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A Water-soluble Tweezers-like Metalloreceptor: Binding and Selective Catalytic Properties

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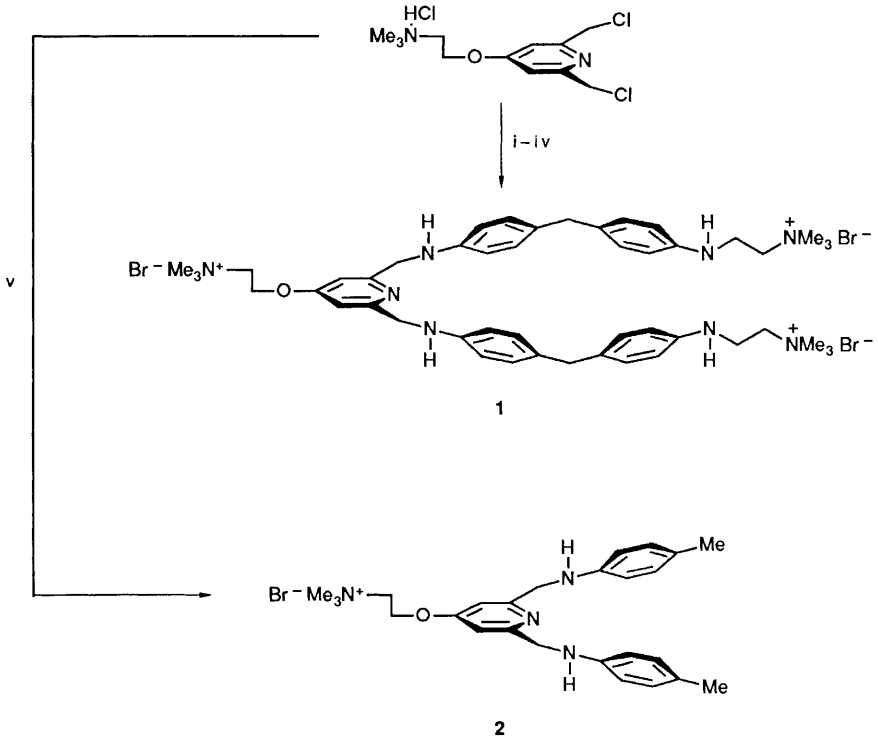
The amphiphilic molecule **1** binds lipophilic substrates below its critical aggregate concentration and, in a complex with two Cu^{II} ions, is a catalyst for the hydrolytic cleavage of activated esters of β-amino acids and an inhibitor of that of α-amino acids.

Supramolecular[1] systems capable of chelating metal ions and substrates (either micellar aggregates[2] or cyclodextrin[3] and cyclophane[4] derivatives) have been investigated in several laboratories as polytopic receptors and catalysts for the cleavage of esters.

We present here a preliminary account of the synthesis and properties of the water soluble receptor **1** designed: (*a*) to bind lipophilic substrates in its hydrophobic cleft defined by the two diphenylmethane subunits as tweezers; (*b*) to chelate Cu^{II} ions: one (strongly) at the diamino-pyridine subunit and the other (more weakly) at the anilino nitrogens close to the two terminal ammonium ions. Molecular models indicate that by complexing the two metal ions, **1** may assume, at least in dilute solutions, a pseudo-cyclic structure which may include a



Scheme 1 *Reagents and conditions*: i, bis(4-tosylaminophenyl)methane, K_2CO_3, dimethylformamide (DMF), 70 °C, 3 h; ii, 1-*N*,*N*-dimethylamino-2-chloroethane hydrochloride, K_2CO_3, DMF, 70 °C, 3 h; iii, MeBr, CH_2Cl_2, room temp., iv, 90% H_2SO_4, 50 °C, 4 h, then ion exchange (Br^-); v, *N*-tosyl-4-methylaniline, K_2CO_3, DMF, 70 °C, 4 h, then steps iii and iv

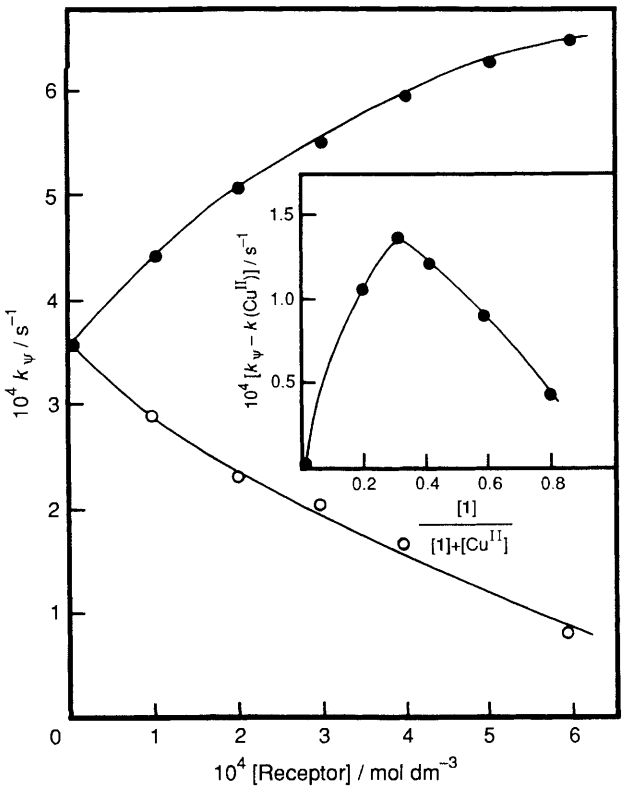


Fig. 1 Observed rate constants, k_ψ, for the cleavage of β-AlaPNP by receptors **1** (●), and **2** (○), in the presence of Cu^{II} (see text for conditions). *Inset:* Kinetic Job plot for the cleavage of β-AlaPNP by **1** and Cu^{II} [$k(Cu^{II})$ refers to the observed rate constant determined upon addition of Cu^{II} only].

suitable substrate and, possibly, act as a *selective* metallocatalyst. As a reduced structure of **1**, ligand **2** was also prepared and investigated for comparison.

Compounds **1** and **2** were synthesised as described in Scheme 1.† Compound **1** is soluble in water up to 0.1 mol dm^{-3} and forms aggregates at a concentration higher than 2.5×10^{-3} mol dm^{-3} (critical aggregate concentration,[5] c.a.c., as determined by ^{1}H NMR spectroscopy). *Below* the c.a.c. and *without added* Cu^{II} ions, **1** binds hydrophobic molecules like 1,8-anilinonaphthalenesulphonate, ANS, and naphthalene with binding constants of 2300 ± 50 dm^3 mol^{-1} (by fluorescence measurements) and 900 ± 150 dm^3 mol^{-1} (by ^{1}H NMR) respectively. Compound **2** is also soluble in water; however, fluorescence or ^{1}H NMR measurements do not indicate any ability to bind either ANS or naphthalene in water under the conditions used for **1**. This is suggestive evidence that organic molecules are effectively complexed and may reside in an hydrophobic region of (monomeric) **1**.‡

In the presence of $Cu(NO_3)_2$, the formation of chelates between Cu^{II} ions and **1** is highlighted by the appearance of an absorption band at 410 nm in the UV–VIS spectrum. Spectrophotometric studies carried out by changing the relative concentrations of **1** and Cu^{II} indicate that two metal

† Compound **1** has m.p. > 250 °C; ^{1}H NMR (CD_3OD), δ 3.20 (s, 9H), 3.26 (s, 18H), 3.50–3.68 (m, 8H), 3.70 (s, 4H), 3.79 (m, 2H), 4.40 (s, 4H), 4.49 (m, 2H) and 6.53–7.02 (m, 18H). FAB MS (nitrobenzyl alcohol matrix): *m/z* 933 ($M^+ - Br^-$).

Compound **2** has m.p. 189–191 °C; ^{1}H NMR (CD_3OD), δ 2.21 (s, 6H), 3.24 (s, 9H), 3.82 (br t, 2H), 4.36 (s, 4H), 4.47 (br t, 2H) and 6.52–6.95 (m, 10H). FAB MS (glycerol matrix): *m/z* 500 ($M^+ + H^+$).

‡ This supports the idea that a cleft-like structure (as drawn in Scheme 1) is present when **1** is dissolved in water even in the absence of any added metal ion.

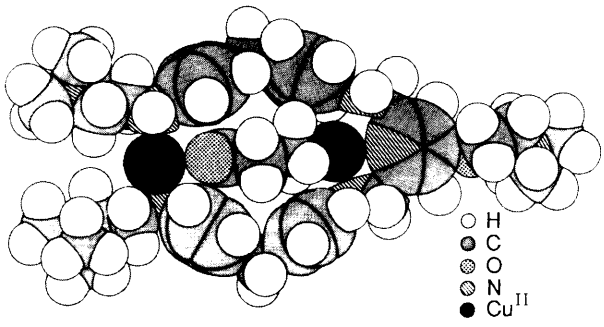


Fig. 2 CPK model of the proposed supramolecular complex made of **1**, two Cu^{2+} ions, and β-AlaPNP (the *p*-nitrophenyl residue has been omitted for clarity)

ions may be involved to form a ternary complex [Cu^{II}_2·**1**]. Predictably, the same experiments indicate that compound **2** binds a single Cu^{II} ion.

The kinetic effects of the Cu^{II} complexes with **1** and **2** were mainly investigated in the hydrolytic cleavage of the *p*-nitrophenyl esters of leucine (LeuPNP) and β-alanine (β-AlaPNP). The experiments were carried out in aqueous buffer [4-morpholinoethanesulphonic acid (MES), pH 6.2, 25 °C] containing a fixed Cu^{II} concentration {[$Cu(NO_3)_2$] = 4.0×10^{-4} mol dm^{-3}} and increasing ligand concentrations.§ In the presence of Cu^{II} only, the rate of hydrolysis of amino acid esters is catalysed by the metal ion;[6] any ligand, whose complexes are not catalysts on their own, is expected to decrease the rate (apparent inhibition), since the metal ions bound to the ligand are no longer available for the substrate. The hydrolysis of LeuPNP (and other non-natural α-amino acid esters such as the *p*-nitrophenyl ester of imidazole-4-carboxylic acid and picolinic acid) is retarded by both **1** and **2** virtually to the same extent (more than one order of magnitude at [ligand] = 6×10^{-4} mol dm^{-3} in the case of LeuPNP). A quite different behaviour was observed in the hydrolysis of β-AlaPNP, however (as shown in Fig. 1); in this case, ligand **1** *enhances* whereas ligand **2** *decreases* the rate of the hydrolytic cleavage of the β-amino acid ester. A similar trend was observed with the *p*-nitrophenyl ester of *o*-aminobenzoic acid. A kinetic version of the Job plot[7] (Fig. 1, inset) shows that the largest kinetic effect using **1** is obtained for the complex with two Cu^{II} ions. The acceleration observed in the case of **1** is certainly not impressive; however, the overall effect must be correctly estimated by comparison with that of **2**: one order of magnitude in the rate constants is involved at the largest [ligand] explored.¶

Inspection of a Corey–Pauling–Koltun (CPK) model of this complex shows that when the amino group of the β-amino acid ester is bound to the Cu^{II} ion within the receptor cleft, the carbonyl group of the ester faces the second Cu^{II} ion (see Fig. 2) which may act as a Lewis acid catalyst subunit for its cleavage promoted by some external or, more likely, metal-coordinated H_2O molecule. It is noteworthy that, owing to the shorter distance between the amino and the carbonyl group, such an interaction is not achieved in the case of an α-amino acid backbone.

This is the rationale here offered. Owing to the flexibility of the system, other non-productive complexation geometries are possible and work is in progress aimed at improving the efficiency and the selectivity of receptors such as **1**.

§ Kinetic experiments were performed under pseudo-first order condition using $[substrate]_0 = 1 \times 10^{-5}$ mol dm^{-3} and following spectrophotometrically the release of *p*-nitrophenol at 317 nm.

¶ The kinetic effects observed using Zn^{II} ([Zn^{II}] = 5×10^{-3} mol dm^{-3}, pH 7.5) apparently show a similar picture, although they were much smaller than those with Cu^{II}, in the presence of either **1** or **2**.

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