Specific Guest Orientation in Guest–Host Association with a Transition Metal Complex containing a Permanent Void

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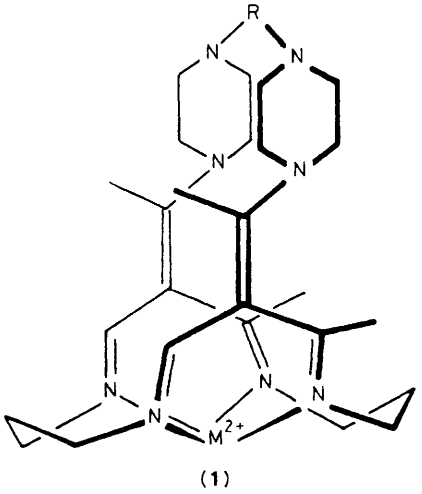
^{1}H N.m.r. longitudinal relaxation time measurements in aqueous solution are used to estimate distances from the protons of guest molecules to a paramagnetic copper(II) macrobicyclic complex whose ligand is known to facilitate O_2 binding to both Co^{II} and Fe^{II} while in addition being sufficiently spacious to accommodate a number of organic substrates for potential autoxidation.

It is proposed that selective substrate binding is an essential element in the design of a new generation of oxidation catalysts that are co-ordination compounds patterned after metal-containing enzymes.[1] The intriguing cytochrome P450 enzymes[2,3] activate dioxygen[4,5] in the presence of orientated organic substrates, thereby promoting selective oxygenation.[6,7] These new co-ordination catalysts will also be capable of self destruction, and substrate competition provides the basis for their preservation. For this reason we have chosen to investigate a parent ligand (whose Fe^{II} and Co^{II} complexes both bind[8,9] and activate[10] dioxygen) and appended to it a superstructure that produces a spacious void, suitable as a host for many organic guest molecules.[1] The guest will protect the host (catalyst) from suicidal inactivation as long as the guest–host equilibrium is always essentially saturated and the guest–host association is rapid compared to the rate of O_2 activation. Oxidation catalysts (**1**) represent the first examples of synthetic guest–host inclusion complexes containing a transition metal ion capable of activating dioxygen in the presence of an



(**1**)

orientated, oxidizable substrate. We present here data confirming this design principle.

Guest–host association in water between guest molecules and the complex (**1**), M=Cu^{II}, R = tetramethyl-*p*-xylylene,† was studied using the effect of the paramagnetic copper ion upon the spin-lattice relaxation rates, T_1, of the protons of the guest. The well established reductions in T_1 that are observed in the presence of unpaired electrons have been quantified in the Solomon–Bloembergen equation (1) here represented in

$$r\ (\text{in Å}) = C\left\{PT_{1p}\left[\frac{3\tau_c}{1 + (3.94 \times 10^{13}\nu_I^2\tau_c^2} + \frac{7\tau_c}{1 + (1.71 \times 10^{19}\nu_I^2\tau_c^2}\right]\right\}^{1/6} \qquad (1)$$

terms of the distance, r, between the nucleus being relaxed and the unpaired electron.[11,12] The parameters have their usual meanings[12] and $C = 539$ Å s$^{1/3}$.

Measurement of T_{1p} is achieved by two sets of standard inversion recovery T_1 experiments.[12,13] At least ten different values of the variable delay parameter were used to determine accurately the relaxation times by a non-linear least-squares, three parameter fitting procedure,[14] yielding the data given in Table 1. From equation (1) it is clear that a knowledge of τ_c will allow calculation of r. τ_c may be readily estimated from the frequency (ν_I) dependence[12] of T_{1p} [equation (1)] and although, to date, only two field strengths have been used (^{1}H at 300 and 200 MHz) the values obtained with several guests (0 8—1.6 × 10^{-10} s at 304 K) are entirely consistent with expected values.[12,15] These values of τ_c are the result of the solution of pairs of simultaneous equations based on equation (1) for every individual proton of each guest at the two field strengths. Using this value of τ_c and the T_1 data in Table 1, equation (1) may be used to give distances of the respective protons of the guest from the copper(II) nucleus. In the concentration ranges used, the distances calculated are independent of excess of guest present; this confirms that the guest–host equilibria are saturated. In all cases we have assumed that the guest:host ratio in the association complex is 1. This is reasonable on the basis of molecular models and *X*-ray data for the host molecule which show that while one guest will comfortably occupy the cavity of the host a second guest is sterically precluded from entering the same cavity.‡

The data display pronounced trends. Considering first the essentially 'linear' guest n-butanol, the data in Table 1 clearly show that this not only associates with the host molecule but that it does so with a preferred orientation; namely with the hydrocarbon portion of the chain inside the cavity nearest the metal and the hydrophilic alcohol group extending out into the solution, away from the protected void. Further, studies with methanol, ethanol, and propanol guests place the α-carbon, and therefore the OH group, at the same distance from the copper nucleus.

These results imply three conclusions. First, they confirm the design principle: the cavity of the host *is* large enough and hydrophobic enough to attract and accommodate an organic guest and, secondly, the association does not take place through a co-ordination phenomenon (binding of the alcohol to the metal ion) since clearly if this were to happen the distances given in Table 1 would have to be reversed in relative magnitude. This second point is particularly important because it means that the metal co-ordination site of a suitable metal ion may be occupied by a dioxygen moiety while still having the potential of allowing the guest–host association to occur. Finally, the parallel behaviour of a series of alcohols shows that the OH group remains associated with the solvent sheath while the alkyl group protrudes into the cavity.

With the guest molecule 2,6-dimethylphenol one observes similar behaviour. The distances given in Table 1 must be viewed in the knowledge that, for both the *meta* and methyl

Table 1. Relaxation data[a] for guest molecules with host (**1**), M = Cu, R = tetramethyl-*p*-xylylene.

Guest-2,6-dimethylphenol ($P = 1.54 \times 10^{-3}$)[b]

Protons	Me	*meta*	*para*
$(T_1)_0$[d]/s	4.08 ± 0.09	9.45 ± 0.20	7.88 ± 0.13
(T_1)[e]/s	3.15 ± 0.13	4.20 ± 0.06	2.90 ± 0.10
r[f]/Å	7.4 ± 0.4	6.7 ± 0.1	6.1 ± 0.1
	(± 0.6)	(± 0.4)	(± 0.4)

Guest-n-butanol ($P = 1.18 \times 10^{-3}$)[c]

Protons	α	β	γ	Me
$(T_1)_0$[d]/s	5.63 ± 0.52	5.33 ± 0.30	6.25 ± 0.20	6.20 ± 0.14
(T_1)[e]/s	5.13 ± 0.50	4.22 ± 0.05	4.60 ± 0.04	3.71 ± 0.22
r[f]/Å	>7.4	7.5 ± 0.4	7.3 ± 0.1	6.6 ± 0.2
		(± 0.6)	(± 0.5)	(± 0.4)

[a] Data at ν 300 MHz and T 304 K using a Bruker WM300 spectrometer. [b] [Host] 6.48 × 10^{-5} M, [guest] 4.21 × 10^{-2} M. [c] [Host] 6.48 × 10^{-5} M, [guest] 5.48 × 10^{-2} M. [d] Longitudinal relaxation time in the absence of paramagnetic ion. [e] Longitudinal relaxation time in the presence of paramagnetic ion. [f] From equation (1) using measured value of τ_c 1.0 × 10^{-10} s. Errors quoted are errors in T_1 measurements and, in parentheses, the systematic errors from τ_c estimates (1.2 ± 0.4 × 10^{-10} s).

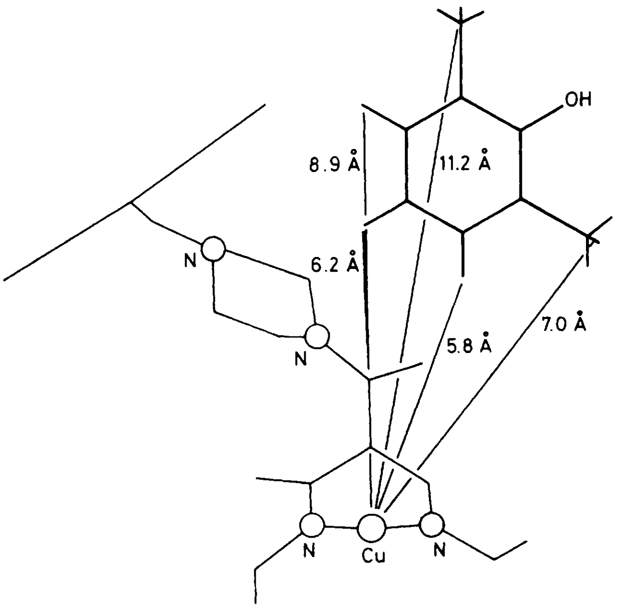


Figure 1. The position of the guest molecule 2,6-dimethylphenol with respect to the copper ion of the host as determined by relaxation data. The host molecule framework (viewed edge-on) is drawn to scale using crystal structure parameters for complex (**1**), M = Ni, R = anthracene-9,10-diyl.[1]

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† *p*-Xylylene = *p*-phenylenedimethyl.

‡ Relaxation data for the tetramethylammonium ion, which because of its charge and size is considered a 'non-guest', give $r > 14$ Å (at the mol ratios used for the organic guests). This very large distance confirms that relaxation is induced by an outer-sphere 'bulk' relaxation phenomenon for this ion. This effect is intrinsically present in all experiments of this type in addition to the more specific relaxation of the guest–host association. The calculated contribution of this outer-sphere effect to the relaxation data reported in Table 1 for organic guests is negligible compared to the experimental errors (*ca.* 1%).

protons, these are sixth power averaged distances for the equivalent protons present in the guest.§ From the precise stereochemical relationship of the protons of this guest and the distances in Table 1, one can estimate graphically an approximate position for the copper nucleus relative to the guest molecule which is a best fit, consistent with all the distances. Such a process yields a solution which is shown in Figure 1. (The major uncertainty lies in the degree of rotation of the phenol about its two-fold axis.)

The data presented further demonstrate the phenomenon of guest–host association in molecules of type (**1**). Furthermore, they illustrate that such complexation is hydrophobically driven and that the interaction displays a pronounced orientational selectivity probably as a result of both steric and hydrophobic relationships. This behaviour is strongly reminiscent of the cytochrome P450 enzymes where such specific orientation leads directly to highly selective oxidation of hydrophobic substrates in the ternary complex. The imitating of both the ternary complex and selective oxygenations are the targets of current research into this developing area of catalysis by co-ordination compounds.

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§ We are indebted to a referee who pointed out the precise nature of this sixth power average. As stated by Mildvan[12] this is a root-mean-sixth average: explicitly $1/r^6_{\mathrm{avg}} = (1/2)(1/r^6_{\mathrm{A}} + 1/r^6_{\mathrm{B}})$, where r_{avg} is the observed average distance and r_{A} and r_{B} are the distances to the two distinct protons which contribute to this average.