5.53 (br s, 1 H), 5.82 (d, $J = 2$ Hz, 1 H), 6.61 (d, $J = 2$ Hz, 1 H), 7.20–7.80 (m, 3 H), 8.20–8.40 (m, 1 H)] as a light yellow oil in 81% overall yield from **12**.

The total synthesis of secodine was completed by removal of the β,β,β-trichloro-*tert*-butyl carbamate protecting group by treatment of a solution of **13** in 10:1 methanol–acetic acid (0.02 M) with excess powdered zinc (20 equiv) at 0 °C for 20 min, aqueous $NaHCO_3$ workup, rapid removal of solvents at 0 °C, and purification by flash chromatography[18] (20% 2-propanol–CH_2Cl_2) to give **2**[13] [^{1}H NMR ($CDCl_3$) δ 1.00 (t, $J = 7$ Hz, 3 H), 1.6–3.3 (m, 12 H), 3.80 (s, 3 H), 5.45 (m, 1 H), 6.11 (d, $J = 1$ Hz, 1 H), 6.47 (d, $J = 1$ Hz, 1 H), 7.0–7.8 (m, 4 H), 9.2 (br s, 1 H); *m/e* Calcd for $C_{21}H_{26}O_2N_2$: 338.1994. Found: 338.1930] as a viscous oil in 76% yield.[13,22]

The above synthesis clearly demonstrates the applicability of the Claisen ortho ester rearrangement of indole-3-glycolamides for the construction of 2,3-disubstituted indoles, as well as the utility of **9** for the introduction of an α-substituted acrylate moiety under mild, nonbasic conditions. We are currently investigating the use of this strategy for the synthesis of a number of *Aspidosperma* and *Iboga* alkaloids.

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[22] Although secodine dimerizes rapidly at room temperature, the protected precursor **13** is stable for several weeks when stored under argon at 0 °C. For studies concerning the related, naturally occurring dimeric alkaloids, the secamines and presecamines, see: (a) Evans, D. A.; Smith, G. F.; Smith, G. N.; Stapleford, K. S. J. *J. Chem. Soc., Chem. Commun.* **1968**, 859. (b) Cordell, G. A.; Smith, G. F.; Smith, G. N. *Ibid.* **1970**, 191.

Guest-Host Association by Transition-Metal Complexes Containing Permanent Voids—Progress toward Models for the Ternary Complex of Cytochrome P450

Kenneth J. Takeuchi and Daryle H. Busch*

Chemistry Department, The Ohio State University
Columbus, Ohio 43210

Nathanial Alcock

Chemistry Department, University of Warwick
Coventry, CV4 7 AL, England

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Cytochrome P450 monooxygenase enzymes[1,2] produce highly selective oxygenations[3,4] of organic substrates by simultaneously activating dioxygen[5,6] and undergoing a hydrophobic[6] guest–host association between the enzyme and the target substrate. We are concerned with the design, synthesis, and study of totally synthetic transition-metal species having the ability to emulate cytochrome P450 by forming ternary complexes of this kind. Structure I shows a family of bicyclic ligands whose cobalt(II) and iron(II) complexes exhibit exceptional O_2-carrying capacities.[7,8] The earlier studies used relatively small bridging groups R^1 (structure I) that produced a limited cavity having sufficient volume to accommodate *only* small ligands such as O_2,[7,8] CO,[9] NCS^-,[10] etc.

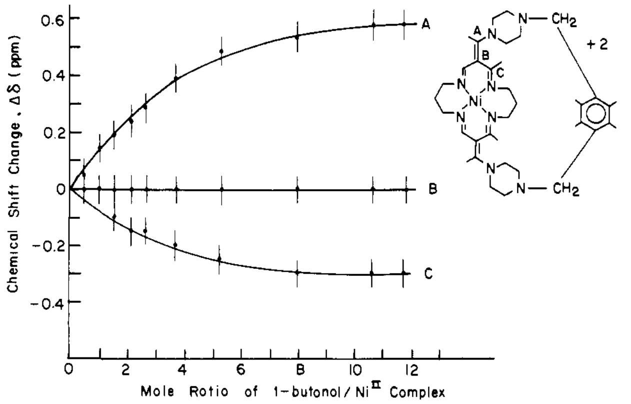
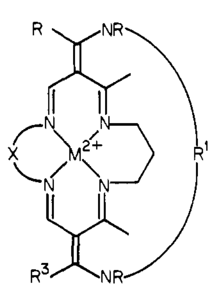


Figure 1. ^{13}C NMR, changes in chemical shifts for atoms of the host (Ni^{2+} complex of structure II, R = durene) as the concentration of guest (*n*-butyl alcohol) is changed, D_2O solution, ~30 °C.



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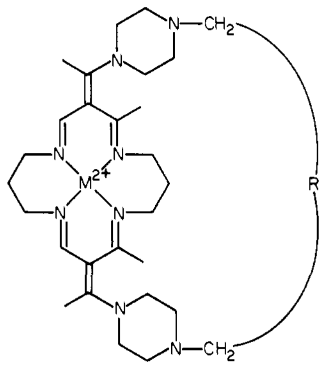

II

Redesign of the bridging unit has now produced related structures having sufficiently commodious persistent voids to engulf many potential organic substrates (structure II, R = anthracene, benzene, durene, or pyridine). By deriving structure II from structure I, we are assured that the appropriate metal complexes will interact with O_2 as required for the formation of the ternary complex. The interaction that remained to be demonstrated is the guest–host association and that is the subject of this report. Guest–host associations resulting from hydrophobic interactions have been most widely studied with oligomeric cyclodextrins[11] and paracyclophanes[12,13] acting as hosts. Although there are several examples of cyclodextrins containing metal ions,[14] we are aware of no previous examples in which a transition metal is an essential part of the wall of a permanent void designed to serve as host for a hydrophobic guest.

The preparation of these complexes is illustrated by the anthracene derivative as follows. [Ni{(MeOEthi)$_2$Me$_2$[16]tetraeneN$_4$}](PF_6)$_2$[15] (0.005 mol) in acetonitrile was added dropwise to piperazine (0.1 mol) in methanol. An orange crystalline product (III) was isolated from the acetonitrile/methanol solution; yield, 1.2 g (29.2%). Anal. Calcd for $NiC_{26}H_{44}N_8P_2F_{12}$: C, 38.20; H, 5.43; N, 13.71. Found: C, 38.14; H, 5.58; N, 13.65. The product [Ni{(piperazineEthi)$_2$Me$_2$[16]tetraeneN$_4$}](PF_6)$_2$ (0.00244 mol)

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[15] For a discussion of abbreviations, see ref 9.

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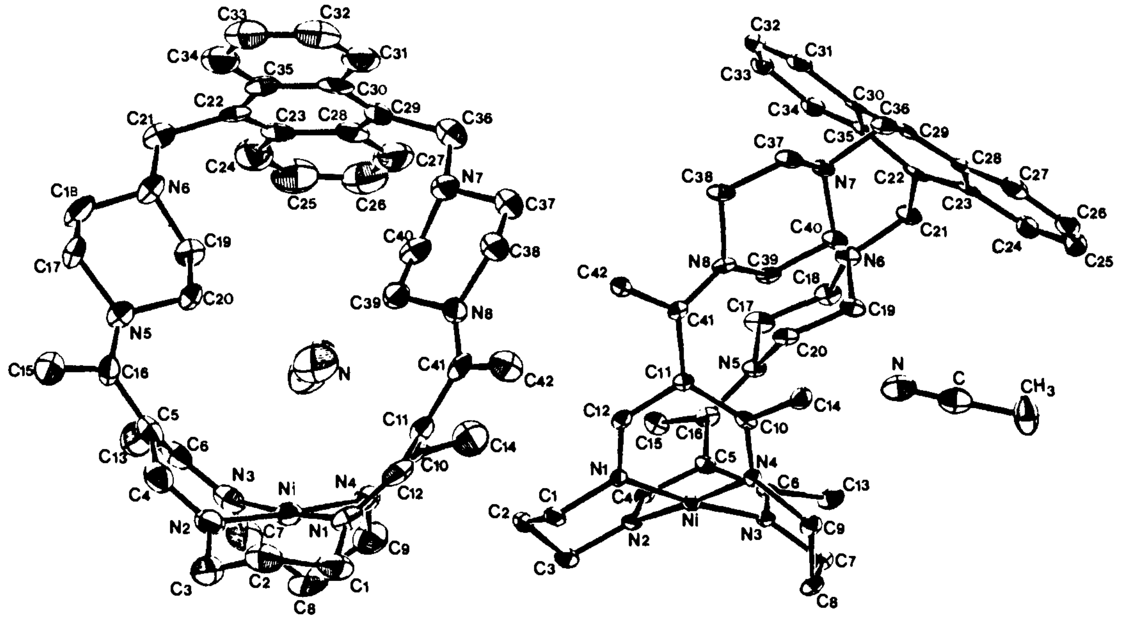

Figure 2. ORTEP drawings of the host species [Ni{9,10-anthracene(CH_2piperazineEthi)$_2$Me$_2$[16]tetraeneN$_4$}]$(PF_6)_2\cdot 2CH_3CN$.

(III) and 9,10-bis(chloromethyl)anthracene (0.00244 mol) were refluxed for 24 h in acetonitrile. The solution was reduced in volume, and triethylamine and ethanol were added. An orange crystalline product (II, R = anthracene) was recovered from the triethylamine/acetonitrile/ethanol solution; yield, 1.18 g (47.2%). Anal. Calcd for $NiC_{42}H_{54}N_8P_2F_6$: C, 49.48; H, 5.34; N, 10.99. Found: C, 49.51; H, 5.53; N, 10.93.

Preliminary NMR studies have demonstrated the occurrence of the guest–host association in aqueous solutions. The assignments were consistent with those previously reported.[16] The nickel(II) complex of structure II, having R = durene, served as host while *n*-butyl alcohol acted as the guest. [Ni{3,6-durene-(CH_2piperazineEthi)$_2$Me$_2$[16]tetraeneN$_4$}]$Cl_4\cdot 5.5H_4O$ (9.89×10^{-5} mol) was dissolved in 2.6 mL of D_2O. Proton decoupled ^{13}C NMR spectra were then recorded on the solution in the presence of increasing amounts of n-butyl alcohol (from 5.3×10^{-5} to 1.17×10^{-3} mol).

Figure 1 shows the manner in which the chemical shift difference $\Delta\delta$ changes with the moles of *n*-butyl alcohol added ($\Delta\delta$ = chemical shift for the resonance in the absence of *n*-butyl alcohol minus the chemical shift in the presence of a certain concentration of *n*-butyl alcohol). For carbon atom A, the magnitude of $\Delta\delta$ initially increases as butyl alcohol is added but it reaches a limiting value, suggesting saturation of the expected association equilibrium. The fact that the chemical shift of each carbon atom has its own unique response to the addition of *n*-butyl alcohol is an indication that the guest–host interaction is indeed a specific one and not a bulk phenomenon. The variation in $\Delta\delta$ has been used to estimate the association constant[17] for this guest–host complexation, ($K_a = 17\ M^{-1}$, $T \simeq 30$ °C). The hydrophobic nature of the interaction is supported by the fact that such chemical shifts are not observed in similar experiments in acetonitrile, acetone, or nitromethane solutions.

The results of an X-ray crystallographic study are equally significant. A red-brown crystal of dimensions $0.2 \times 0.5 \times 0.2$ mm of [Ni{9,10-anthracene(CH_2piperazineEthi)$_2$Me$_2$[16]tetraeneN$_4$}]$(PF_6)_2\cdot 2CH_3CN$ was subjected to a complete X-ray structure determination: space group $P2_1/n$; $a = 13.798$ (3), $b = 16.976$ (3), $c = 22.769$ (6) Å; $\beta = 103.55$ (2)°; $\lambda_{MoK\alpha} = 0.71069$ Å; $T = 16 \pm 0.5$ °C; $\mu = 5.14$ cm^{-1}; $\rho_{obsd} = 1.42$, $\rho_{calcd} = 1.40$ g cm^{-3}; $\omega = 2\theta$ scan technique for all reflections $2\theta \leq 40$; 6459 independent reflections of which 3697 had intensities $>3\sigma(F)$ above background. The solution using only $3\sigma(F)$ data was by the heavy atom method, and full-matrix least-squares methods were used in refinement. In the final least-squares calculation, anisotropic parameters for all nonhydrogen atoms were used, and generated hydrogen atom contributions, with no refinement, were added. Agreement factors: $R = 7.4\%$, $R_W = 9.9\%$, GOF = 1.97.

The most striking feature of the structure is the large void in the ligand (Figure 2). The NiN_4 plane and the anthracene group are relatively rigid boundaries to the ligand grotto. The distance from the nickel atom to the center of the anthracene is 8.26 Å, and the plane of the anthracene is tilted 30.7° with respect to the NiN_4 plane. The larger opening to the void is 8.94 Å (between the midpoints of line N1N2 and C30C35), and the smaller opening is 7.61 Å (between midpoints of lines N3N4 and C23C28). The other two walls of the cavity are comprised mainly of the six-membered piperazine rings, and these groups have the ability to rotate through substantial arcs about the C41N8 and C16N5 axes.

The location of the molecule of CH_3CN part way in the cavity emphasizes a fascinating variability in the character of the void. The detailed interactions between the intercalated CH_3CN and its host is probably different from the mode of inclusion of other guests, especially in aqueous solutions. In the solid, the CH_3CN rests in the cleft between the anthracene and NiN_4, with its nitrogen atom oriented so as to maximize van der Waals interactions with eight ligand hydrogens (C_7, C_9, C_{13}, C_{14}, C_{19}, C_{20}, C_{39}, C_{40}, Figure 2). Notably, one edge of each piperazine ring is rotated into the cavity in order to accommodate these van der Waals contacts, and it is these interactions that fix the location of the acetonitrile. Detailed NMR studies on the analogous complex (II) having R = benzene show that this is not the dominant ligand conformation in some solvents. The benzene group rotates freely, a motion that is allowed only if the piperazines are rotated out of the way. Ongoing studies[18] are concerned with ascertaining details of the guest-host complexing.

It has been shown that the ligands of II can be removed from nickel(II) and coordinated to other metal ions. Preliminary studies indicate that the O_2 affinity and the reversibility of the O_2 binding to cobalt(II) are affected by guest-host complexation. This and possible oxygenation reactions of organic substrates are the subjects of continuing studies.

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[18] The support of the National Science Foundation is gratefully acknowledged. Assistance with calculations relating to the X-ray structure determination by Drs. G. G. Christoph and N. Matsumoto and Mr. K. Gilbert and assistance in the NMR measurements by Dr. C. Cottrell are deeply appreciated.