Quadrupolar [14](*meta-para*)$_2$Heterophanes and [14]*meta*Heterophanes Containing Stable 3,5-Bis[1-methyl-4(3)-pyridiniomethyl]-1,2,4-triazolate Building Block

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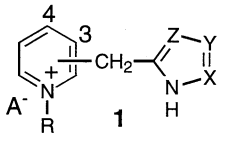
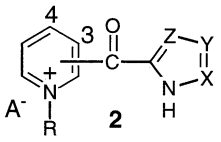
Access to novel quadrupolar [14] (*meta-para*)2azolophane with a 3,5-bis[1-methyl-4-pyridiniomethyl]-1,2,4-triazolate subunit reveals that the structural features conferred by the heterophane architecture lead to molecules that are stable to oxidation, in contrast with their building block. The stability of [14]*meta*azolophanes is consistent with the betainic subunits.

A concurrent application of the areno-analogy principle[1] and the captodative effect[2] has been exemplified for several examples of 1-alkyl-4(3)-(1*H*-azolyl)pyridinium salts **1**.[3] Accordingly, the character of the non-classical acceptor and donor heteroaromatic moieties modifies the proclivity of the captodative methylene spacer to spontaneous oxidation to the oxomethyl analogues **2**. However, the quaternary pyridinium salts with a 1*H*-1,2,4-triazol-3(5)-yl group **3** and **4** have displayed distinct behaviour; hence, *air* oxidation was sufficient for transformation of compound **3** (R=Me) into the corresponding oxomethyl derivative of type **2**, whereas compound **4** (R=Me) turned out to be very stable,[3] as was the corresponding inner salt **5** (R=Me).[4]

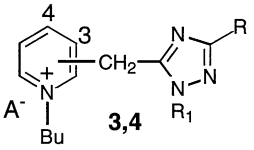


1

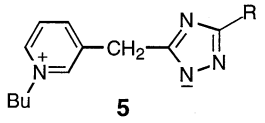


2

6π (π–acceptor) 6 or 10π (π–donor)



3,4



5

3 (4-Pyridinio) R_1 = H; A^- = I^-
4 (3-Pyridinio) R_1 = H; A^- = I^-

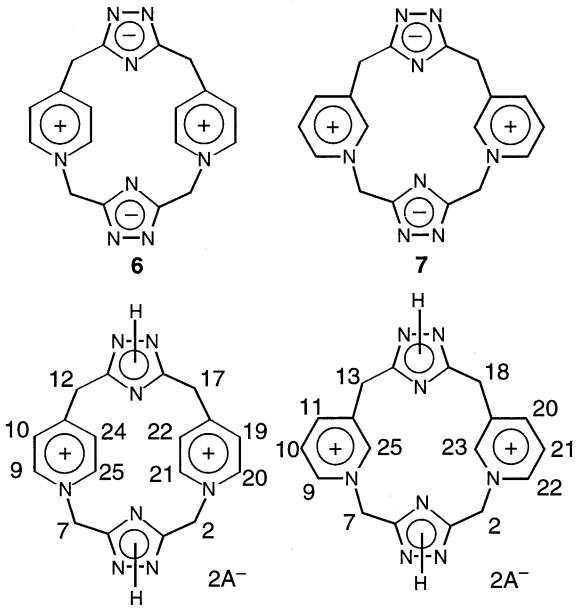
R = Me, Ph

These results prompted us to expand this work towards more elaborate heteropolyaromatic substrates such as the quadrupolar [14] (*meta-para*)2heterophane **6** and [14]*meta*heterophane **7**, together with their immediate precursors **8** and **9**.[5]

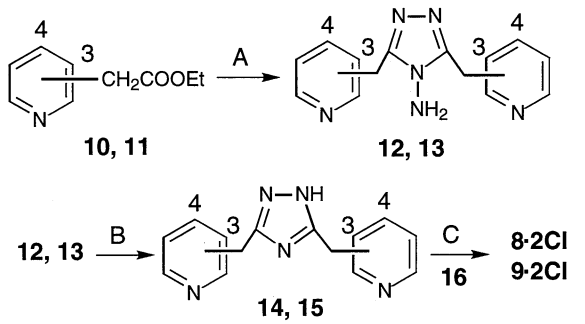
[14]Heterophanes **8** and **9** were obtained in good yields by macrocyclization of the protophanes **14** and **15** with 3,5-bis(chloromethyl)-1*H*-1,2,4-triazole **16**[9] (Scheme 1). The intermediates **14** and **15** were prepared by a standard two-step procedure, starting from ethyl 4(3)-pyridylacetates **10** and **11**.

The key macrocycle **9** was then converted into the corresponding quadrupolar [14]heterophane **7** using an anion-exchange resin (OH^- form),[10] whereas the insolubility of **8**·**2Cl** in alcohols and/or water precluded its transformation into the quadrupolar [14] (*meta-para*)2heterophane **6** (Scheme 2).

An alternative route to the targeted heterophane **6** was then explored[11] (Scheme 2), starting with condensation of protophane



6 **7** **8** **9**



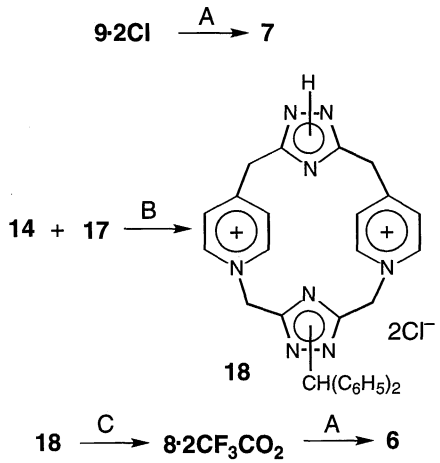
10, 11 **12, 13** **14, 15**

8, 14, 12, 10 : 4-pyridyl(pyridinio)
9, 15, 13, 11 : 3-pyridyl(pyridinio)

Scheme 1. Reagents and conditions: (A) **12**: $NH_2NH_2{\cdot}H_2O$, 6 h at 100 °C, 5 d at 150 °C, 2 h at 165 °C (75%); **13**: $NH_2NH_2{\cdot}H_2O$, 6 h at 100 °C, 8 d at 140 °C, 3 h at 165 °C (85%); (B) **14**: (i) $NaNO_2$, HCl 3N, H_2O, 0 °C to r.t., 45 m. (ii) Na_2CO_3 to pH 8 (68%); **15**: (i) $NaNO_2$, HCl 3N, H_2O, 0 °C to r.t., 1 h. (ii) Na_2CO_3 to pH 8 (84%); (C) **8**: dry CH_3CN, reflux, 48 h (45%); **9**: dry CH_3CN, reflux, 24 h (60%).

14 with the 1-diphenylmethyl-3,5-bis(chloromethyl)-1*H*-1,2,4-triazole **17**.[8c]

The structures of the new compounds were unambiguously characterized on the basis of their IR and ^1H NMR.[12] For all [14]azolophanes reported, the ^1H NMR spectra (22 °C) in D_2O at 300 MHz showed two different singlets for the methylene proton



Scheme 2. Reagents and conditions: (A) IRA-401 (OH^- form) (>80%); (B) Dry CH_3CN, reflux (13%); (C) TFA, phenol, reflux (82%).

atoms. Comparison of the chemical proton shifts of quadrupolar macrocycles **6**, **7** with those of their corresponding precursors **8**, **9** reveals that the δH values of the methylene spacers are some of the most affected; they shift to lower frequencies (see ΔδH),[13] providing evidence of charge distribution within the quadrupolar system.

In contrast to the building block of type **3**,[3a] the quadrupolar [14] (*meta-para*)$_2$heterophane **6** and its precursor **8** turned out to be very stable in air, whereas the stability of [14]*meta*heterophanes **7** and **9** was predictable since no atmospheric oxidation was observed for betainic counterparts **5**.[4] Whatever the structural features that prevent oxidation may be, the [14]heterophane framework modulates the susceptibility to oxidation and permits access to the hitherto unknown stable quadrupolar title molecules **6** and **7**.

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4 Modulating the nature of the non-classical acceptor and donor heteroaromatic groups, according to the areno-analogy principle,[1] in compounds of general type **1** it has been possible to design stable quaternary heteroaromatic salts **4** (R=Me,[3] and R=Ph) and therefore, to obtain the new 1-alkyl-3-pyridiniomethyl-1,2,4-triazolate inner salts **5** (R=Me, Ph) for which no atmospheric oxidation was observed.[3b]

5 The ring components present in heterophanes[6] are normally uncharged heteroaromatic moieties and in the few cases in which they bear a charge, they are normally quaternary pyridinium nuclei.[7] Moreover, pyrimidinium cations have also been inserted within [1$_n$]heterophane systems[8a,b], and we have recently reported[8c] the first examples of novel quadrupolar [14]*meta*heterophanes with heterocyclic betaines as building blocks, for which the two atoms linking the π-deficient imidazolium nuclei and the methylene spacer form *C-N'* bonds. For [14] (*meta-para*)$_2$heterophanes **6** and **8** and also for [14]*meta*heterophanes **7** and **9** the pyridinium nuclei and the interannular group are linked by two *C-C'* bonds from the 3,5-bis[1-methyl-4(3)-pyridiniomethyl]-1,2,4-triazolate moiety, the other two being *C-N'* bonds.

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10 a) The use of an ion-exchange Amberlite IRA-401 resin (OH^- form) is the method of choice for the preparation of imidazolium(pyridinium) azolate inner salts with several interannular spacers.[10b] b) E. Alcalde, *Adv. Heterocycl.Chem.*, **60**, 197 (1994).

11 Debenzhydrylation of compound **18** seems to be the method of choice for obtention of macrocycle **8·2CF$_3$CO$_2$**, which is more soluble in alcohol/water than the corresponding chloride **8·2Cl**, and can thus be transformed into the quadrupolar compound **6**.

12 Data are quoted for the macrocycles **6-9**. They melt at higher temperatures than their corresponding protophanes. Unfortunately, it was not possible to obtain single crystals of [14]azolophanes **6-9** suitable for X-ray structure analysis.

Compound 6: mp > 350 °C. ^{1}H NMR (300 MHz, D_2O, 22 °C): δ = 3.95 (4H, s, CH_2-12,17), 5.49 (4H, s, CH_2-2,7), 7.40 (4H, d, *J* = 6.9 Hz, CH-10,19), 8.22 (4H, d, *J* = 6.9 Hz, CH-9,20).

Compound 8·2CF$_3$CO$_2$: mp 267 °C. ^{1}H NMR (300 MHz, D_2O, 22 °C): δ = 4.18 (4H, s, CH_2-12,17), 5.75 (4H, s, CH_2-2,7), 7.61 (4H, d, *J* = 6.9 Hz, CH-10,19), 8.49 (4H, d, *J* = 6.9 Hz, CH-9,20).

Compound 7: mp > 325 °C. ^{1}H NMR (300 MHz, D_2O, 22 °C): δ = 4.00 (4H, s, CH_2-13,18), 5.55 (4H, s, CH_2-2,7), 7.78 (2H, s, H-23,25), 7.81 (2H, dd, *J* = 6.2, 8.0 Hz, CH-10,21), 8.29 (2H, d, *J* = 8.0 Hz, CH-11,20), 8.65 (2H, d, *J* = 6.2 Hz, CH-9,22).

Compound 9·2Cl: mp > 325 °C. ^{1}H NMR (300 MHz, D_2O, 22 °C): δ = 4.21 (4H, s, CH_2-13,18), 5.77 (4H, s, CH_2-2,7), 7.89 (2H, dd, *J* = 5.9, 7.5 Hz, CH-10,21), 8.40 (2H, d, *J* = 7.5 Hz, CH-11,20), 8.49 (2H, s, CH-23,25), 8.73 (2H, d, *J* = 5.9 Hz, CH-9,22).

13 The differences in proton chemical shifts in D_2O between the quadrupolar macrocycle **6** and its corresponding macrocyclic precursor **8** were found to be Δδ CH_2 *ca.* –0.24 ppm, Δδ H-10,19 = –0.21 ppm and Δδ H–9,20 = –0.27 ppm. For compounds pair **7** and **9** the higher chemical shift difference was found to be Δδ H-23,25 = –0.71