Synthesis of Macrobicyclic Ligands containing Pyrazole Subunits: the *N,N′*-Bipyrazolyl Cryptand

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The pyrazolyl cryptands [bpz.bpz.bpz] (**1**) and [2.2.bpz] (**2**) have been obtained in a one-step, non high-dilution macrobicyclization reaction, from a 1,1′-bipyrazole derivative; similarly, tripodal ligands (**7**)—(**9**) with pyrazole structures are described.

Macropolycyclic ligands incorporating heterocyclic subunits are of particular interest in co-ordination chemistry, since macrocycles having heteroatoms situated inside the rigid cavity display enhanced metal ion binding properties. In the 2,2′-bipyridine (bpy) and 1,10-phenanthroline (phen) series, macrobicyclic cryptands containing one ([2.2.bpy],[1] [2.1.phen],[2] [2.2.phen][2]) or three ([bpy.bpy.bpy],[2] [bpy.bpy.phen],[2] [phen.phen.phen][2,3]) heterocyclic chains have been reported. These compounds can combine the 'cation inclusion' nature of cryptands with the photoactivity of metal complexes of polypyridine or phenanthroline ligands in electron- and energy-transfer processes.[4]

No similar examples of macrobicyclic cryptand structures have yet been described in the pyrazole series, despite the known ability of this heterocycle to bind diverse metal ions.[5] We report herein the first examples of 1,1′-bipyrazolyl (bpz) cryptands, namely [bpz.bpz.bpz] (**1**) and [2.2.bpz] (**2**). Molecular models (Corey–Pauling–Koltun) revealed that these molecules are endowed with cavities somewhat smaller than their bipyridine analogues, but better adapted to form either hexa- or octa-co-ordinate complexes, due mainly to the ease of twisting around the N–N bond in *N*,*N*′-linked biazoles.[6]

For the synthesis of (**1**), 3,3′-dimethoxycarbonyl-1,1′-bipyrazole (**3a**)[7] was reduced to the corresponding bis-alcohol (**3b**) ($LiAlH_4$, tetrahydrofuran, 89%),† which was, in turn, transformed into the bis-bromomethyl derivative (**3c**) (PBr_3, diethyl ether, 76%). Reaction of (**3c**) with anhydrous NH_3 (Na_2CO_3, dry MeCN, 100 °C) afforded (**1**) in 19% yield. On the other hand, the reaction of (**3c**) with 1,7,10,16-tetraoxa-4,13-diazacyclo-octadecane (Merck's Kryptofix 22) under analogous conditions, gave [2.2.bpz] cryptand (**2**) in 56% yield. It is noteworthy that no high-dilution conditions were needed for the last, direct one-step macrobicyclization reaction yielding (**1**) from (**3c**), nor for the synthesis of (**2**). As for bpy and phen analogues,[2] this may result from both a templating effect of the sodium cation and from the rigidity of

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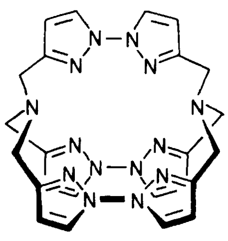
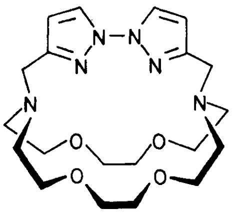
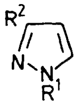
† Satisfactory elemental analyses, as well as n.m.r. (^1H and ^{13}C) and mass spectra were obtained for all new compounds. (**1**) M.p. >250; (**2**) 225—227; (**7**) and (**8**) oils; (**9**) 93—95 °C.

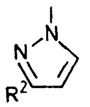


[bpz.bpz.bpz]
(1)

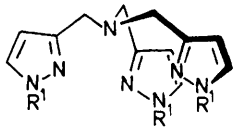


[2.2.bpz]
(2)

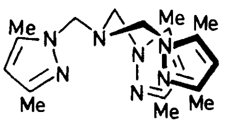


(3) R^1 =


(4) R^1 = H
(5) R^1 = Me
(6) R^1 = CH_2Ph
a; R^2 = CO_2Me
b; R^2 = CH_2OH
c; R^2 = CH_2Br



(7) R^1 = H
(8) R^1 = Me
(9) R^1 = CH_2Ph



(10)

the bridges introduced. Nevertheless, no sodium cation was detected in a purified sample of (**1**), contrary to the result observed in the bpy and phen families.

In addition to the synthesis of macrobicycles (**1**) and (**2**), we have also prepared, by analogous routes, the tripodal pyrazolyl ligands (**7**)—(**9**) from the corresponding 1-substituted 3-pyrazolyl esters (**4a**)—(**6a**), in 35, 41, and 39% overall yields, respectively. A related pyrazolyl tripod (**10**) has been prepared by Bertini *et al.* from $N(CH_2Cl)_3$ and 3,5-dimethylpyrazole, and its Co^{2+} complex has been tested as a model for carbonic anhydrase.[8] The synthesis of compounds like (**7**)—(**9**) is not limited to symmetrical pyrazoles, and allows for further structural variation, *i.e.*, the separation of two tripodal units by appropriate chains, joined together to form a large enough cryptand to accommodate two metal ions. These possibilities, and the complexation studies of (**1**) and (**2**), are being investigated, and will be published elsewhere.

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