# A New Reagent for Synthesis of Cages for Metal Ions

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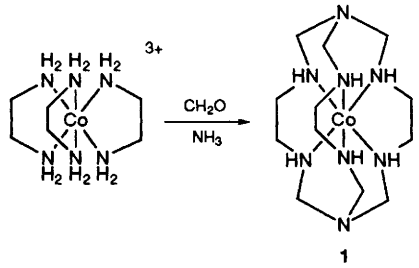
A new strategy has been developed to attach *N*-methylpyridine and its derivatives simply and directly to the $Co^{III}$ sarcophagine cage frame (sar = 3,6,10,13,16,19-hexaazabicyclo[6.6.6]icosane).

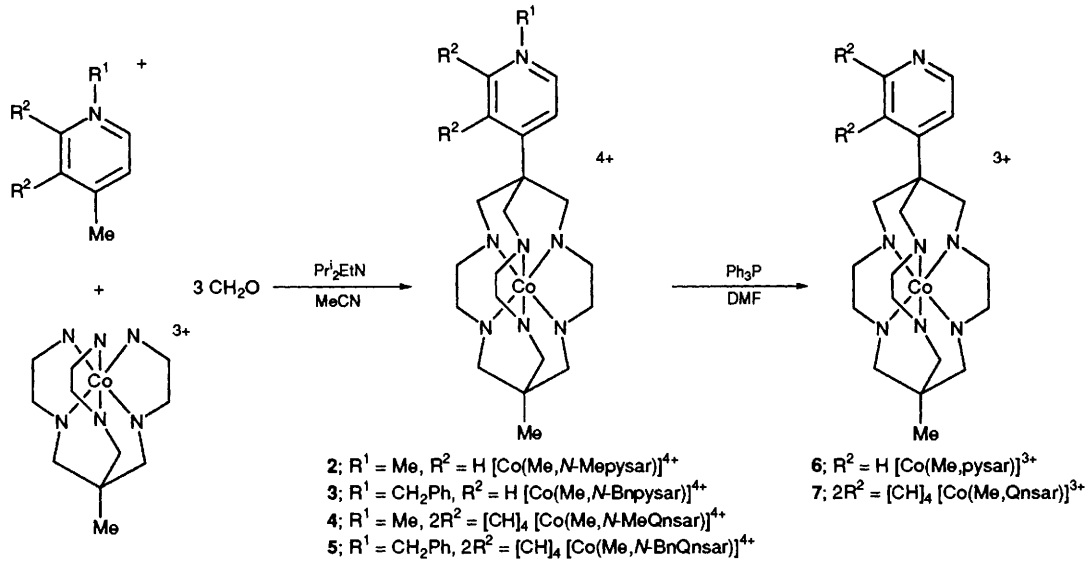
Template condensation of $[Co(en)_3]^{3+}$ (en = ethane-1,2-diamine) with formaldehyde and ammonia gave the $Co^{III}$ complex of the octaazabicycle **1** which was given the trivial name [cobalt(III)sepulchrate]$^{3+}$.[1,2] In the sepulchrate ligand the apical atoms of the ligand caps are the nitrogen atoms derived from ammonia formally acting as a tribasic acid under the condensation conditions. In further developments, nitromethane was substituted for ammonia as a capping reagent in the synthesis of several macrobicyclic complexes.[3–5] The present paper reports on the application of *N*-alkylated 4-picoline derivatives as tribasic acids for the encapsulation reaction.

Alkyl groups α and γ to the ring nitrogen of pyridine are significantly more reactive towards proton exchange than alkyl groups attached to a benzene ring. This arises from the stabilization of the carbanion by delocalisation over the pyridine ring. Proton removal from an α- or γ-alkyl group is made even easier when the ring nitrogen bears a positive charge as in quaternary salts and *N*-oxides. For example, these molecules react with aldehydes in the presence of mild basic catalysts giving appropriate vinyl-pyridine derivatives.[6,7]

Recent work[8,9] has shown that the capping reactions can proceed efficiently in nonaqueous conditions and it has now been found that *N*-alkylated 4-picoline or *N*-alkylated 4-methylquinoline react with paraformaldehyde and $[Co(sen)]^{3+}$ [sen = 4,4′,4″-ethylidynetris(3-azabutan-1-amine)] in acetonitrile solution in the presence of diisopropylethylamine, over 24 h at *ca.* 20 °C, giving the sarcophagine derivatives **2–5** (yields 50–60%). The methyl groups in 4-picoline and 4-picoline-*N*-oxide were apparently not suffi-




**1**




**2**; $R^1$ = Me, $R^2$ = H [Co(Me,*N*-Mepysar)]$^{4+}$
**3**; $R^1$ = $CH_2Ph$, $R^2$ = H [Co(Me,*N*-Bnpysar)]$^{4+}$
**4**; $R^1$ = Me, $2R^2$ = $[CH]_4$ [Co(Me,*N*-MeQnsar)]$^{4+}$
**5**; $R^1$ = $CH_2Ph$, $2R^2$ = $[CH]_4$ [Co(Me,*N*-BnQnsar)]$^{4+}$

**6**; $R^2$ = H [Co(Me,pysar)]$^{3+}$
**7**; $2R^2$ = $[CH]_4$ [Co(Me,Qnsar)]$^{3+}$

ciently acidic since they did not give encapsulated products under the same conditions.

The activating *N*-benzyl substituent was removed by refluxing the pyridinium salts **3** and **5** in dimethylformamide (DMF) with one equivalent of triphenylphosphine[10] to give complexes **6** and **7**, respectively (yield 90%).

All complexes **2**–**7** were characterised by satisfactory elemental analysis,† UV–VIS spectra† and $^1H$ and $^{13}C$ NMR spectra.‡ Owing to the time-averaged $C_3$ symmetry of the cages in solution, $^{13}C$ NMR spectra of compounds **2**–**7** are simple and consist of four strong signals arising from the cage methylene groups in the region of δ 54–57. Two low intensity signals, δ 43–44 and 50–51, are assigned to the quaternary carbon atoms attached to the methyl and aromatic substituents, respectively. The signal for the cap methyl group was observed at δ *ca.* 21 and the remaining $^{13}C$ NMR signals are ascribed to the carbon atoms of the aromatic moiety.[9]

The $^1H$ NMR spectra were also simplified owing to the symmetry of the cage. Besides signals characteristic of the substituents, two pairs of doublets due to the two sets of cap $CH_2$ groups and an ABCD spin system due to the ethylenediamine protons were observed in 300 MHz spectra of compounds **2**–**7**.‡ The ratio of integrated intensities for the individual proton signals of substituents and cage was 1 : 3 consistent with the average $C_3$ symmetry of the cage. The pyridine cap methylene signals were shifted *ca.* 0.5 ppm and quinoline cap methylene signals *ca.* 0.9 ppm downfield relative to the methyl cap methylene protons owing to the deshielding effect of the aromatic rings.

The electrochemistry of the quaternary pyridinium and quinolinium derivatives **2**–**5** in 0.2 mol $dm^{-3}$ NaCl at a glassy carbon electrode showed reversible waves centred at −0.56 ($\Delta E$ = 0.068), −0.57 ($\Delta E$ = 0.067), −0.54 ($\Delta E$ = 0.065) and −0.55 V ($\Delta E$ = 0.070) (*vs.* Ag/AgCl/saturated KCl electrode), respectively, using cyclic voltammetry with a scan rate of 100 mV $s^{-1}$. Dequaternised derivatives **6** and **7** measured in 0.2 mol $dm^{-3}$ [HEPES = 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid] buffer (pH = 7.05) showed reversible waves at −0.62 ($\Delta E$ = 0.072) and −0.61 V ($\Delta E$ = 0.071), respectively. Despite the higher charge of the quaternised derivatives the effect on the potential was rather small, much less than the difference arising from $NH_2$ and $NH_3^+$ as 1,8-substituents[4] (*ca.* 0.3 V), presumably because they are more distant from the metal centre.

The pyridine derivatives **2** and **6** were separated into catoptric forms by chromatography on a SP-Sephadex C-25 column using $Na_2[Sb_2\{(+)tartrato\}_2]$ (0.15 mol $dm^{-3}$) as eluent. (Fraction 1 of **2** $[M]_{510}$ = −7026 deg $mol^{-1}$ $dm^3$ $m^{-1}$ $[M]_{589}$ = −2188; fraction 2 of **2** $[M]_{510}$ = +7172, $[M]_{589}$ = +2177 in $H_2O$. Fraction 1 of **6** $[M]_{510}$ = −4498, $[M]_{589}$ = −1546; fraction 2 of **6** $[M]_{510}$ = +4461, $[M]_{589}$ = + 1537 in 0.2 mol $dm^{-3}$ HEPES buffer, pH = 7.30).

The electron self-exchange rate between the *N*-methylpyridinium cage $Co^{II}$ and $Co^{III}$ complexes was determined by measuring the change in optical rotation of solutions containing either the chiral isomers Λ-[Co(Me,*N*-Mepysar)]$^{4+}$ and Δ-[Co(Me,*N*-Mepysar)]$^{3+}$ or their enantiomeric forms, as described[1,2] for [Co(sep)]$^{2+/3+}$. Similar rate determinations were made for the dealkylated derivatives [Co(Me,pysar)]$^{3+/2+}$. The self-exchange rate constants obtained by this method $k_{ex}$ = 1.44 ± 0.15 $mol^{-1}$ $dm^3$ $s^{-1}$ (25 °C, $I$ = 0.2 mol $dm^{-3}$ NaCl) and 2.4 ± 0.1 $mol^{-1}$ $dm^3$ $s^{-1}$ (HEPES, pH 7.30, 25 °C, $I$ = 0.2 mol $dm^{-3}$), respectively, are similar to those measured for analogous $Co^{II/III}$ cage complexes.[11] There was a possibility that the latter reacting partners might communicate more effectively through stacking of the two π substituents in the activated complex but the results indicate, along with other data,[11] that the relatively rapid self-exchange rate is a property of the type of cage and the metal ion, and is less dependent on the peripheral substituents. The effect of the charge difference is also not very significant for the two couples in the 0.2 mol $dm^{-3}$ medium which indicates the work terms are relatively small under these conditions and in keeping with other observations.[11]

† Calc. for $C_{20}H_{38}N_7Cl_4Co{\cdot}4H_2O$ (protonated **6**): C, 37.0; H, 7.1; N, 15.1; Cl, 21.8; Co, 9.1%. Found: C, 37.4; H, 7.2; N, 15.0; Cl, 21.5; Co, 9.4%. Calc. for $C_{24}H_{40}N_7Cl_4Co{\cdot}3H_2O$ (protonated **7**): C, 42.3; H, 6.8; N, 14.4; Cl, 20.8; Co, 8.65%. Found: C, 42.4; H, 6.6; N, 14.1; Cl, 19.5; Co, 8.3%. Similar agreement was obtained for compounds **2**–**5**. UV–VIS spectra: [Co(Me,H$^+$pysar)]$Cl_4{\cdot}4H_2O$ (protonated **6**) in 0.1 mol $dm^{-3}$ HCl; $\lambda_{max}$ = 221 nm (ε = 19250 $mol^{-1}$ $dm^3$ $cm^{-1}$), $\lambda_{max}$ = 251 (ε = 18750), $\lambda_{max}$ = 343 (ε = 127), $\lambda_{max}$ = 468 (ε = 152). [Co(Me,H$^+$Qnsar)]$Cl_4{\cdot}3H_2O$ (protonated **7**) in 0.1 mol $dm^{-3}$ HCl; $\lambda_{max}$ = 202 (ε = 35960), $\lambda_{max}$ = 238 (ε = 47930), $\lambda_{max}$ = 320 (ε = 7316), $\lambda_{max}$ = 470 (ε = 155).

‡ $^{13}C\{^1H\}$ NMR of [Co(Me,H$^+$pysar)]$Cl_4{\cdot}4H_2O$ (protonated **6**) in $D_2O$, δ in ppm relative to $SiMe_4$ [δ(NaTPS) = −1.1 ppm]: 20.9 (Me), 43.8 (*C*-Me), 50.3 (C-py), 54.5, 56.2, 56.4, 56.7 ($CH_2$), 127.2 (3,5-py), 143.5 (4-py), 159.0 (2,6-py). $^1H$ NMR of [Co(Me,H$^+$pysar)]$Cl_4{\cdot}H_2O$ (protonated **6**) in $D_2O$, δ in ppm relative to $SiMe_4$: 0.94 (singlet, Me), 2.47, 3.11 (2 d, Me-cap $CH_2$), 3.07, 3.69 (2 d, py-cap $CH_2$), 2.83, 3.41 (2 m based on $NCH_2CH_2N$), 8.17, 8.88 (2 d, aromatic CH). Except for signals arising from the pyridine and quinoline moieties the $^{13}C$ and $^1H$ NMR spectra of compounds **2**–**5** and **7** were similar.

The results display not only a new capping reagent but a new type of substituent for the cages which can itself be derivatised readily. It is apparent that more elaborate π systems could be built into the cage bridgehead in this manner to add photoactive centres or intercalating agents to target DNA sites. Encapsulated metal ions containing such aromatic groups may be useful for coupled energy capture–electron relay systems, as fluorescent probes and as reagents to sever nucleic acids at selective sites.

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