Containers for Cations

# Membership Rules for a Molecular Box: The Admission Process and Protection Provided to Guest Molecules**

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Molecular containers are the smallest possible agents for sensing, sorting, and sequestering ions and molecules.[1] Molecular cages based on transition-metal vertices often easily self-assemble, and those with inorganic frameworks are of special interest because their rigidity, uncommon in organic ligands,[2–5] could give rise to high selectivity with respect to guest size.

Prussian Blue (PB) and its variants[6–8] are insoluble cyanometallate polymers consisting of boxlike subunits that exhibit ion-exchange behavior. We and others have previously described molecular PB analogues with encapsulated cations.[9–12] Lacking so far, however, are examples of empty (or voided) ionophilic boxes, which could provide insights into the ion-inclusion process, which is fundamentally relevant to the behavior of PB analogues and the design of a new class of ion-sequestering agents.[13]

We have previously reported that the cage $[\mathrm{Cs}{\subset}\{\mathrm{CpCo(CN)_3}\}_4(\mathrm{Cp^*Ru})_4]^+$ ($\mathbf{Cs{\subset}Co_4Ru_4}^+$; $\mathrm{Cp^*} = \mathrm{C_5Me_5}$, $\mathrm{Cp} = \mathrm{C_5H_5}$) forms by the cesium-ion templated condensation of $[\mathrm{CpCo(CN)_3}]^-$ and $[\mathrm{Cp^*Ru(NCMe)_3}]^+$.[14] When the cesium ion is omitted from this recipe, an intractable mixture is obtained. Herein we report that when mediated by the templating ion $\mathrm{EtNH_3}^+$ self-assembly indeed proceeds to give the empty molecular box $[\{\mathrm{CpCo(CN)_3}\}_4(\mathrm{Cp^*Ru})_4]$ ($\mathbf{Co_4Ru_4}$) in high purity and good yield (Figure 1).

In contrast to $\mathrm{EtNH_3}^+$, $\mathrm{MeNH_3}^+$ templates self-assembly with inclusion to form $\mathbf{MeNH_3{\subset}Co_4Ru_4}^+$. The high selectivity of these molecular containers is highlighted by comparison of the van der Waals volumes of the $\mathrm{MeNH_3}^+$ (43.3 Å$^3$) and $\mathrm{EtNH_3}^+$ (60.2 Å$^3$) ions.

In addition to ESI-MS and $^1$H NMR spectroscopy, $\mathbf{Co_4Ru_4}$ was also characterized crystallographically, the results of which indicate that the cage interior is indeed empty, despite its large volume (≈ 135 Å$^3$ based on internuclear distances). The availability for the first time of an empty ionophilic box enables the study of ion binding with respect to kinetic and

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[**] This research was funded by the US Department of Energy.

Supporting information (kinetic data) for this article is available on the WWW under http://www.angewandte.org or from the author.

DOI: 10.1002/ange.200219562

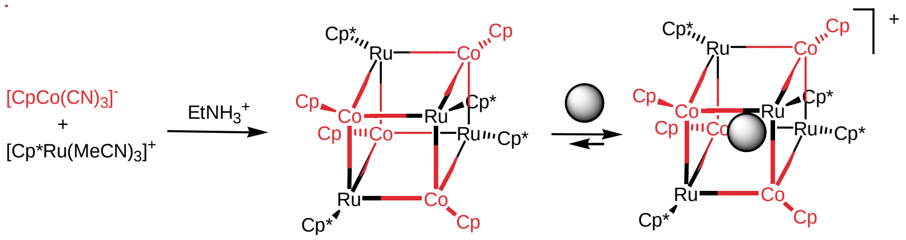

***Figure 1.*** Formation of empty and filled molecular boxes; ● $=N_2H_5^+$, $MeNH_3^+$, $NH_4^+$, $Cs^+$, $K^+$, $Rb^+$, $Tl^+$; — = –CN.

thermodynamic selectivities. We found that **$Co_4Ru_4$** readily binds $K^+$, $Rb^+$, $Cs^+$, $Tl^+$, $NH_4^+$, $MeNH_3^+$, and $N_2H_5^+$ ions (see Figure 1) but not the smaller $Na^+$ ion ($r_{ionic} = 1.16$ Å) or divalent cations.

The kinetic selectivity of **$Co_4Ru_4$** was probed by treatment of THF solutions of **$Co_4Ru_4$** with an MeCN solution equimolar in $KPF_6$ and CsOTf ($OTf = CF_3SO_3$) and then monitoring the process by NMR spectroscopy or ESI-MS spectrometry. These reactions rapidly formed **$K\subset Co_4Ru_4^+$** together with ≈3% **$Cs\subset Co_4Ru_4^+$**. Whereas the $K^+$ ion inserts more rapidly, **$Cs\subset Co_4Ru_4^+$** is the only complex detected after seven days (Figure 2a,b). We propose that the smaller size of the $K^+$ ion ($r_{ionic} = 1.52$ Å) facilitates its insertion, but as a result of a better fit (ionic radius versus box volume) and affinity for π CN ligands,[15,16] the $Cs^+$ ion ($r_{ionic} = 1.81$ Å) is thermodynamically preferred. In another ion-competition experiment, the cation of $NH_4PF_6$ ($r_{ionic} \approx 1.75$ Å)[17] was shown to insert at approximately the same rate as that of CsOTf, but subsequent equilibration is immeasurably slow. For $MeNH_3BF_4$ versus CsOTf, the $MeNH_3^+$ ion inserts faster than the $Cs^+$ ion, although there is a subsequent slower conversion into **$Cs\subset Co_4Ru_4^+$** (Figure 2c,d).

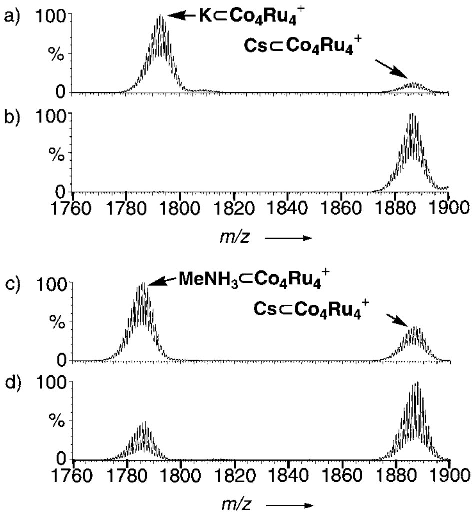

***Figure 2.*** Electrospray mass spectra for a 0.0057 M MeCN solution of **$Co_4Ru_4$** upon treatment with 2 equivalents each of $KPF_6$ and CsOTf after 10 min (a) and after seven days (b), and after treatment with two equivalents each of $MeNH_3BF_4$ and CsOTf after 10 min (c) and after seven days (d).

In terms of mechanism, the collective evidence points to ion insertion into **$Co_4Ru_4$** through a $\{Co_2Ru_2(CN)_4\}$ "window". The differing kinetic and thermodynamic selectivities of **$Co_4Ru_4$** (see above) can best be explained if the cage remains intact during ion insertion. Labeling experiments are consistent with this view. We found that THF solutions of **$Co_4Ru_4$** and its close analogue $[\{CpCo(CN)_3\}_4\{(C_5Me_4Et)Ru\}_4]$ (**$Co_4Ru_4'$**) reacted with CsOTf to give **$Cs\subset Co_4Ru_4^+$** (m/z: 1886) and **$Cs\subset Co_4Ru_4'^+$** (m/z: 1942), respectively. Products of scrambling, such as $[Cs\subset\{CpCo(CN)_3\}_4(Cp^*Ru)_3\{(C_5Me_4Et)Ru\}]^+$ were not observed. The results of these labeling experiments could also be explained if insertion of the $Cs^+$ ion occurred by rupture of a single Ru–N bond followed by admission of the $Cs^+$ ion through this opening in an otherwise intact box. Arguing against labile Ru–N linkages is the inertness of **$Co_4Ru_4$** towards $Et_4NCN$; it is very unlikely that any exposed ruthenium site could resist attack by the $CN^-$ ion, an extremely potent nucleophile.

Kinetic measurements revealed that the rate of conversion of **$K\subset Co_4Ru_4^+$** into **$Cs\subset Co_4Ru_4^+$** slowed during the course of the reaction, which reflects the build-up of free $K^+$ ions that increasingly compete with the entering $Cs^+$ ions [Eq. (1) and (2)].

$$\mathbf{K\subset Co_4Ru_4^+} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} K^+ + \mathbf{Co_4Ru_4} \tag{1}$$

$$Cs^+ + \mathbf{Co_4Ru_4} \xrightarrow{k_2} \mathbf{Cs\subset Co_4Ru_4^+} \tag{2}$$

A dissociative ion-exchange process is indicated, whereby the rate-limiting step is loss of the $K^+$ ion from **$K\subset Co_4Ru_4^+$** followed by uptake of the $Cs^+$ ion. A rate equation for the kinetic model describing this two-step process can be formulated, provided $k_{-1}/k_2$ is known (details in Supporting Information). The ratio of the rates of insertion of $K^+$ and $Cs^+$ ions into **$Co_4Ru_4$**, $k_{-1}/k_2$, was determined from competition experiments (see above), the rates of ion insertion into **$Co_4Ru_4$** being fast relative to the rate of ion exchange. Plots of $\{(k_{-1}/k_2)[\mathbf{K\subset Co_4Ru_4^+}] - a\ln[\mathbf{K\subset Co_4Ru_4^+}]\}$ versus time were linear under conditions where $[Cs^+]_0 > 10[\mathbf{K\subset Co_4Ru_4^+}]_0$. Four sets of kinetic measurements allowed us to determine $k_1 = 1.2\times10^{-4}\,s^{-1}$ (60 °C). The rate of formation of **$K\subset Co_4Ru_4^+$** ($k_{-1}$) was shown to be $135\,s^{-1}M^{-1}$, even at room temperature. From $k_1$ and this lower bound for $k_{-1}$, $K_K$, the binding constant for $K^+$ ions by **$Co_4Ru_4$** (defined in this case as $k_{-1}/k_1$), is approximately $10^6$. Previous competition experiments on $[M\subset\{Cp^*Rh(CN)_3\}_4\{Mo(CO)_3\}_4]^{3-}$ (which cannot be obtained as a voided box) showed that the $Cs^+$ ion binds $>10^4$ more strongly than the $K^+$ ion;[12] extrapolating to the present case, we estimate that $K_{Cs}$ is $>10^{10}$.

The slow ion-exchange rates and cagelike structure suggest that **$Co_4Ru_4$** should chemically protect its guests. To assess this protection, we examined the H–D exchange of the guest in **$NH_4\subset Co_4Ru_4^+$**. The $^1H$ NMR signal for

$\mathbf{NH_4{\subset}Co_4Ru_4}^+$ appears as a 1:1:1 triplet, indicative of the absence of proton exchange. The signal is unaffected by exposure of the compound to $D_2O$ for several hours, whereas ammonium ions characteristically undergo H–D exchange at diffusion-limited rates at neutral pH value.[18] H–D exchange is accelerated somewhat in the presence of free $ND_4BF_4$, and is complete in around 25 h at room temperature in MeCN solution. Deuteration occurs by proton transfer, not by exchange of the ammonium ions since we can detect the initial formation of $\mathbf{NDH_3{\subset}Co_4Ru_4}^+$, as indicated by its distinctive coupling pattern in the $^1$H NMR spectrum. The guest cation in $\mathbf{NH_4{\subset}Co_4Ru_4}^+$ is completely unaffected by quinuclidine, which is a stronger base than ammonia ($pK_a =$ 19.56 vs. 16.46).[19] $^{14}$N and $^1$H NMR measurements (Figure 3) show that H–D exchange between $ND_4^+$ and $\mathbf{MeNH_3{\subset}Co_4Ru_4}^+$ is also slow.

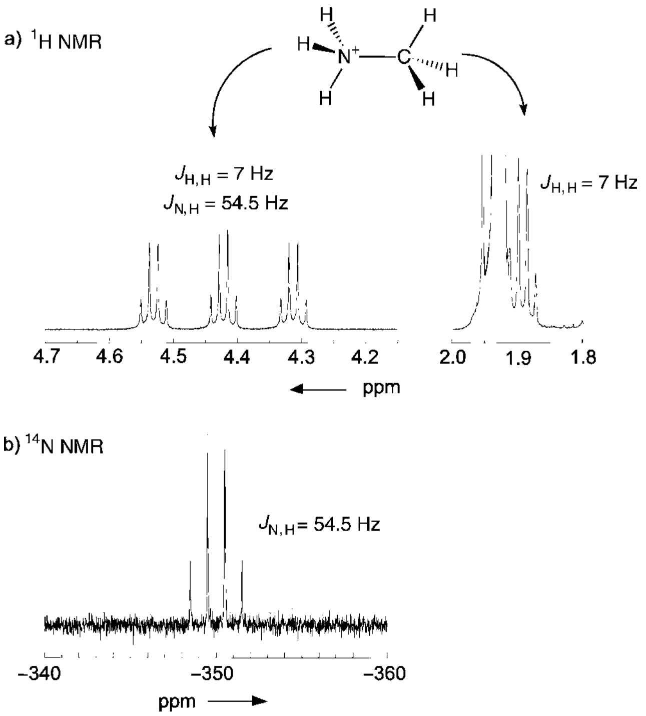

*Figure 3.* a) 500 MHz $^1$H NMR spectrum of $\mathbf{MeNH_3{\subset}Co_4Ru_4}^+ BF_4^-$, b) $^{14}$N NMR spectrum of $\mathbf{MeNH_3{\subset}Co_4Ru_4}^+ BF_4^-$ (in $CD_3CN$).

To summarize, an ionophilic molecular box has been synthesized with the aid of a templating ion. The kinetic and thermodynamic selectivities are distinctive, in large measure because of the pronounced effects of atomic size on the binding and ion-exchange rates. The cage indeed shields guest ions from reagents in the surrounding solution.

## *Experimental Section*

$\mathbf{Co_4Ru_4}$: A solution of PPN[CpCo(CN)$_3$] (290 mg, 0.39 mmol; PPN = triphenyl[(triphenylphosphanylidene)amino]phosphonium) and $EtNH_3BF_4$ (13 mg, 0.10 mmol) in MeCN (50 mL) was added to a solution of [Cp*Ru(NCMe)$_3$]PF$_6$ (197 mg, 0.39 mmol) in MeCN (20 mL). After 5 h, the red microcrystals were collected and then extracted into $Et_2O$ (50 mL). Evaporation gave dark red microcrystals, yield: 140 mg (80 %). $^1$H NMR ([D$_8$]THF; 500 MHz): $\delta =$ 1.67 (s, 60 H), 5.35 ppm (s, 20 H). ESI-MS (*m*/*z*): 1754 ([H{CpCo(CN)$_3$}$_4$(Cp*Ru)$_4$]$^+$). FAB (*m*/*z*): 1753 ([{CpCo(CN)$_3$}$_4$(Cp*Ru)$_4$]$^+$). Elemental analysis (%) calcd for $C_{72}H_{80}Co_4N_{12}Ru_4$: C 49.32, H 4.60, N 9.59; found: C 49.01, H 4.93, N 9.78

$\mathbf{MeNH_3{\subset}Co_4Ru_4}$: A solution of PPN[CpCo(CN)$_3$] (290 mg, 0.39 mmol) and $MeNH_3BF_4$ (12 mg, 0.10 mmol) in MeCN (50 mL) was added to a solution of [Cp*Ru(NCMe)$_3$]PF$_6$ (197 mg, 0.39 mmol) in MeCN (20 mL). After 2 h, the solvent volume was reduced (to approximately 10 mL) to produce dark-red microcrystals of [MeNH$_3$⊂{CpCo(CN)$_3$}$_4$(Cp*Ru)$_4$]PF$_6$, which were washed with cold MeCN (2 mL); yield: 135 mg (71 %). IR (KBr): $\tilde{\nu}_{CN} = 2158$, 2127 cm$^{-1}$; $^1$H NMR ($CD_3CN$): $\delta = 1.66$ (s, 60 H), 1.89 (q, $J_{H,H} = 7$ Hz, 3 H; $CH_3NH_3^+$), 4.09 (q of t, $J_{H,H} = 7$ Hz, $J_{N,H} = 55$ Hz, 3 H; $CH_3NH_3^+$), 5.57 ppm (s, 20 H); $^{14}$N NMR ([D$_6$]acetone, vs. MeCN;): $\delta = -71.65$ (Co-CN-Ru), −349.9 ppm (q, $CH_3NH_3^+$, $J_{N,H} = 55$ Hz); ESI-MS *m*/*z* 1786 ([MeNH$_3$⊂{CpCo(CN)$_3$}$_4$(Cp*Ru)$_4$]$^+$); elemental analysis (%) calcd for $C_{73}H_{86}Co_4F_6N_{13}PRu_4$: C 45.42, H 4.49, N 9.43; found: C 45.36, H 4.66, N 9.57. The same species can be synthesized by treatment of a solution of $\mathbf{Co_4Ru_4}$ with $MeNH_3BF_4$.

*Ion Competition Experiments*: $\mathbf{Co_4Ru_4}$ with $CsO_3SCF_3$ versus $KPF_6$. (similar for Cs$^+$ versus $MeNH_3^+$ and Cs$^+$ versus $NH_4^+$). A solution of $\mathbf{Co_4Ru_4}$ (10 mg, 0.0057 mmol) in THF (10 mL) was added in one portion to a well-stirred homogeneous solution of both $CsO_3SCF_3$ (3.2 mg, 0.0114 mmol) and $KPF_6$ (2.1 mg, 0.0114 mmol) in MeCN (1 mL). The reaction was monitored by ESI-MS (sample concentration $= 10^{-11}$ mol µL$^{-1}$). Experiments were run in duplicate.

*Kinetics of ion exchange*: The differential and integrated rate laws for the kinetic model in Equations (1) and (2) are:

$d[\mathbf{Cs{\subset}Co_4Ru_4}^+]/dt = (k_1[\mathbf{K{\subset}Co_4Ru_4}^+][Cs^+])/\{(k_{-1}/k_2)[K^+] + [Cs^+]\}$

integrating:

$(k_{-1}/k_2)[\mathbf{K{\subset}Co_4Ru_4}^+] - a(\ln[\mathbf{K{\subset}Co_4Ru_4}^+]) = -k_1[Cs^+]t + X$

where

$a = [Cs^+]_0 + (k_{-1}/k_2)[\mathbf{K{\subset}Co_4Ru_4}^+]_0$

$k_{-1}/k_2 = 32.8$ (in THF:6 MeCN)

$X = (k_{-1}/k_2)[\mathbf{K{\subset}Co_4Ru_4}^+]_0 - a(\ln[\mathbf{K{\subset}Co_4Ru_4}^+]_0)$

The value of $k_{-1}/k_2 = 32.8$ was obtained by addition of a solution of $\mathbf{Co_4Ru_4}$ to a solution equimolar in $KPF_6$ and CsOTf (where $[K^+]_0 = [Cs^+]_0 \gg [\mathbf{Co_4Ru_4}]_0$) in 1:6 THF:$CD_3CN$ solution followed by integration of the $C_5H_5$ NMR signals at $\delta = 5.605$ and 5.609 ppm. The measurements were taken for [Co$_4$Ru$_4$]:([KPF$_6$] or [CsOTf]) = 1:2, 1:3, and 1:4. Kinetic rate measurements were monitored for 12 h at 60 °C in 1:6 THF:$CD_3CN$ solvent mixture. All four experiments employed $2.21 \times 10^{-3}$ M $[\mathbf{K{\subset}Co_4Ru_4}^+]_0$; measurements where $[Cs^+]_0$ was 0.0221, 0.0663 M, 0.0884 M, and 0.1105 M gave $k_1 = 1.2 \times 10^{-4}$ s$^{-1}$.

Crystal data: $C_{90}H_{107}Co_4N_{21}Ru_4$, $M_r$ 2122.97, cubic, *I*23; $a = b = c =$ 18.014(3) Å; $\alpha = \beta = \gamma = 90°$; $V = 5872(3)$ Å$^3$; $Z = 2$; $\rho_{calcd} =$ 1.206 Mg m$^{-3}$, $F(000) = 2156$, 175 parameters: $R1 = 0.0408$, $wR2 =$ 0.963, GOF = 1.007 for all 1798 data ($I > 2\sigma(I)$). Single crystals of $\mathbf{Co_4Ru_4}$ were mounted on glass fibers using Paratone-N (Exxon) and were analyzed on a Siemens Platform/CCD automated diffractometer at 193 K. Data were processed using SAINT.[20] The structures were solved using direct methods and refined using full-matrix least-squares analysis on $F^2$ using the program SHELXTL.[21] Hydrogen atoms were fixed in idealized positions with thermal parameters 1.2 times those of the attached carbon atoms. Data were corrected for absorption on the basis of integration. CCDC-187755 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Received: June 19, 2002
Revised: January 15, 2003 [Z19562]

**Keywords:** cage compounds · cations · cobalt · cyanide · host–guest systems · ruthenium

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