The $^1$H NMR $J_{5,6}$ values of 3 Hz for both **1** and **2** therefore show that the guanosine moiety is axially connected to DMBA. *Molecular models reveal that these features then uniquely define the absolute configurations as well as the point of attachment of the guanosine moiety* of **1** and **2** (see **3** and **4**).[15] This leads to configurations 5*S*,6*S* for **1** and 5*R*,6*R* for **2**; i.e., both are products from the 5*R*,6*S* epoxide.[16] Although the direction of electric transition moments of the guanine nucleus is still not established,[17] it is gratifying to note that, as shown by the solid lines in **3** and **4**, the chirality between the chromophoric axes of *structures derived independently of the CD* are indeed "antipodal" and are in agreement with the "antipodal" CD data (Figure 1).

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(13) The low-resolution MS were run on a computerized Finnigan 3300 system. The high-resolution MS data were obtained on an MS-902 instrument, VG Datasystem 2020, Cornell NIH. The *m/e* 404 and 386 peak intensities were too weak for high-resolution analyses owing to sample scarcity.
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(16) The diastereomers of **1** and **2** were not isolated from the in vitro experiments; in spite of the fact that (±)-DMBA 5,6-oxide was employed, they are either not formed or formed in too minute quantities. However, since the oxirane is attacked by the ribose 2′-OH group which is attached to a chiral center, it is reasonable that only one of the diastereomers is formed preponderantly.
(17) Footnote in ref 4, p 2314.
(18) The studies were supported by DHEW CA 11572, NSF CHE76-18435 (to K.N.) and CA 21111 (to D.G.).

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## Binuclear Cryptates. Binuclear Copper(I) and Copper(II) Inclusion Complexes of Polythia Cylindrical Macrotricyclic Ligands

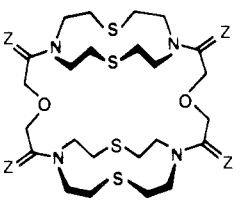
*Sir:*

Macro*poly*cyclic ligands may form *polynuclear cryptate complexes* by inclusion of two or more metal cations into the intramolecular cavities; distance and arrangement of the metal cations may be regulated via ligand structure. Such systems present much interest as models of polynuclear biological complexes or as polynuclear catalysts, especially if *cascade complexes*[1-3] may be formed by inclusion of substrate molecules between the cations.

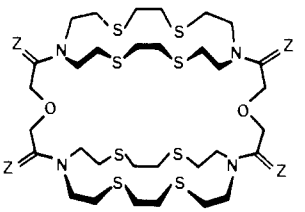
We have previously described two types of macropolycyclic structures which may present such properties: cylindrical macrotricyclic ligands containing "face-to-face" macrocyclic subunits[3-5,6] and bis(tren) macrobicyclic molecules incorporating two coaxially aligned tripodal subunits.[1] The cylindrical macrotricycles have a particularly attractive topology[2-5,7,8] since the lateral macrocycles may serve to select and hold the cations while the central cavity is available for substrate inclusion (Figure 1).

The previous macrotricycles were designed for the study of binuclear alkali and alkaline-earth complexes.[2-5] We now report (i) a general synthetic method for the construction of cylindrical macrotricycles which contain *different* macrocyclic subunits, and which may therefore complex two different cations or stabilize different oxidation states; (ii) the synthesis of the new macrotricyclic ligands **1–3** bearing nitrogen and sulfur binding sites, and (iii) preliminary complexation experiments which yield binuclear copper complexes and relate to the biologically important copper proteins, subject to much current interest.[9-14]

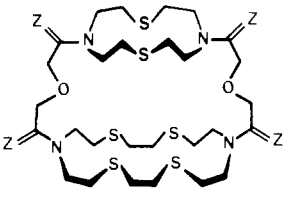
The synthetic strategy allows the incorporation of different macrocycles, whereas the earlier method[3,4] may introduce different bridges linking the macrocycles. It involves (a) attachment of two appendages at diagonally opposed positions



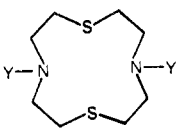
1 Z = $H_2$
10 Z = O



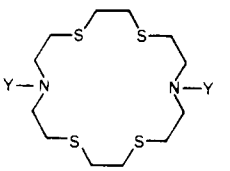
2 Z = $H_2$
11 Z = O



3 Z = $H_2$
12 Z = O



4a Y = H
4b Y = $CH_3$
5 Y = $COCH_2OCH_2COOH$
6 Y = $COCH_2OCH_2COO$-p-nitrophenyl



7a Y = H
7b Y = $CH_3$
8 Y = $COCH_2OCH_2COOH$
9 Y = $COCH_2OCH_2COO$-p-nitrophenyl

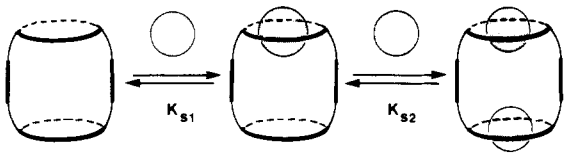



**Figure 1.** Schematic representation of the formation of binuclear cryptate complexes with cyclindrical macrotricyclic ligands like compounds **1**, **2**, and **3**.

of a suitable macrocycle; (b) activation of the free termini of these appendages; and (c) condensation with the second macrocycle.

The 12-membered macrocycle [12]-$N_2S_2$, **4a** (mp 79–80 °C), was obtained by high dilution condensation[15] of $S(CH_2COCl)_2$[16] with $S(CH_2CH_2NH_2)_2$[17] to the corresponding bislactam (mp 195–196 °C, 55% yield) which was then reduced with diborane (90% yield).[15] The 18-membered macrocycle [18]-$N_2S_4$, **7a**, was prepared following our earlier procedure.[18] Eschweiler-Clarke methylation of **4a** and **7a** yields **4b** (mp 67–68 °C) and **7b** (mp 45–46 °C).

Treatment of **4a** and **7a** with 3-oxaglutaric anhydride affords the diacids **5** (mp 230–231 °C, 70% yield) and **8** (mp 185–186 °C, 80% yield), respectively. Treatment with *p*-nitrophenyl sulfite converts the diacids **5** and **8** into the active esters **6** (mp 248–250 °C, 85% yield) and **9** (glassy solid, 70% yield).

To increase the rate of the *p*-nitrophenyl ester–amine reaction, the high dilution condensation[15] was performed in refluxing pyridine. The procedure has only been partially optimized; using another solvent or activating group may improve yields. Reaction of compounds **6** and **9** with the macrocycles **4a** and **7a**, respectively, affords the macrotricyclic tetraamides **10** (mp >250 °C, 10–30% yield)[19] and **11** (mp 190–191 °C, 60% yield); condensation of **9** and **4a** gives product **12** (glassy solid, 50% yield). The three compounds **10**, **11**, and **12** were reduced with diborane to the highly crystalline cylindrical macrotricyclic polythiatetraamines [12]-[12], **1** (mp 162–163 °C, 75% yield), [18]-[18], **2** (mp 130–131 °C, 80% yield), and [12]-[18], **3** (mp 135–136 °C, 80% yield).

In these substances **1–3** each macrocyclic subunit may serve as a receptor site for a metal cation. Because of the difference in ring size and number of S- and N-binding sites, macrocycles [12]-$N_2S_2$ **4** and [18]-$N_2S_4$ **7** may present different complexation properties. The initial studies have been concerned mainly with copper complexes. Whereas the colorless copper(I) complex of **4b** is rapidly oxidized to the intense blue copper(II) complex when exposed to air, the copper(I) complex of **7b** is much more stable in the same conditions. The redox potentials of the copper(II) complexes of **4b** and **7b** are +495 mV and +695 mV, respectively, confirming the stabilization of the copper(I) state by the [18]-$N_2S_4$ macrocycle **7b**.[20a]

The three macrotricyclic ligands **1**, **2**, and **3** give complexes of 1:2 ligand/salt stoichiometry with both copper(I) and copper(II) perchlorates as shown by isolation of the copper(II) complexes and by spectroscopic studies. The copper(I) complexes are colorless and the copper(II) complexes of **1**, **2**, and **3** are, respectively, intense violet, green, and blue. The formation of the copper(I) complex of **2** may be followed by $^{13}C$ NMR spectroscopy. Addition of increasing amounts of copper(II) perchlorate to **1** gives first a green solution at 1:1 ratio ($\lambda_{max}$ 575 nm) and a violet solution at 2:1 ratio ($\lambda_{max}$ 555 nm).[21] Addition of 1 equiv of copper(I) and 1 equiv of copper(II) salt to dissymmetric ligand **3** should give a *mixed* complex; the electronic spectrum indicates that the copper(I) and copper(II) cations are probably located in the 18- and 12-membered rings, respectively.

By analogy to previous results,[3-5] complexation of a metal cation by each macrocyclic subunit of ligands **1–3** yields *binuclear cylindrical macrotricyclic cryptates*, as schematically represented in Figure 1. Based on previous crystal structure data,[13,14] the intercationic distances may be grossly estimated to ~5, 7, and 6 Å for binuclear complexes of **1**, **2**, and **3**, respectively. Thus, there is space for inclusion, between the cations, of a substrate of compatible size and suitable binding properties. No accurate results about stability constants are available at present, but, from the electronic spectra of ligand solutions titrated with copper perchlorates,[21] it appears that both $K_{s1}$ and $K_{s2}$ (Figure 1) are $>10^2$.

The copper(II) complexes of ligand **1–3** may be considered as binuclear models of the copper proteins like macrocyclic thiaether complexes are mononuclear models.[13,14] Thus, in addition to a strong electronic band near 400 nm, an intense absorption in the 600-nm region is observed for the bis(copper(II) complexes of **1** (375 nm ($\epsilon$ 3500), 565 (1200), **2** (430 nm ($\epsilon$ 5000), 590 (1000)), and **3** (375 nm ($\epsilon$ 3500), 565 (1100)), as well as for the copper(II) complexes of **4b** (370 nm ($\epsilon$ 5000), 605 (1200)) and **7b** (415 nm ($\epsilon$ 2600), 695 (600)).[21,22]

Whereas the bis copper(I) complexes of **1**, **2**, and **3** all present a UV band in the 260-nm region, the complexes of **1** and **3** show another absorption in the 350–370-nm region.[21] With ligand **1** the band (355 nm) appears only after adding >1 equiv of copper(I); it is thus characteristic of the *binuclear copper(I) cryptate* [(2Cu(I)⊂**1**].

Electrochemical reduction of [2Cu(II)⊂**1**] indicates the reversible transfer of two electrons at +445 mV.[20b] The markedly positive potentials measured for this complex and for the complexes of **4b** and **7b** (see above) fall in the domain of those found for copper(II) complexes of polythiamacrocycles[14] and of copper proteins.[9]

The difference between mononuclear and binuclear species is clearly apparent in the EPR powder spectra. Although both spectra are of the axial type,[23a] the copper(II) complex of monocycle **4b** has $g_{\parallel} < g_{\perp}$ (2.047, 2.112), whereas the binuclear complex (2Cu(II)⊂**1**) has $g_{\perp} < g_{\parallel}$ (2.040, 2.133). In the latter case $G = (g_{\parallel} - 2)/(g_{\perp} - 2) = 3.3$; $G < 4.0$ may indicate significant exchange coupling.[23b]

Insertion of a substrate molecule ($O_2$, $N_2$, etc.) between the two metal cations of binuclear complexes leads to cascade complexes which may have interesting properties for fixation and binuclear catalysis (like the reduction of the included molecules). Although there is no definitive evidence that such processes occur, similar electronic spectra (bands at 330, 370, broad absorption 550–850 nm) are obtained when adding $KO_2$ to 2Cu(II)⊂**1** or oxygen to 2Cu(I)⊂**1**. Also, the intensity of the 355-nm band of the latter complex is strongly affected by $O_2$ and CO. These changes might involve *binuclear* reactions of superoxide[24] and oxygen (e.g., fixation, reduction[25]) and have relevance to biological processes (copper proteins, superoxide dismutase).[9]

Studies of symmetrical or unsymmetrical macrotricyclic ligands should afford new types of homo- or heteronuclear transition metal complexes, potential bioinorganic models, as well as entries into new chemical processes involving two or more metal cations held in a predetermined arrangement.

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(19) The variable yields arise from the difficulty of monitoring the concentration of reagent **6** owing to its very low solubility. **10** can also be obtained in low yield (5–10%) in one step by high dilution reaction of **4a** with $O(CH_2COCl)_2$ following a previously described method.[4] Other procedures are being investigated.
(20) $E_{1/2}$ values vs. SHE at 25 °C determined by normal pulse polarography and cyclic voltammetry (J. P. Gisselbrecht and M. Gross, unpublished results): (a) propylene carbonate solutions, $\mu$ = 0.1, $(n\text{-hexyl})_4ClO_4$ (in the same conditions copper(II) perchlorate shows a potential of +494 mV/SHE for the copper(II)/copper(0) couple); (b) aqueous solutions, $\mu$ = 0.1, KCl, copper(II)/copper(0) +334 mV (in propylene carbonate solution the bis copper(II) complex of **1** shows a reversible transfer of two electrons at +545 mV).
(21) Solvent: propylene carbonate/chloroform 1:1. Owing to the spontaneous partial reduction of copper(II) to copper(I) when [18]-$N_2S_4$ subunits are present, the $\epsilon$ values for the copper(II) complexes of **2** and **3** are approximate.
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## Nature of Alkyl Transfer in Reactions of Grignard Reagents with Ketones[1]

*Sir:*

Now that the mechanisms of formation of hydrol and pinacol[2] in Grignard reactions with ketones have been determined, the description of the alkyl transfer from the Grignard reagent to the carbonyl carbon atom is the most significant question that remains to be answered. With respect to the nature of this alkyl transfer, Holm and Crossland[3] have presented convincing evidence for a rate-determining single-electron transfer (SET) step (eq 1) in the reaction of *t*-$C_4H_9MgCl$ with benzophenone in diethyl ether involving the intermediate formation of a "free" radical and radical anion. The ability to "trap" or "observe" the intermediate radical or the radical anion would be instrumental in establishing the integrity of the proposed mechanism.

$$\text{"RMgX"} + Ph_2C{=}O \rightarrow [R\cdot + Ph_2\dot{C}{-}O^{-+}MgX] \rightarrow \text{products} \quad (1)$$

With this in mind, radical probes were incorporated into the R group of Grignard reagents such that free-radical character would be observed as isomerization or cyclization of the particular probe. The radical probes studied are illustrated in Table I.

The absence of isomerization or cyclization in the 1,2-addition products of "*cis*-propenylmagnesium bromide" (a vinylic Grignard) and "5-hexenylmagnesium bromide" (a primary Grignard), respectively, with benzophenone indicates that either the reaction is polar or, if SET, no "free" radical character is exhibited. On the other hand, when 1,1-dimethyl-5-hexenylmagnesium chloride (a tertiary Grignard) was allowed to react with benzophenone, the resulting products consisted of 62% 1,6 addition and 38% 1,2 addition. Although no cyclization of the probe was observed in the 1,2-addition product, cyclization was observed for 74% of the 1,6-addition product.

The ratio of cyclized to uncyclized 1,6-addition products (74:26) established the radical nature of the 1,6-addition process and also indicates that the rate of probe cyclization is comparable with the rate of 1,6-addition product formation ($R_{cyc} \simeq 10^5\ s^{-1}$).[4] It is important to note that the ratio of 1,6-addition to 1,2-addition products (62:38) indicates that the rate of formation of 1,6-addition product is faster than the rate of 1,2-addition product formation. Thus, 1,2-addition product is being formed at a rate slower than that of cyclization of the probe but no cyclization was observed in the 1,2-addition product. Since Holm's results eliminate the possibility of a polar 1,2-addition reaction, the only reasonable rationalization of these findings is that, after the transfer of the electron from the Grignard reagent to the benzophenone, R· of the Grignard is still tightly bound to the magnesium as a radical cation ($RMgX^{+}\cdot$). Collapse of the radical anion–radical cation pair to form 1,2-addition product would preclude cyclization.

We have also found that the radical anion as well does not appear to be a "free ketyl" in reactions of either primary or tertiary Grignard reagents with benzophenone. We have found that the radical anion scavenger (*p*-dinitrobenzene[5]) completely eliminates pinacol formation in the reaction of "$CH_3MgBr$" and "*t*-$C_4H_9MgCl$" with 2-methylbenzophenone, but has no effect on the ratio or rate of formation of 1,2- and 1,6-addition products. The pathway to pinacol formation has been shown to involve a "free ketyl" [6] which is susceptible to electron transfer to *p*-dinitrobenzene.[7] Thus formation of 1,2- and 1,6-addition products must not involve a "free ketyl" (eq 2-4).

$$RMgX + Ph_2C{=}O \rightarrow [RMgX]^{+}\cdot[Ph_2\dot{C}{-}O^{-}] \quad (2)$$

$$p\text{-DNB} + [Ph_2\dot{C}{-}O^{-}] \rightarrow [p\text{-DNB}]^{-}\cdot + Ph_2C{=}O \quad (3)$$

$$[p\text{-DNB}]^{-}\cdot + [RMgX]^{+}\cdot \rightarrow p\text{-DNB} + RMgX \quad (4)$$

In light of the "bound" nature of the R-group radical and ketyl, it seems necessary for the mechanism of *t*-$C_4H_9MgCl$ with benzophenone to involve a radical anion–radical cation pair which can (a) collapse to 1,2-addition product or (b) dissociate to from a radical anion and a free radical within the solvent cage which in turn can collapse to conjugate addition products or escape the solvent cage to form benzopinacol, as shown in the proposed mechanism (eq 5).

It is possible that all Grignard reactions with ketones proceed through a SET pathway by the proposed mechanism. However, the stability of the radical-cation complex should be determined by the stabilities of the incipient radical (R·) and