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# Measurement of Association Constants in Metal Orotate Complexes by $^1$H NMR Spectroscopy: the Metal Substituent Effect on Triple Hydrogen Bonding Ability

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The metal substituent effect on complementary triple hydrogen bonding pairs was investigated by $^1$H NMR spectroscopy. The results demonstrated that the metal ion reduced the hydrogen bonding ability of the ADA complex [$NBu_4$][Rh(cod)(orotate)] with 2,6-diaminopyridine.

*Keywords:* Hydrogen bond; metal; NMR; association constant

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## INTRODUCTION

Complementary hydrogen bonding interactions are fundamental to biological recognition processes, and recently they have been elegantly exploited for the design and synthesis of supermolecules. Generally, supermolecules have been characterised in the solid state by crystallographic techniques. However, solution state studies are arguably more relevant to the molecular recognition process, providing a quantitative measure of the strength of association and allowing comparisons to be made between different hydrogen bonding modes and with other types of molecular association. The quantitative aspects of complementary hydrogen bonding have been studied theoretically by Jorgensen[1] and Mingos[2], and a limited amount of experimental data has been provided by Zimmerman[3], Lippert[4] and Constable.[5]

We have been interested in the inclusion of metal ions into hydrogen bonding networks because of their potential for generating interesting magnetic, redox and optical properties in the solid state. However, if crystal engineering of this type is to become a reality, primary data on the effect of introducing metal ions into the hydrogen bonded aggregates are required. In previous investigations of metal orotate complexes (orotate = doubly deprotonated 2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid), which possess an ADA (acceptor-donor-acceptor) hydrogen bonding motif, we observed both

dimerisation (Figure 1a), and complementary base pairing in the solid state with the DAD molecule 2,6-diaminopyridine (dap) *via* triple hydrogen bonds (Figure 1b).[6] In this paper, we describe quantitative investigations of these associations in solution.

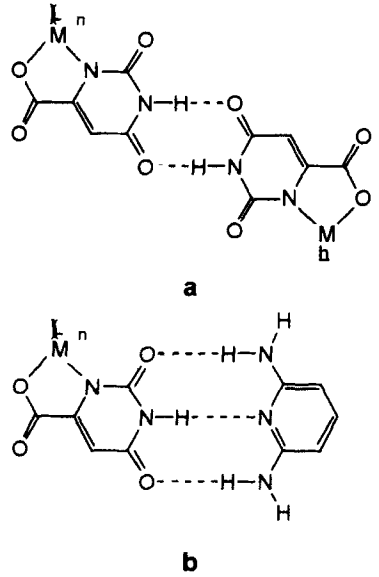


**Figure 1** Dimerisation, **a**, and base pairing, **b**, in metal orotate complexes observed in the solid state (L = coligand).

## *RESULTS AND DISCUSSION*

The rhodium orotate complex $[NBu_4][Rh(cod)(orotate)]$ **1** (cod = *cis, cis*-1,5-cyclooctadiene) was used because it is highly soluble in organic

solvents, and because its dimerisation and base pairing with dap have been characterised in the solid state.[6b] In the present work, solution equilibria were examined by $^1$H NMR spectroscopy and the chemical shift data obtained were analysed with the EQNMR program.[7]

We began by investigating its dimerisation in $CDCl_3$ solution. The concentration dependence of the chemical shift of its N-H proton ($\delta_{NH}$) provided a clear indicator of association (Figure 1a), analysis of which yielded an association constant $K_d(\mathbf{1}\cdot\mathbf{1})$ of 3.95 (± 0.9) $M^{-1}$. The concentrations of monomer **1**, and dimer **1.1** present as a function of gross concentration is indicated in Figure 1b.

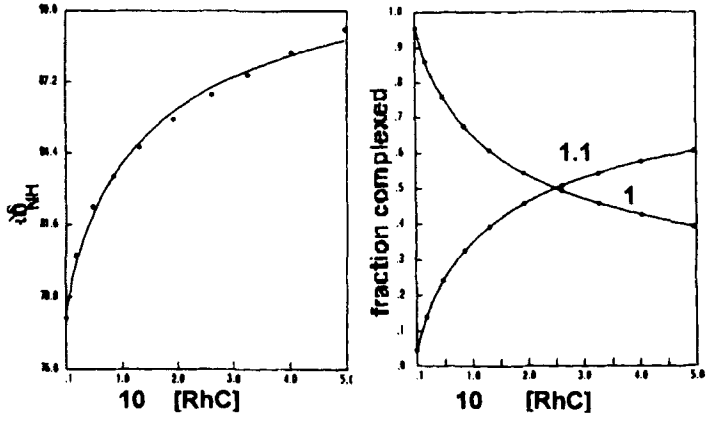



Figure 2 Concentration dependence of $\delta_{NH}$ (left) and derived fractional amounts of monomer and dimer (right).

The interaction of complex **1** with dap *via* complementary triple ADA:DAD hydrogen bonding in $CDCl_3$ solution was similarly examined through the chemical shift of the orotate N-H resonance, which is highly influenced by the concentration of dap, as shown in Figure 3.

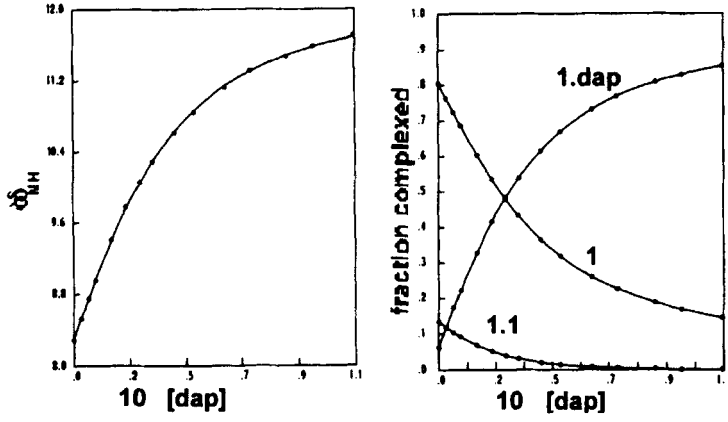



Figure 3 Dependence of $\delta_{NH}$ on concentration of dap (left), and derived fractional amounts of monomer, dimer and base-paired adduct present (right).

The corresponding calculated association constant $K_a$ (**1**·dap) 47.2 (± 0.5) is higher than the dimerisation constant $K_d$(**1**·**1**) since it involves the formation of three hydrogen bonds rather than two. When the

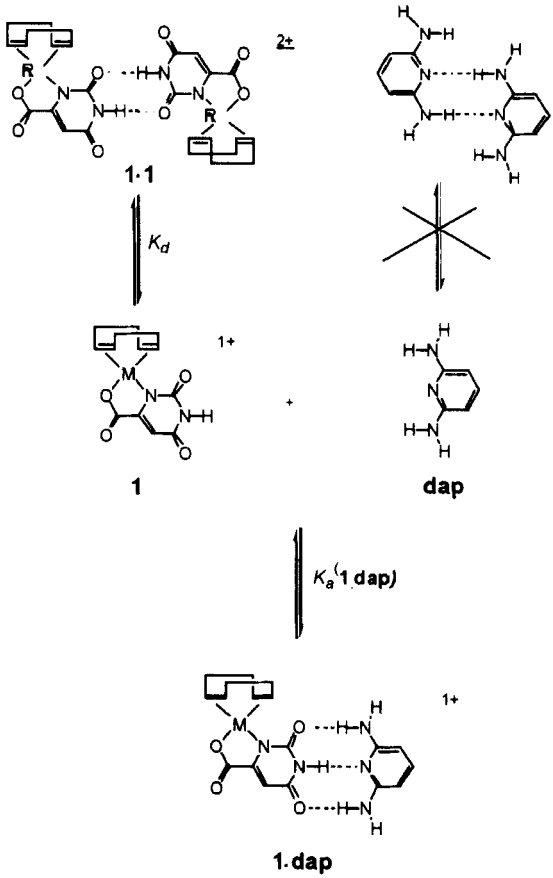
possibility for simultaneous self-association of complex **1** is allowed for in the analysis of the chemical shift data, the calculated $K_a'(\mathbf{1}\cdot\text{dap})$ value, as expected, is slightly higher, at 57.2(± 6.3). Since the dimerisation constant for complex **1** is not very large it was impossible to allow the EQNMR programme to refine reliably all the parameters. Therefore, re-calculation of the association constant was made by constraining the values for the dimerisation constant of complex **1**, $K_d(\mathbf{1.1})$ and the chemical shift for the dimer, $\delta_{\mathbf{1.1}}$ to the independently determined values, and allowing the programme to refine the chemical shift for the free complex **1**, $\delta_{\mathbf{1}}$, the chemical shift for the complex, $\delta_{\mathbf{1}\cdot\text{dap}}$, and the equilibrium constant $K_a'(\mathbf{1}\cdot\text{dap})$. The larger uncertaintly (11%) here is possibly due to the very low concentration of dimer existing in the system and the large number of parameters. However, there was good agreement between the experimental and calculated data. The quantities of monomer, dimer and based-paired complex at each concentration are indicated in Figure 3 (right).

Importantly, the $K_a(\mathbf{1}\cdot\text{dap})$ 47.2 (± 0.5) value of 47.2 $M^{-1}$ is smaller than for the purely organic triple ADA:DAD hydrogen bonding pairs, which are normally in the range 70 $M^{-1}$ to 140 $M^{-1}$ as reported by Zimmerman,[2] and smaller than the value of 143 $M^{-1}$ for the uracil-dap pair as obtained from the SPT-type calculation by Jorgensen[3] (Figure 4a). This difference is consistent with the DFT calculations

reported by McGrady and Mingos.[5] These predicted that the metal ion substituent influences the strength of hydrogen bonding interactions, and that its net effect of decreasing the ligand electron density is to reduce the strength of hydrogen bonding in an ADA metal complex, where the proton acceptors outnumber the donors. In complex **1** the electron density on the ligand is decreased compared to free uracil due to coordination to the metal. This reduces the acceptor ability of the two oxygen atoms (with a simultaneous increase of the hydrogen donor ability of NH). Since an excess of acceptor is borne by the DAD rhodium(I) orotate complex (Figure 4b) the hydrogen bonding ability of the whole molecule was reduced, and smaller association constant was obtained. The DFT calculations also suggested that the converse is true in DAD complexes, where the proton donors are in excess, *i.e.* that the presence of the metal increases hydrogen bonding ability. This is consistent with the preliminary experimental results of Lippert,[4] which show that the hydrogen bonding strength of a DAD molecule is enhanced by coordination to a metal ion because of the excess of donor groups.

In principle, dap could itself also undergo self-association *via* AD:DA double hydrogen bonding interactions. However, the small variation in the $\delta_{NH}$ value (about 0.03 ppm) over a relatively large dap concentration range (0.007 M - 0.08 M) indicated that very little self-

association occurs. The deduced overall equilibrium scheme for the **1**-dap system is therefore as illustrated in the Scheme.




**Scheme** Overall equilibrium scheme for the **1.dap** system

Additional studies were also carried out on the association of the platinum complexes [Pt(dppe)(orotate)] (Figure 4c) and [Pt(dppe)(5-aminoorotate)] (Figure 4d)[6a,6c] with dap in $CDCl_3$ at room temperature. The former complex has an orotate ligand and the latter an amino orotate ligand. The association constant (without taking into account self-association) of [Pt(dppe)(orotate)] with dap is $K_a$ (Pt-dap) = 31.8 ± 0.8 $M^{-1}$ and of complex [Pt(dppe)(5-aminoorotate)] with dap is $K_a$ ($NH_2$Pt-dap) = 54.6 ± 1.4 $M^{-1}$, both of which are also smaller than those for organic ADA:DAD pairs and are similar to the association constant of **1** with dap. The association constant of the complex [Pt(dppe)(5-aminoorotate)] (Figure 4d) with dap is higher than both complexes **1** and [Pt(dppe)(orotate)] (Figure 4c). This could possibly be caused by the extra $NH_2$ group on the orotate ligand which releases electron density to the rest of the molecule. Therefore, the results again suggested that in an ADA metal complex the increase of electron density will increase the hydrogen bonding ability with DAD complementary molecules. The association constant of complex **1** with dap is also slightly higher than for [Pt(dppe)(orotate)] (Figure 4c). Comparisons between the Rh and Pt complexes are complicated by the different steric demands of their coligands.[6b] However, we note that this difference is possibly because the metal in [Pt(dppe)(orotate)] **3c** is dicationic making it more electron withdrawing than Rh(I) in the anion [Rh(cod)(orotate)]$^-$ **1**.

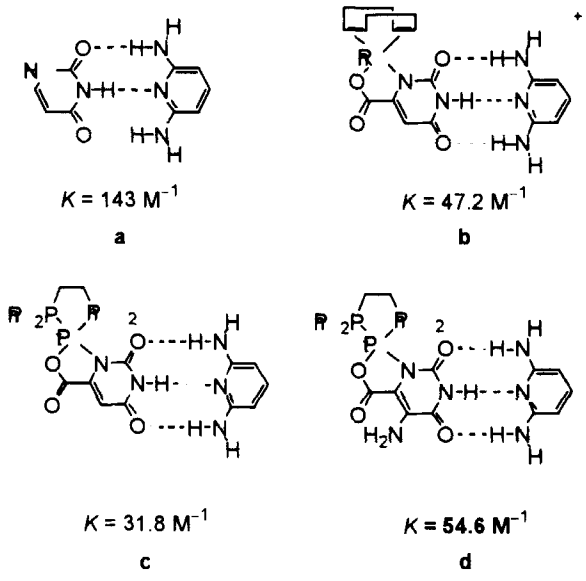



**Figure 4** Comparison of association constants for purely organic and metal-containing base-paired adducts

The relevant thermodynamic quantities due to **1-dap** association were obtained in the temperature range 25°C to 49°C. The $\Delta G_o^{\theta}{}_{298}$ = −9.5 kJmol$^{-1}$ value is slightly smaller than those reported for the organic ADA:DAD pairs by Zimmerman,[2] which range from −10.4 kJmol$^{-1}$ to −12.1 kJmol$^{-1}$. As expected the reaction is exothermic and $\Delta H_o$ = −23.7 (± 0.8) kJ mol$^{-1}$, which is slightly smaller than for the A-U pair and is higher than for the U-U pair reported by Y.

Kyogoku.[8] The value for $\Delta S_o$ = -47.3 (± 2.6) J $mol^{-1}$, is similar to values for the association of A-A, U-U and A-U pairs in chloroform reported by Kyogoku.[8] The negative value for $\Delta S_o$ indicates the expected decrease in entropy of the reaction on formation of the complex.

The effect of the solvents on the **1**·dap association were also investigated. The equilibrium constants were determined (taking into account dimerisation of **1**) to be $K_a$ = 92.3 (± 7.6) $M^{-1}$ in $CD_2Cl_2$, 57.2(± 6.3) $M^{-1}$ in $CDCl_3$ and 2.46 (± 0.2) $M^{-1}$ in $d_6$-DMSO. In $CD_2Cl_2$, which has weak hydrogen bonding ability, the association constant of **1** with dap is larger, whereas in $d_6$-DMSO, which has a strong hydrogen bonding ability, the association of **1** with dap is weak. This is consistent with the results reported earlier[1,9] and is attributed to the competition of the solvent for hydrogen bonding sites.

Studies of the association between complex **1** and dap, 2-aminopyridine and pyridine gave the association constants $K_a$ = 92.3 (± 7.6) $M^{-1}$, $K_a$ = 13.8 ± 0.6 $M^{-1}$ and undetectable respectively in $CD_2Cl_2$. Not surprisingly, the triple hydrogen bond adduct has the highest association constant. This decreases by an order of magnitude when only double hydrogen bonds are formed, and no association is detected when only one hydrogen bond is possible.

## CONCLUSION

This investigation has demonstrated that the hydrogen bonding ability of a functionalised metal complex can be affected by the metal in a way which is readily rationalised. In the ADA metal complex $[NBu_4][Rh(cod)(orotate)]$ **1**, the low constant for association with dap is due to reduction of the ligand electron density by coordination to the metal.

## EXPERIMENTAL

Complex **1** was synthesised according to ref. 6. $^1H$ NMR spectra were recorded on a Jeol JNM-EX270 FT NMR spectrometer at 25°C in $CDCl_3$ unless otherwise stated, and referenced internally to TMS.

Measurement of dimerisation: The following amounts of complex **1** were added to a 5-mm NMR tube containing 500 µl $CDCl_3$: initially 2.0mg, then 5.0 mg, 9.0 mg, 11.0 mg, 14.0 mg, 18.0 mg, 20.0 mg, 25 mg, 30 mg (etc.). $\delta_{NH}$ was recorded after each addition.

Measurement of the association between **1** and dap: A 0.02 M solution of **1** in $CDCl_3$ (8 mg in 0.5 ml) was prepared in a 5 mm NMR tube, and $\delta_{NH}$ was determined. A 0.15 M solution of 2,6-diaminopyridine

in $CDCl_3$ (32.8 mg in 2 ml) was also prepared. The dap solution was then added, initially in 10 μl portions, and the chemical shift of the NH proton was recorded after each addition. After 40 μl was added, the aliquot size was increased to 25 μl. After a total of 140 μl was added, the aliquot size was increased to 50 μl until total of 240 μl had been added, when 100 μl was added. Finally, 200 μl and 500 μl were added until the NH signal was too weak to be observed.

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