2X**−**4·2X**

	compound yield (%)[a,b]			
			4·2X	
TBA·X	**2·2X**	**3·2X**	via A	via B
none	42	42	<20	50
none + $AgPF_6$[c]		20		
TBA·Cl	70	83	<20	67
TBA·Cl[d]		88		
TBA·Br	34	75	<20	
TBA·I[e]	42−54	45−64	<20	
TBA·BF_4[e]	22−24	17−25		
TBA·PF_6[e]	27−41	8−14		
TBA·H_2PO_4[e]		13−20		
TBA·HSO_4[e]		29−45		
TBA·NO_3[e]		16−22		
TBA·F[e,f]		33−36		

[a] All yields are the average of more than two experiments (ref 13). [b] No macrocyclization was observed when TBA·CN or TBA·CH_3CO_2 was used. [c] 2 equiv of $AgPF_6$. [d] Dried TBA·Cl was used (ref 14). [e] The anion content of the heterophane was not evaluated. [f] Dried TBA·F was used (ref 14).

The anion-directed formation of the model **3·2Cl** shows that both chloride and bromide anions selectively increased

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(7) (a) We have synthesized an ensemble of dicationic [14]imidazoliophanes—*e.g.* **3·2X**—containing two imidazolium motifs for anion recognition linked in a 1,3-alternating fashion (ref 7b). Unconventional C−H···Cl^- hydrogen bonds are the noncovalent forces driving the anion interactions shown by these simple [14]imidazoliophanes (*e.g.* **3·2Cl**) both in the solid state and in solution, where proton NMR studies also revealed the importance of hydrogen bonds in controlling the tendency to anion recognition (ref 8). (b) Alcalde, E.; Alvarez-Rúa, C.; García-Granda, S.; García-Rodriguez, E.; Mesquida, N.; Pérez-García, L. *Chem. Commun.* **1999**, 295−296.

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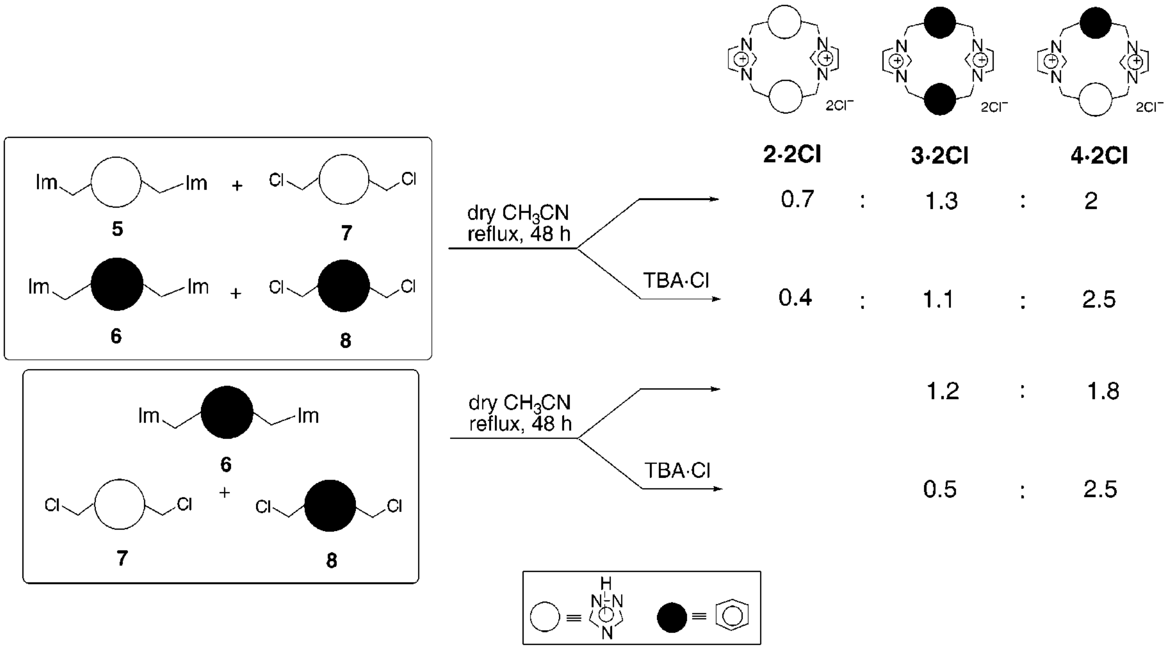
(9) Protophanes **5** (ref 5) and **6** (ref 7b) were obtained by reaction of imidazole with 3,5-bis(chloromethyl)triazole **7** or 1,3-bis(chloromethyl)benzene **8**.

(10) (a) First, we explored the optimal initial concentration of the starting materials for model imidazoliophane **3·2Cl**—protophane **6** and bis(chloromethyl)benzene **8**. The yield of **3·2Cl** increased almost linearly with concentration up to 5 mM; above this concentration, the yield was invariable—*ca.* 70%. However, the macrocyclization reactions leading to **2·2X**−**4·2X** were performed at lower concentration, 2.3 mM, due to solubility limitations of the *s*-triazole reactants and to reduce the experimental error in the evaluation of the template effect. (b) Using high dilution conditions no significant changes in the yield of azoliophanes related to **2**·2Cl were observed (ref 5b).

Scheme 2. The Competitive Experiments Combining Trinuclear Protophanes **5** and **6** and Bis(chloromethyl)Derivatives **7** and **8** To Build [1_4]Imidazoliophanes **2·2Cl**−**4·2Cl**, Showing the Ratio of the Macrocycles Formed



the yield by 41% and 33%, whereas in the presence of other anions (*e.g.* PF_6^- and BF_4^-) the yield was lower (Table 1).[14] To assess the influence of water on the anion-templated macrocyclization reactions, we performed experiments leading to azoliophane **3·2X** in the presence of previously dried **TBA·Cl** and **TBA·F**. The increased yields obtained (see Table 1) give additional experimental support to the operation of the anion-templated assistance, since anion solvation may diminish the anion ability to direct the macrocyclization reaction.

Accordingly, chloride anions lead to the formation of a hydrogen-bonded intermediate in which C−H···Cl⁻ hydrogen bonds occur and the optimal conformation favors the cyclization step; thus, the molecular recognition motifs for anion templation involve the interaction of a multicentered chloride ion with the π-deficient and aromatic moieties as hydrogen bond donors.[15]

In the formation of azoliophane **2·2X**, only chloride ion templation produced a yield increase of 28% (Scheme 1, Table 1), as a consequence of the diminished ability of 1,2,4-triazole nuclei to form hydrogen bonds around the anions in the optimal geometry for the kinetically controlled ring closure step.[16] Then, macrocycle formation was not so directedly assisted.

In addition, enhanced reactivity of 3,5-bis(chloromethyl)-triazole **7** modulates the macrocyclization reaction by accelerating the condensation step, which is also kinetically controlled.[4,17] Accordingly, [1_4]imidazoliophane **4·2X** was prepared via two differents paths, A and B, and the dependence of the "3 + 1" stepwise method efficiency

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(11) By ESMS and ^{1}H NMR analysis of the filtrates from the macrocyclization, neither linear nor cyclic oligomeric products were formed, whereas in all the assays performed *N*-protonated protophanes **5H·X**, **5H**^{2}**·2X**, or **6H·X**, **6H**^{2}**·2X** were recovered.

(12) We also optimized the amount of tetrabutylammonium salt to be added as the source of anions. We performed the macrocyclization affording **3**·2Cl in the presence of different amounts of **TBA**·Cl, and we found a maximum yield (83%) when *5 equiv* was used; this was the quantity used in all the experiments performed to evaluate the effect of the anion template on the synthesis of the title phanes **2**·2X−**4**·2X (Table 1).

(13) (a) All yields are averages of more than two experiments. (b) Heterophanes **2·2X**−**4·2X** were isolated in high yields. However, quoted yields were calculated according to the following protocol: when a solid precipitated at the end of the reaction, it was filtered and identified as pure macrocycle. The content of macrocycle in the filtrates was estimated by ^{1}H NMR of one aliquot after removal of the solvent. The final yield was considered the sum of both partial yields. When no material precipitated at the end of the reaction, yields were calculated by ^{1}H NMR of one aliquot of the reaction solution. (c) Liquid chromatography was used to quantifiy the extension of the anion exchange in **2·2X**−**4·2X**—induced by performing the macrocyclization reaction in the presence of different anions.

(14) Tetrabutylammonium salts used in the template experiments are commercially available, and they were used as received, despite the fact that some of them contain an undetermined amount of water.

(15) (a) X-ray diffraction analysis of **3·2Cl·2H$_2$O** (refs 7b and 15b) revealed that the molecular recognition motifs for anions are based on highly directional multicentered [C−H···Cl⁻] hydrogen bonds established between the chloride ions with both aromatic hydrogen atoms on the *m*-xylyl spacer and the acidic protons on the imidazolium rings. (b) Its macrocyclic cavity is a square of *ca.* 5 Å side, and the chloride anions occupy an outer position above and below the main plane defined by the methylene spacer groups (ref 15c). (c) In the solid state, some calix[4]pyrroles have been reported to adopt a conelike conformation such that the four NH protons can hydrogen bond to the halide anion—the fluoride complex and the chloride complex (ref 15d,e). (d) Gale, P. A.; Sessler, J. L.; Král, V.; Lynch, V. *J. Am. Chem. Soc.* **1996**, *118*, 5140−5141. (e) Gale, P. A.; Sessler, J. L.; Král, V. *Chem. Commun.* **1998**, 1−8.

(16) (a) The optimal conformation required for the anion-directed macrocyclization relies on the hydrogen bond interaction between the halide anion and the NH group in the 4*H* tautomeric form of 1,2,4-triazole which is the less favored tautomer in solution (ref 16b). (b) Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. *Adv. Heterocycl. Chem.* **1976**, *1*, 284−287.

(17) (a) Nucleophilic substitution reactions are suitable for studying the consequences of the Kauffmann's areno-analogy principle and its application within π-excessive heteroaromatic systems (ref 17b). (b) Kauffmann, T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 1−19.

revealed that when the starting materials were **5** and **8**, macrocyclization was clearly less efficient than when reactants **6** and **7** were used instead (Scheme 1). The yields obtained in pathway A were, moreover, not anion dependent, in contrast with the chloride templating effect observed through the alternative pathway (Table 1). These results show a clear preference for the ring closure for protophanes containing 1,3-substituted benzene rings rather than 1,2,4-triazole subunits.

To shed further light on the preferences observed in the "3 + 1" approach, competitive experiments were set up between the protophanes **5** and **6** and the bis(chloromethyl)-derivatives **7** and **8**—both in the absence and in the presence of **TBA·Cl**. The standard protocol was used, mixing equimolecular amounts of each component. According to the ^{1}H NMR analysis, the reaction mixture composition led to the formation of macrocycles **2·2Cl**:**3·2Cl**:**4·2Cl** in relative proportions 0.7:1.3:2 (Scheme 2). The predominant formation of imidazoliophane **4·2Cl** under competition conditions supports the additive effects of both condensation and anion-templated ring closure steps.

The anion-templating was further observed when the competition experiment was carried out in the presence of **TBA·Cl**: the abovementioned macrocycles were formed in a 0.4:1.1:2.5 ratio.

Finally, competitive experiments between protophane **6** and both bis(chloromethyl)derivatives **7** and **8** afforded macrocycles **3·2Cl**:**4·2Cl** in a 1.2:1.8 ratio, whereas in the presence of **TBA·Cl** the ratio was 0.5:2.5 (Scheme 2). Formation of **4·2Cl** as the main product confirms the relevance of both the condensation step rate and the anionic assistance in the ring closure step within the macrocyclization.

In conclusion, chloride anions template the synthesis leading to [1_4]imidazoliophanes **2·2X-4·2X**, with potential to behave as abiotic receptors. Thus, halide anions generated in situ during the "3 + 1" macrocyclization process act as self-templates through the formation of hydrogen bonds with the reaction intermediate in the ring closure step. The competitive experiment results indicate that the intermolecular condensation and anion-templated intramolecular cyclization play a significant role in the "3 + 1" stepwise convergent synthesis.

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