Mixed Substrate Supermolecules: Binding of Organic Substrates and of Metal Ions to Heterotopic Coreceptors containing Porphyrin Subunits

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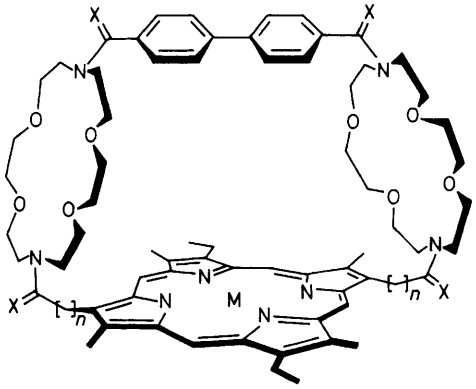
The macrotetracyclic and macropentacyclic compounds (**1**)—(**3**), which combine porphyrin rings and [18]-N_2O_4 aza-oxamacrocycles as substrate selective binding subunits, complex diammonium ions ^+H_3N–$[CH_2]_n$–NH_3^+ (anchored to the [18]-N_2O_4 sites and included in the central molecular cavity), and/or Zn^{II} ions (bound to the porphyrin groups), thus yielding organic/inorganic mixed substrate supramolecular structures.

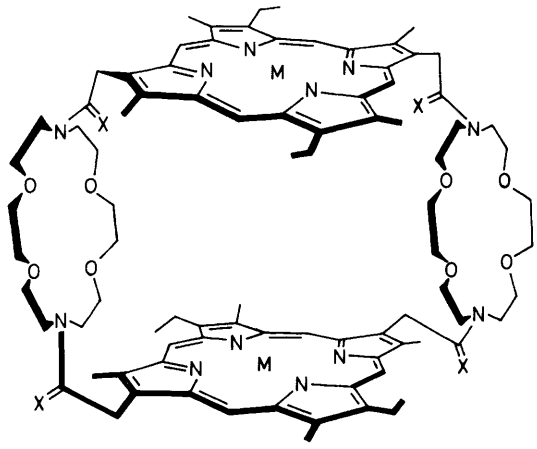
Multisite complexing agents, incorporating subunits for binding both metal ions and organic substrate (*heterotopic coreceptors*), might allow interactions and reactions (*cocatalysis*) to take place between metal-centred reactive sites and co-bound molecular substrates.[1,2] Such *metallocatalysts* could also mimic essential features of metalloenzymes.[3]

We have designed several systems of this type[1] and report here the synthesis of coreceptors (**1**)—(**3**), and the formation of mixed substrate supramolecular complexes by binding of both metal cations and of primary diammonium ions.[4,5]

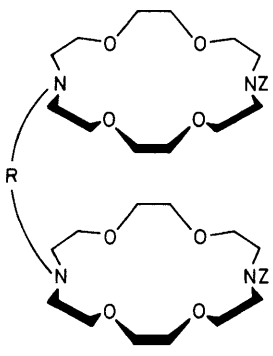
Treatment of the monoprotected [18]-N_2O_4 macrocycle (**4**)[6] with (**5**) gave (**6**) which, after hydrogenolysis, afforded (**7**) (two steps, quantitative yield). Reaction of (**7**) with the C(2) di-*p*-nitrophenyl ester porphyrin (**8**)[7] in pyridine at 55 °C under high dilution (HD) conditions,[7,8] followed by chromatography (silica gel, 1% MeOH in CH_2Cl_2 eluent) yielded the tetra-amide (**10**) (54% yield). Reduction of (**10**) to the tetra-amine (**1**) was effected in virtually quantitative yield using a sequence which involved protecting the porphyrin as the zinc(II) complex by reaction with zinc acetate, reducing



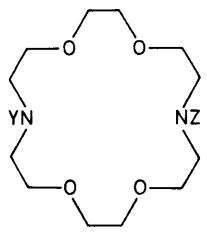
(**1**) *n* = 1, X = H_2, M = H_2
(**2**) *n* = 2, X = H_2, M = H_2
(**10**) *n* = 1, X = O, M = H_2
(**11**) *n* = 2, X = O, M = H_2
(**16**) *n* = 1, X = H_2, M = Zn
(**17**) *n* = 2, X = H_2, M = Zn



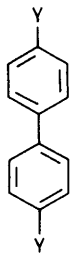
(**3**) X = H_2, M = H_2
(**15**) X = O, M = H_2
(**18**) X = H_2 M = Zn



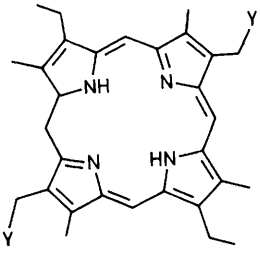
(**6**) R = A, Z = CO_2CH_2Ph
(**7**) R = A, Z = H
(**13**) R = B, Z = CO_2CH_2Ph
(**14**) R = B, Z = H



(**4**) Y = H, Z = CO_2CH_2Ph
(**12**) Y = Z = H
(**19**) Y = Z = Me



A, Y = CO
(**5**) Y = COCl



B, Y = CO
(**8**) Y = $CO_2C_6H_4NO_2$
(**9**) Y = $CH_2CO_2C_6H_4NO_2$

with diborane, and demetallating with concentrated HCl.† Similarly, the C(3) di-*p*-nitrophenyl ester porphyrin (**9**)[7] was converted *via* (**11**) into tetra-amine (**2**) (45% yield for two steps). Compound (**3**) was prepared by two routes: (i) direct HD condensation of (**8**) with the [18]-N_2O_4 macrocycle (**12**), to yield (**15**), followed by reduction with diborane as described above (10% yield for two steps), or (ii) HD reaction of (**4**) with (**8**) [to yield (**13**)], deprotection with concentrated HCl [to afford (**14**)], HD condensation with (**8**) [to give (**15**)], and subsequent reduction (25% yield for four steps).

The macrotetracycles (**1**), (**2**), and the macropentacycle (**3**) define three and four lateral cavities respectively, and a central cavity suitable for substrate inclusion (maximum length *ca.* 12—15 Å). They are members of the class of cylindrical cryptands[1,2,6,9,10] and are *tritopic* and *tetratopic coreceptors* incorporating three or four substrate-selective binding subunits: [18]-N_2O_4 macrocycles which may anchor primary ammonium groups,[1,2,9,11] and porphyrins for metal ion complexation. Cryptand (**3**) is also a member of the β-linked 'face-to-face' dimeric porphyrin series.[7,12]‡§

Molecular substrate binding to (**1**), (**2**), and (**3**) may be studied by ^{1}H n.m.r. spectroscopy.[2,14] Addition of ^+H_3N–$[CH_2]_n$–NH_3^+, n = 9 (substrate S_9^{2+}) dipicrate to these compounds gave complexes of 1 : 1 stoicheiometry displaying large high field shifts for the CH_2 signals of the substrate (Table 1)¶ indicating its inclusion in the central molecular cavity (see below).[2,9,14,15]

Metal cation complexation to the porphyrin units of (**1**)—(**3**) gives the metalloreceptors (**16**)—(**18**). Isosbestic behaviour was observed in the 450—700 nm range of the visible spectrum when compounds (**1**), (**2**), or (**3**) in $CHCl_3$ were slowly titrated with zinc acetate in MeOH. Since complete conversion into the diamagnetic zinc(II) porphyrin[13b] was observed after the addition of only one equivalent of zinc (per porphyrin site), little if any, competing complexation occurs from the [18]-N_2O_4 sites.‖

Binding of metal-ions and molecular substrate is observed with the metalloreceptors (**16**)—(**18**). As with (**1**), addition of S_9^{2+} dipicrate to (**16**) gave a 1 : 1 complex displaying large high field shifts for the CH_2 ^{1}H n.m.r. signals of the substrate (Figure 1).§ The εCH_2 peak at δ −2.60 was *ca.* 3.9 p.p.m. upfield from the corresponding reference peak in the complex of S_9^{2+} with (**19**), and 2.0 p.p.m. upfield of the maximally shifted CH_2 peaks in related complexes derived from the bis-biphenyl bridged analogue of (**1**).[2] These shifts are comparable to those found in a 'strapped' porphyrin[17] in which an alkyl chain is covalently constrained to lie above the ring. Complex formation also occurs when (**16**) is treated with the S_8^{2+} or S_{10}^{2+} substrates, but not with the S_7^{2+} or S_{11}^{2+} species, demonstrating that substrate binding is *selective*.[2,9,10,15] Similar behaviour is observed for the homologous metallocoreceptor (**17**). Selected results are given in Table 1. The large upfield shifts of the CH_2 protons in the bound substrates are due to the shielding effect of the porphyrin and, to a lesser extent, biphenyl bridging groups. As with the macrocyclic diammonium cryptates,[2,9,15] the substrates are therefore bound within the central molecular cavity of the receptors (**1**), (**2**), (**16**), and (**17**) forming mononuclear η^2-cryptates by the simultaneous binding of the primary alkyl ammonium groups to the [18]-N_2O_4 subunits. Figure 2 gives schematic representations of the (metal ion + organic

Table 1. ^{1}H N.m.r. chemical shifts of the bound ^+H_3N–$[CH_2]_n$–NH_3^+ substrates in the molecular cryptates of coreceptors (**1**)—(**3**) and metalloreceptors (**16**)—(**18**).[a]

Cryptand	n	Substrate CH_2 chemical shifts			
		β	γ	δ	ε
(**1**)	9	−0.08 −0.28[c]	−1.27 −1.53[c]	−2.00 −2.20[c]	−2.69
(**2**)	9	0.25	−1.03	−1.60	−2.38
(**3**)	9	[b]	−2.2	−4.0	−5.5
(**16**)	8	−0.83 −1.37[c]	−1.91	−2.43	
(**16**)	9	0.02 −0.44[c]	−1.24 −1.48[c]	−2.11	−2.60
(**16**)	10	0.42	−0.98	−1.91	−2.48 −3.00[c]
(**17**)	8	[b]	−1.4	−1.6	
(**17**)	9	0.28	−1.03	−1.69	−2.47
(**17**)	10	[b]	−0.69	−1.48	−2.32
(**18**)	8	−2.31	−3.12	−4.36	
(**18**)	9	−1.64	−2.88	−4.88	−6.80
(**18**)	10	−0.60	−2.3	−4.3	−5.3

[a] 200 MHz ^{1}H N.m.r. spectra in CD_2Cl_2 : CD_3OD 9 : 1 (v/v) at 18 °C. Shifts δ given *vs.* Me_4Si. Peak assignments were based in part on comparison with a 'strapped' porphyrin[17a] and by analogy with earlier results.[2,15] The signals of the α-CH_2 protons could not be assigned, being probably hidden under resonances of the receptor. [b] Not assigned. [c] Doublet observed.

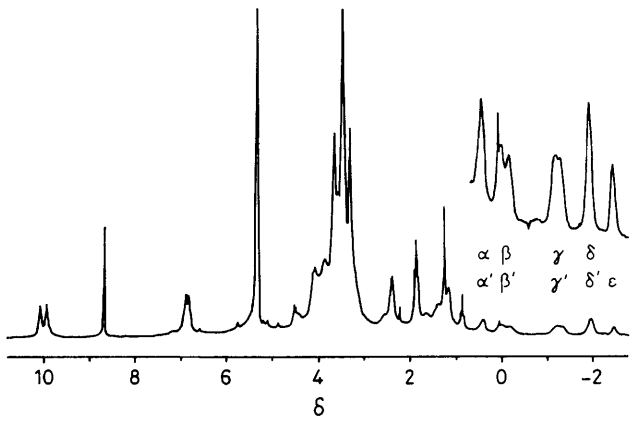


Figure 1. ^{1}H N.m.r. spectrum at 200 MHz of the supramolecular complex (**16**)·S_9^{2+} formed from the metalloreceptor (**1**) and the substrate ^+H_3N–$[CH_2]_9$–NH_3^+.¶

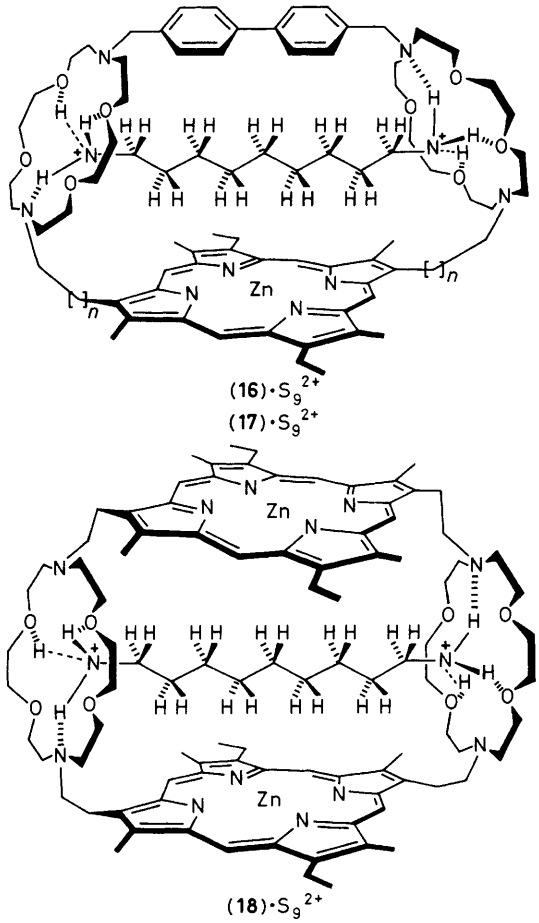
† All new compounds described gave spectroscopic data and elemental analyses consistent with their structure.

‡ An indication that (**3**) is a porphyrin dimer is given by the blue shift of the Soret band for this compound (λ_{max} = 388 nm) as compared to the porphyrin monomer (**2**) (λ_{max} = 397 nm). This shift is even more pronounced in the zinc complexes (**18**) (λ_{max} = 385 nm) and (**17**) (λ_{max} = 405 nm) (ref. 13a).

§ Although Corey–Pauling–Koltun models suggest interconversion should be possible, compound (**3**), in analogy to other members of the β-linked 'face-to-face' series, can exist in two diastereoisomeric forms. Similarly, compounds (**1**) and (**2**) are chiral provided that the rate at which the porphyrin ring 'flips' around the transverse β-pyrrolic bridging axis is not appreciable.

¶ All complexation studies were carried out on CD_2Cl_2 : CD_3OD 9 : 1 (v/v) solutions at 18 °C. ^{1}H N.m.r. spectra were measured at 200 MHz and in some cases also at 400 MHz. In the case of metalloreceptors (**16**)—(**18**), u.v.–visible spectroscopy was used to check that organic substrate complexation did not lead to demetallation.

‖ When the analogous titration was performed with copper(II) acetate, isosbestic behaviour was not observed; the [18]-N_2O_4 macrocycle has a *ca.* 10^4 higher affinity for Cu^{II} than for Zn^{II}, (ref. 16).



(16)·S_9^{2+}
(17)·S_9^{2+}
(18)·S_9^{2+}

Figure 2

substrate containing) supramolecular complexes derived from (**1**) and (**2**).**

When the bis-porphyrin metalloreceptor (**18**), or its free base (**3**) are treated with S_9^{2+} or S_{10}^{2+} substrates, complexes form which are sparingly soluble.*** The resulting ^{1}H n.m.r. spectra were thus complicated by the additional presence of both free receptor and uncomplexed substrate. Since, however, only the complexed substrate displayed CH_2 signals upfield of Me_4Si, assignment of peaks remains straightforward. In fact, the εCH_2 protons are observed at δ −6.80 for the complex formed from (**18**) and the S_9^{2+} (Figure 1, Table 1), a shift of over 8 p.p.m. from the reference complex formed from (**19**)!

The supramolecular complexes depicted in Figure 2 are prototypical of the general class of mixed-substrate co-complexes formed by heterotopic coreceptors. Numerous variations are conceivable involving the subunits (such as 2,2′-bipyridine bridges or nitrogen-sulphur macrocycles[1,18]) as well as the overall macropolycyclic architecture. The complexation of both organic and inorganic substrates offers numerous opportunities to induce and modulate physical as well as chemical interactions and reactions between the co-bound species.

Added in proof: The crystal structure of the Cu^{II} complex of (**1**) (M = Cu) has been determined and will be published elsewhere.

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** The dissymmetry of (**16**)·S_9^{2+} is reflected in the splitting of the signals for the β and γCH_2 protons (Figure 1), as also observed with the other complexes formed from (**1**) and (**16**) (Table 1). These splittings suggest that rotation of the ^+H_3N–$[CH_2]_9$–NH_3^+ substrate about the N,N-axis and/or rotations of the porphyrin units are slow, so that the supramolecular complexes derived from (**1**) and (**16**) are chiral on the n.m.r. time scale (see footnote §). Complexes derived from the larger homologues (**2**) and (**17**) do not show such splittings but present broad signals.

*** If substrate S_8^{2+}, for which appreciable but not optimal binding is to be expected, is added to (**3**) or (**18**) significantly more soluble complexes are obtained. With the S_{11}^{2+} substrate there is no evidence of complexation and complete solubility is retained.

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