DALTON COMMUNICATION

Hydrogen-bond recognition of nucleosides by oligopyridine ligands and their ruthenium complexes

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The compound L^1 was formed by the covalent attachment of a thymine residue to a 2,2′:6′,2″-terpyridine metal-binding domain; L^1 and its ruthenium(II) complexes show specific hydrogen-bonding interactions with 2′,3′-isopropylidene-adenosine L^4 in chloroform or acetonitrile solution {log K[RuL^1(tpy)]$^{2+}$: L^4 ≈ 1.44 at 298 K, MeCN}.

Ever since the first elucidation of the structure of duplex DNA,[1] the elegance of the specific hydrogen-bonding interactions shown by nucleosides and nucleotides has fascinated the synthetic chemist. It is only recently that supramolecular chemists have attempted to combine the power of metal-directed assembly with hydrogen-bond recognition features.[2,3] Preliminary results indicate that hydrogen-bond stability is enhanced when one of the components is attached to a cationic metal complex.[2] Although Lehn and co-workers[3] have described elegant helicands bearing nucleotide substituents, these involve long multi-step synthetic pathways and no molecular recognition studies have been published. In this communication we describe a simple approach to nucleotide-substituted oligopyridines and demonstrate hydrogen-bonding interactions with complementary partners.

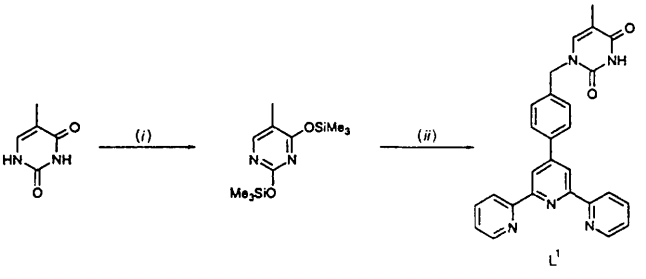
Thymine was heated with an excess of hexamethyldisilazane to give an intermediate silyl enol ether[4] which was treated immediately with 4′-(4-bromomethylphenyl)-2,2′:6′,2″-terpyridine[5] in dichloroethane. The silylated species produced was not isolated, but the crude product was deprotected with tetrabutylammonium fluoride in aqueous tetrahydrofuran (thf) to give L^1 as a yellow powder in 61% yield after recrystallisation from ethanol (Scheme 1).† The attachment of the 2,2′:6′,2″-terpyridine (tpy) domain to the thymine does not impair its ability to form hydrogen bonds. The most convenient assay of hydrogen-bond formation comes from shifts of NH protons in the ^{1}H NMR spectrum. In L^1 NH^{Thy} is observed as a broad singlet at δ 8.24 in the ^{1}H NMR spectrum in $CDCl_3$ solution. Initially we studied the three-site-recognition partner L^2,[6] which exhibits a single NH^{base} resonance at δ 7.62. In the ^{1}H NMR spectrum of an equimolar mixture of L^1 and L^2 in $CDCl_3$ the NH protons of both components are shifted as the adduct L^3 is formed (Scheme 2). Specifically NH^{Thy} is observed at δ 10.26 (Δδ 2.02) and NH^{base} at δ 8.13 (Δδ 0.41) for solutions 0.048 mol dm^{-3} in each component at 298 K. No resonances assignable to free L^1 or L^2 were observed under such conditions.

† L^1. Yellow powder, m.p. 255 °C. UV ($CHCl_3$); λ_{max} 309, 272, 254, 225 cm^{-1}. ^{1}H NMR ($CDCl_3$): 8.73 (m, 2 H), 8.72 (s, 2 H), 8.68 (d, 2 H, J 7.95), 8.24 (br s, 1 H, imide H), 7.93–7.86 (m, 4 H), 7.44 (d, 2 H, J 7.95), 7.36 (ddd, 2 H, J 7.48, J 4.79, J 1.15 Hz), 7.01 (br s, 1 H), 4.97 (s, 2 H), 1.91 (s, 3 H). Mass spectrum (electron impact): 448 (10, [M + 1]$^+$), 447 (32, $M^{+\cdot}$), 324 (6), 323 (41), 322 (100, [M + 1]$^{+\cdot}$–thymine), 321 (8), 244 (6), 161 (5%).

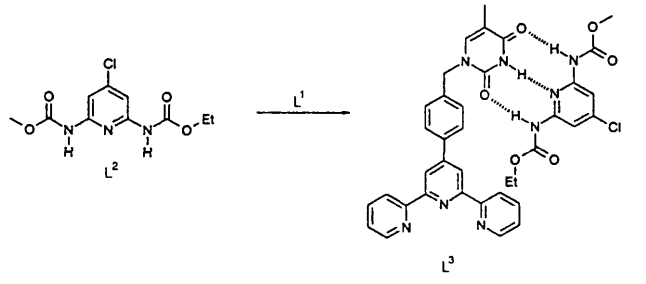
[RuL^1(tpy)][PF_6]$_2$. ^{1}H NMR (CD_3CN): 9.06 (br s, 1 H, imide H), 8.98 (s, 2 H), 8.75 (d, 2 H, J 18.18), 8.62 (d, 2 H, J 8.06), 8.49 (d, 2 H, J 8.09), 8.41 (t, 1 H, J 7.91), 8.18 (d, 2 H, J 8.24), 7.96–7.88 (m, 4 H), 7.68 (d, 2 H, J 8.18), 7.41 (m, 2 H), 7.40 (br s, 1 H), 7.34 (m, 2 H), 7.16 (ddd, 2 H, J 7.48, J 5.59, J 1.30 Hz), 5.03 (s, 2 H), 188 (s, 3 H).

Encouraged by the success with the three-site-recognition partner, we investigated the interaction with the adenosine derivative L^4 (chosen for solubility in organic solvents). Once again, significant shifts of the NH protons were observed with a $CDCl_3$ solution that was 0.048 mol dm^{-3} in L^1 and L^4 as an adduct was formed; NH^{Thy} shifted to δ 11.42 (Δδ 3.18)‡ and NH_2^{Ado} moved from δ 5.87 to δ 6.27 (Δδ 0.40) at 298 K. On the basis of these data, we anticipate a strong hydrogen-bonding interaction between the partners although we are unable to state whether it is in a Watson–Crick or a Hoogsteen sense or indeed, whether the hydroxyl group of L^4 is involved. The low-temperature NMR spectra clearly show that the two NH protons of L^4 are non-equivalent in the presence of L^1. In the absence of concrete evidence we have assumed a Watson–Crick interaction. We have not attempted to quantify the adduct formation with these systems as the presence of the additional pyridine nitrogen atoms of the metal-binding domain are expected to complicate the process.

Our aim was to investigate the effect of co-ordination of the tpy domain of L^1 to a metal centre upon the hydrogen-bonding interaction with L^2 or L^4. The complex [FeL^1_2][PF_6]$_2$ was obtained as a violet salt in 94% yield from the reaction of L^1 with $FeSO_4$·$6H_2O$ in acetone–water followed by precipitation with [NH_4][PF_6]. The ruthenium complex [RuL^1(tpy)][PF_6]$_2$ was formed in 98% yield as a cherry red microcrystalline

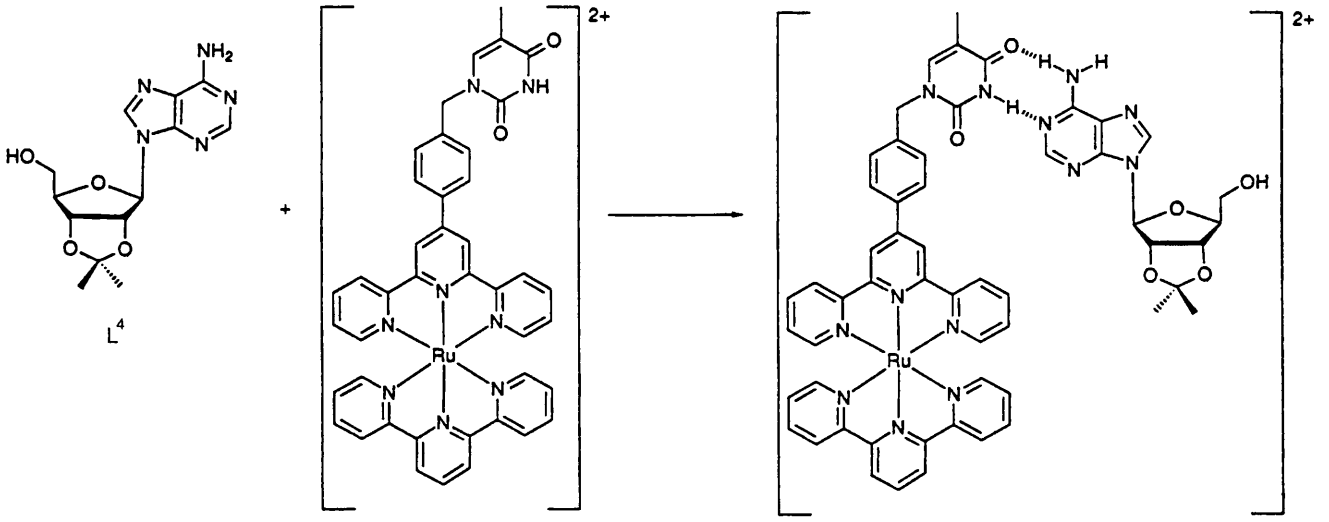


Scheme 1 (*i*) Hexamethyldisilazane; (*ii*) 4′-(4-bromomethylphenyl)-2,2′:6′,2″-terpyridine, $C_2H_4Cl_2$; Bu^n_4NF, thf, H_2O



Scheme 2

‡ Δδ = δ NH^{Thy} {*T*, [RuL^1(tpy)][PF_6]$_2$ + L^4} − δ NH^{Thy} {*T*, [RuL^1(tpy)][PF_6]$_2$}.



Scheme 3

solid from the reaction of L^1 with $[RuCl_3(tpy)]$ [7] in methanol in the presence of *N*-ethylmorpholine followed by precipitation with $[NH_4][PF_6]$. We decided to use the kinetically stable ruthenium(II) complex to probe the interactions with hydrogen-bond partners.

Proton NMR spectra of CD_3CN solutions containing $[RuL^1(tpy)][PF_6]_2$ and L^4 were recorded and the NH^{Thy} chemical shift was found to be both temperature and concentration dependent. As before, the signal shifted to low field in the presence of L^4 and the largest shifts were found to occur at low temperature. Similar behaviour has been reported for the free nucleosides and a mathematical treatment for the extraction of ΔG and K values has been described.[8] The ^1H NMR spectra of 1:1 mixtures of $[RuL^1(tpy)][PF_6]_2$ and L^4 at various concentrations ($1.28 \times 10^{-3} < c < 8.28 \times 10^{-3}$ mol dm^{-3}) and at eleven temperatures ranging between 248 and 298 K were recorded and the $\Delta\delta$ shifts calculated; 44 data points were recorded and a regression analysis according to ref. 8 was performed. Data were fitted by regression analysis using the program Microsoft Excel 5.0 on an IBM 486 PC to equation (1)

$$\delta = \delta^\circ + x\frac{2c_A + e^{\Delta G/RT} - e^{\Delta G/2RT}\sqrt{4c_A + e^{\Delta G/RT}}}{2c_A} \quad (1)$$

in which c_A is the concentration dependence of the mole fraction of component A which is hydrogen bonded at temperature T and x is a function of T. The ΔG values determined varied between -3.07 (± 0.58) kJ mol^{-1} at 248 K and -3.53 (± 0.58) kJ mol^{-1} at 298 K. Regression analysis yielded the thermodynamic quantities $\Delta H = -1.60$ (± 0.58) kJ mol^{-1} and $\Delta S = +22.33$ (± 2.18) J mol^{-1} K^{-1}. The extracted stability constants ranged from $\log K = 1.49$ at 248 K to 1.44 at room temperature.

The cationic complex $[RuL^1(tpy)]^{2+}$ forms strong hydrogen bonds with the adenosine derivative L^4 (Scheme 3). The stability constant is several orders of magnitude greater than that expected for a simple neutral adenosine–thymine interaction, in accord with the observation that other hydrogen-bonding interactions are significantly enhanced to a similar degree when one of the components is co-ordinated to a cationic metal centre.[2] Analysis of the data according to ref. 8 indicated that thymine–thymine self-pairing was insignificant under the conditions in which the measurements were made. One slightly puzzling feature is the positive entropy change associated with the pairing interaction, which contrasts strongly with the negative value reported for some simple adenine–thymine systems.[8] However, we note that some other supramolecular systems have been reported with positive entropy changes for related hydrogen-bonding interactions.[9] We also note that $[RuL^1(tpy)][PF_6]_2$ was consistently obtained as a hydrated species and we strongly suspect the presence of water–thymine interactions; accordingly our thermodynamic data are likely to represent competition between the various possible hydrogen-bond interactions in the system.

We are currently extending these studies to protic solvents and to nucleotides.

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