Molecular recognition in a heteromolecular radical pair system with complementary multipoint hydrogen-bonding†

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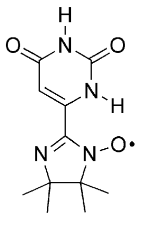
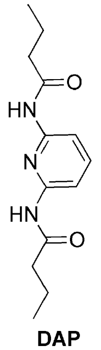
Stable radicals 2-(6-uradinyl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-1-oxyl (Ur6IN) and 4-(*p-tert*-butylaminoxyl-phenyl)-2,6-di(propylamido)pyridine (DAPPN) form heterospin radical pair complexes due to complementary multi-point hydrogen-bonds.

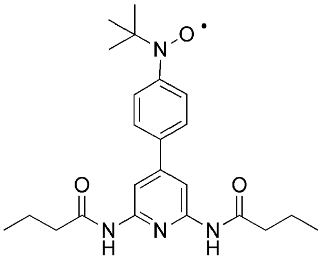
Strongly directional, complementary hydrogen-bonding interactions in biology have provided much inspiration for molecular recognition and assembly strategies in chemistry.[1] In 2005, Taylor *et al.* from our group showed that stable radical 2-(6-uradinyl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-1-oxyl, **Ur6IN**, binds with the complementary three-point hydrogen-bonding receptor 2,6-di(propylamido)pyridine, **DAP**,[3] giving prospects for supramolecular assemblies of different stable radicals (heterospin assembly). Both biological and materials-based uses of radicals can be at least partially controlled and predicted with the assistance from supramolecular assembly strategies. This article reports the synthesis and characterization of a radical-functionalized **DAP** complement to **Ur6IN**: (4-(*p-tert*-butylaminoxyl-phenyl)-2,6-di(propylamido)pyridine, **DAPPN**. Studies of heterospin complementary complexation of **Ur6IN** with **DAPPN** in solution and solid state are also described.



Ur6IN



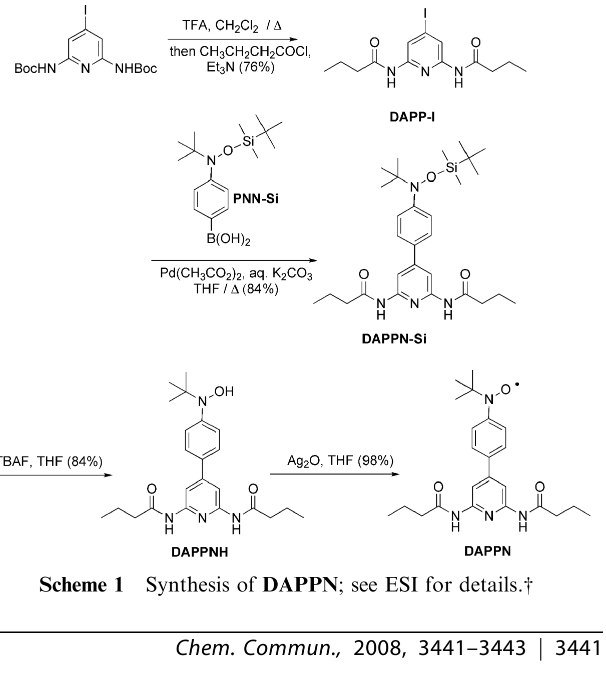
DAP



DAPPN

Ur6IN was made as previously[4] described. **DAPPN** was synthesized as shown in Scheme 1 to give a brick-red powder‡ that forms clear red prisms when crystallized from dichloromethane by slow evaporation. The **DAPPN** X-band EPR spectrum in toluene at 298 K shows hyperfine coupling (hfc) from the nitroxide N and from phenyl protons *ortho* and *meta* to the nitroxide: a(N) = 1.15 mT, a(*ortho*) = 0.22 mT, a(*meta*) = 0.09 mT. Unresolved, additional hfc must be <0.051 mT, based on the spectral linewidth. Multiple attempts at analyzing the X-ray diffraction (XRD) of single crystals of **DAPPN** did not allow us to determine all structural coordinates unequivocally, even at 100 K, so only the unit cell data from these attempts are given.§ However, single crystals of **DAPPN** give very strong EPR signals from the nitroxide spin, and FAB-MS shows the mass spectrum expected for **DAPPN**. These results confirmed the identity of **DAPPN** for the **Ur6IN**·**DAPPN** complementary hydrogen-bonding experiments described below.

Because both **Ur6IN** and **DAPPN** are paramagnetic, it was not convenient to monitor complexation between them by the NMR method used[2] to investigate **Ur6IN**·**DAP** complexation. EPR spectra of 1 : 1 mole ratio solutions of the two in toluene did not show significant deviation from a sum of their individual spectra, even when cooled to about 180 K. This indicates either that the exchange J between the radical sites is much smaller than the hfc ($J \ll a$(N)), or that the amount of the **Ur6IN**·**DAPPN** complex in the solution is too small to detect. EPR hfc changes have been reported for hydrogen-bonded complexes when there is significant spin density on the atoms *at* the site being complexed.[5] That is not the case here, however. Separate UB3LYP/6-31G* computations[6] for a somewhat simplified



Scheme 1 Synthesis of **DAPPN**; see ESI for details.†

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† Electronic supplementary information (ESI) available: Synthesis, EPR, MS, computed spin densities of **DAPPN**, ESI-MS of **Ur6IN**·**DAPPN** and a spin density map of the **Ur6IN**·**DAPPN** model. See DOI: 10.1039/b800779a

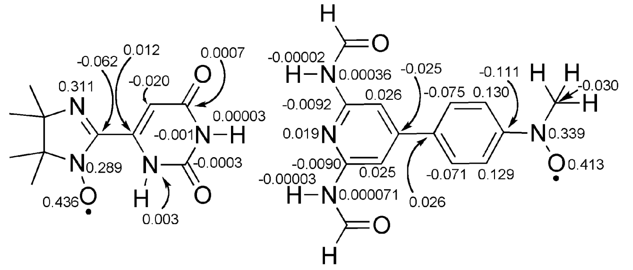
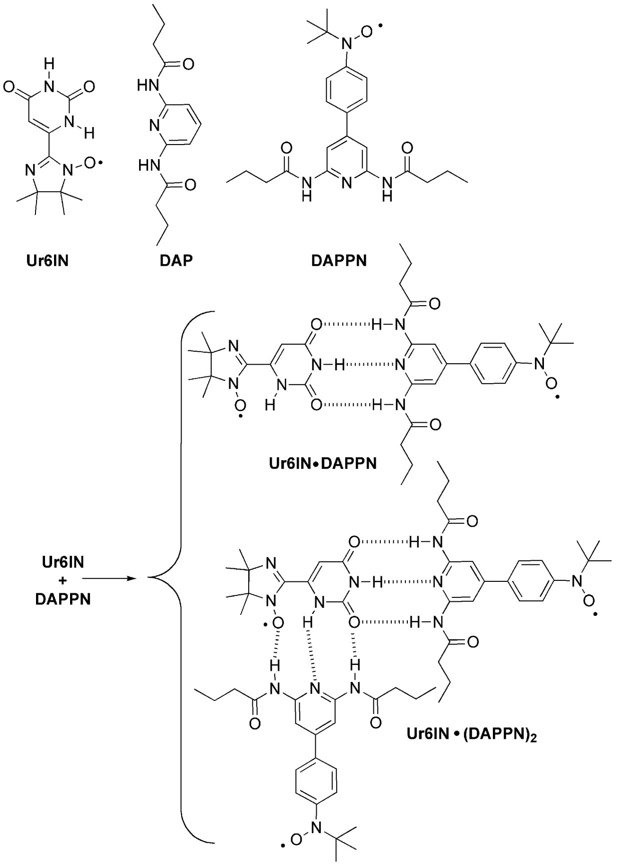


Fig. 1 UB3LYP/6-31G* Mulliken spin density populations for **Ur6IN** and a simplified model structure for **DAPPN**. **Ur6IN** data from ref. 2. Details for **DAPPN** and a spin density map for the pair are given in the ESI.†

model of **DAPPN** and **Ur6IN** give the Mulliken spin density populations shown in Fig. 1. Although the computations confirm that the nitroxide spin in **DAPPN** delocalizes more than the iminoylnitroxide in **Ur6IN**, there is still little overall spin density *at* the sites of 3-point hydrogen-bonding. If one applies a McConnell type relationship between hfc (a[N]) and computed spin density (ρ[N]), $a[\mathrm{N}] = Q\cdot\rho(\mathrm{N})$ with $Q = 3$ mT, the hyperfine on the pyridyl nitrogen is predicted to be only 0.06 mT, which would be at or below the limits of resolution of the observed spectra.[7] The hfc in the uradinyl portion of the spin localized **Ur6IN** is even smaller, so there is little close-contact spin density interaction at the actual sites of hydrogen-bonding in a complementary hydrogen-bonded **Ur6IN·DAPPN** complex.



Ur6IN–DAPPN binary solutions frozen to 77 K showed no dipolar features attributable to a triplet state radical pair; either the zero-field splitting of any solution complexes is small, or the amount of complex is small, or the complex favors a singlet state by so large an energy gap that a triplet state is not thermally populated (this last seems an unlikely scenario). But, ESI-MS analysis of a 10 micromolar solution of a 1 : 1 **Ur6IN** : **DAPPN** mixture in methanol shows the m/z = 662 peak of the heterospin dyad complex **Ur6IN·DAPPN**, and also a weak peak at m/z = 1072 attributable to a **Ur6IN·(DAPPN)$_2$** triad complex. Analogous 1 : 1 and 1 : 2 complexes were found[2] in the ESI-MS analyses of **Ur6IN–DAP** solution mixtures. The structures of these complexes are not directly obvious from the ESI-MS data, but are hypothesized as shown above, based on the likely multi-point donor–acceptor hydrogen-bond interactions.

The 3-point hydrogen-bonding interactions in a dyad between **DAP** and a thymine/uradinyl moiety are energetically worth about 12–25 kJ mol^{-1}. The binding constant found earlier[2] for the **Ur6IN·DAP** complex in methanol yielded ΔG[binding] $\cong$ 12 kJ mol^{-1} at 33 °C. Assuming similar thermodynamics for **Ur6IN·DAPPN**, only a small amount of a 1 : 1 complex is expected under solution conditions for equal amounts of the two radicals at typical concentrations. This would explain why it is difficult to detect the complexes by solution EPR.

Although observing high degrees of complexation in 1 : 1 solutions of donor : receptor dyads like **Ur6IN·DAPPN** can be difficult, solid state assembly should be more favourable, so long as the separate crystallization of the components does not occur. Shiomi *et al.* demonstrated heterospin assembly of two nitronylnitroxide radicals functionalized with a pyridine and a monocarboxylic acid,[8] using a one-site hydrogen-bond, and a nucleic-acid inspired two-site hydrogen-bonded donor–acceptor solid incorporating two different, non-delocalized nitronylnitroxides.[9]

In order to form the **Ur6IN·DAPPN** complex in the solid state, an equimolar solution of the component radicals in toluene was slowly evaporated in a 4 mm o.d. EPR tube under nitrogen to give a powdery orange solid. The EPR spectrum of this solid does not show dipolar features from triplet state zero field splitting down to 5 K; neither do neat solid samples of the individual components. However, the precipitated mixed solid exhibits an EPR half-field transition at 167 mT, characteristic for a triplet state (Fig. 2). Notably, neither of the individual component solids shows a similar peak. The half-field peak shows linear Curie law temperature dependence of doubly-integrated intensity as a function of reciprocal inverse temperature over 7–50 K, so the triplet state from which it arises is nearly degenerate with the corresponding singlet state, or is robustly favored over the singlet state.

The balance of evidence is most consistent with the half-field transition arising from formation of **Ur6IN·DAPPN** complexes in the solid. Although we have not been able to make diffraction grade single crystals of **Ur6IN·DAPPN**, the ESI-MS evidence clearly shows formation of the complex in solution, and only the mixed solid-state results show formation of a radical–radical interaction strong enough to yield a triplet state. The results do not rule out π-stacking or inter-radical close contact from less specific crystal packing interactions, but it is unclear how such interactions would be

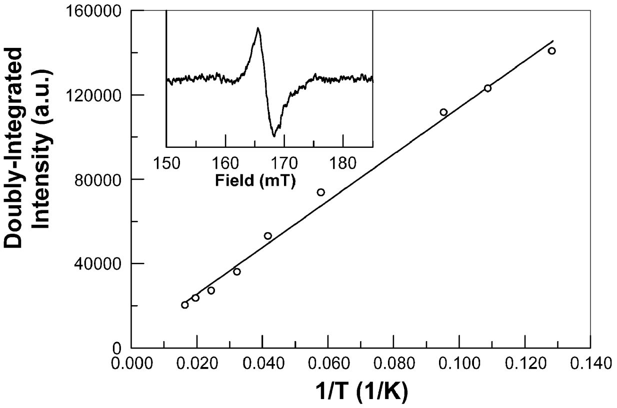


Fig. 2 Curie plot of doubly integrated spectral intensity of the half field EPR band (inset) observed in the powder solid **Ur6IN–DAPPN** mixture. Inset spectrum obtained at 4.8 K, 9.37359 GHz, background subtracted after multiscan signal averaging.

present in the mixed solid if not in the individual component solids. The complementarity of hydrogen-bonding would seem to encourage strongly the formation of the **Ur6IN·DAPPN** complex as postulated above, or a structure very similar to this. The three-point hydrogen-bonding set of interactions should be a strong driving force for molecular assembly in the solid.

In recent years, nitronylnitroxide and nitroxide type radicals with attached nucleosides and related moieties have been studied for a number of reasons.[2–4,8–12] However, few of these have been crystallized to explore their solid state assembly behaviour as molecular one-component solids,[3,4,8–10] so this remains a relatively new area of endeavour among studies of organic radical materials. By extension, the design of heterospin interactions by inducing different radicals (or other open-shell molecules) to co-crystallize offers many additional possibilities for new solid-state behaviours, especially behaviours that are unlikely or unable to occur in one-component solids. The present work and related studies using complementary multi-point hydrogen-bonding interactions have much potential scope for solid state assembly of heteromolecular complexes of spin-bearing organic molecules. Further work is ongoing to study other heterospin solids related to **Ur6IN·DAPPN**.

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Notes and references

‡ For **DAPPN**: mp: 84–86 °C. IR (KBr pellet, cm^{-1}): 3424 (NH str), 1676 ($C{=}O$ str). MS (EI): calc for $C_{23}H_{31}N_4O_3$ m/z = 411.5, found m/z = 412. Analysis: calc for $C_{23}H_{31}N_4O_3$: C, 67.13; H, 7.59; N, 13.61. Found: C 67.93, H 7.86, N 12.07. EPR (toluene, 9.64723 GHz): g = 2.00549, a(N) = 1.15 mT, a(*ortho*) = 0.22 mT (2H), a(*meta*) = 0.09 mT (2H). HPLC (C18 column, 1.2 mL min^{-1}, 7 : 3 MeOH : H_2O): R_t = 8.4 min.

§ *Crystal unit cell data*. Formula $C_{23}H_{31}N_4O_3$, formula weight = 411.5, temperature = 100 K, Monoclinic, $P2_1/c$, a = 10.7221(2) Å, b = 25.4626(4) Å, c = 16.9760(3) Å, β = 96.8291(6)°, V = 4602(3) $Å^3$, Z = 8, D(calc) = 1.188 g cm^{-3}, F(000) = 1768.

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