Gel phase MAS ^{1}H NMR as a probe for supramolecular interactions at the solid–liquid interface

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ArgoGel beads functionalised with mono- and bi-dentate pyridyl ligands give excellent gel phase (MAS) ^{1}H NMR spectra that allow detailed structural characterisation of their non-covalent complexes with metalloporphyrins.

We show here that, in favourable circumstances, gel phase magic angle spinning (MAS) ^{1}H NMR spectroscopy can provide a powerful new tool for probing non-covalent interactions at the solid–liquid interface: such interactions lie at the heart of much of separation science, especially affinity chromatography, and of solid-phase organic synthesis. The recent explosion of polymer-supported chemistry has been accompanied by the development of techniques for coding, tagging and releasing the resulting resin-bound molecules, but there have been few rapid or non-destructive techniques that provide subtle analytical or spatial information for the resin-bound species themselves.[1] Gel phase MAS NMR[2] has recently been applied to structure analysis of molecules attached onto solid supports, and we now demonstrate the potential of this new analytical tool for investigating molecular recognition at interfaces by probing events that occur between polymer-bound pyridyl ligands and a range of porphyrins.

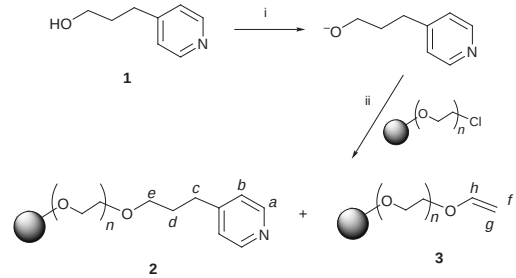
In a conventional solution-state spectrometer, organic solids generally give ^{1}H and ^{13}C NMR resonances with linewidths of 10^4–10^5 Hz due to a combination of strong dipolar interactions and spatial inhomogeneities.[3] If the species of interest is a small molecule attached to a solvent-swollen polystyrene bead *via* a flexible tether, then its molecular mobility can approach that of the solution state. In such circumstances, dipolar interactions are dramatically reduced by averaging and the major line broadening mechanism that remains is the spread of chemical shifts due to spatial inhomogeneities, *i.e.* different effective magnetic fields are experienced by molecules on the inside and outside of a bead or by beads in different parts of the sample tube.[4] This spread of chemical shifts (*ca* 10^3 Hz) can be eliminated by magic angle spinning at relatively low speeds (*ca* 10^3 Hz) in a solution-state spectrometer to give spectra with linewidths that are comparable with small molecules in free solution.

Given our interests in porphyrin-accelerated reactions[5] and in approaches to catalyst discovery that involve selecting potential catalysts *via* strong binding of transition state analogues (TSAs),[6] we wished to investigate the molecular recognition properties of pyridines and TSAs that were covalently bound to polymer beads. Both for the spectroscopic reasons outlined above, and to give maximum molecular accessibility, we chose to attach these ligands to ArgoGel beads: these contain highly flexible PEG chains, grafted to lightly cross-linked polystyrene beads *via* a stable bifurcated linkage, thereby allowing bound molecules to experience a solution-like environment. The attachment of pyridyl ligand **1** onto the beads was performed by deprotonation of the alcohol (Scheme 1) followed by treatment with ArgoGel chloride beads. After reaction, microanalysis suggested complete displacement of chlorine but the nitrogen content was 0.39% instead of the expected 0.59%, highlighting the danger of relying on microanalysis to monitor solid-phase organic reactions. However, after removal of residual broad polymer signals using a CPMG spin-echo sequence,[3] the gel phase MAS ^{1}H NMR spectrum of the beads gave *ca* 1 Hz resolution and allowed direct structural determination of the bound molecules without the need for cleavage [Fig. 1(*a*)].‡ As well as the signals *a*–*e* for **2**, three unexpected signals (*f*, *g* and *h*) were observed. These were assigned to the terminal enol ether by-product **3** resulting from HCl elimination from the resin. Although this is an inconvenient side-product, it proved to be a useful internal standard for binding studies.

Ruthenium porphyrins bind very strongly to pyridine ligands (K *ca* 10^5 M^{-1}),[7] so the pyridyl beads were treated with an excess of ruthenium porphyrin **4**. The dark orange colour of the porphyrin present in the resulting beads did not leach out on washing with a non-coordinating solvent (*e.g.* CH_2Cl_2). After displacement of the solvent molecule in the starting porphyrin, a 1:1 complex had formed on the beads. The CPMG ^{1}H NMR spectrum [Fig. 1(*b*)] showed the characteristic large chemical shift changes experienced by the bound pyridyl ligand due to the porphyrin ring current (Scheme 2); a COSY spectrum confirmed the assignments shown. The CO ligand in the bound complex was evident in a new sharp peak at 1945 cm^{-1} in a spectrum obtained by single bead FT-IR microspectroscopy.[7]

The analogous complex with zinc porphyrin **5** was also prepared. In this case, dark purple beads were obtained which leached porphyrin on washing with CH_2Cl_2. This is not surprising as zinc porphyrins bind relatively weakly (K *ca* 10^3 M^{-1}) to pyridine ligands in solution. The non-spin echo ^{1}H NMR spectrum [Fig. 1(*c*)] of the complex exhibited (superimposed on a broad polymer background) sharp enol ether peaks and two sets of aryl and β signals for the porphyrin itself; these appear to correspond to bound porphyrin within the bead and free porphyrin exchanging with surface-accessible bound porphyrin. The set of inner bound porphyrin signals was assigned by its greater attenuation in a CPMG spectrum [Fig. 1(*d*)]. All the resonances belonging to ligand **2** were broadened beyond detection in this spectrum, presumably due to an exchange process, the details of which are still unclear.

A bipyridyl ligand (which is a TSA for a hetero-Diels–Alder reaction[8] was attached to the resin by the same method as in



Scheme 1 *Reagents and conditions*: i, NaH, THF, 5 h, room temp.; ii, THF, 45 h, 60 °C

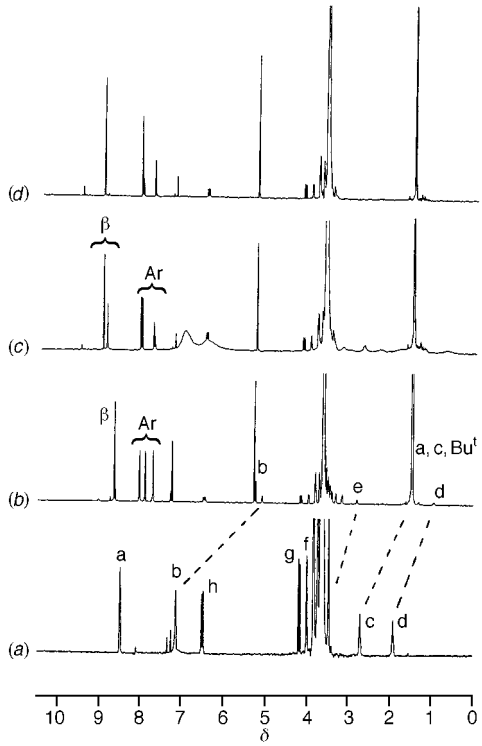
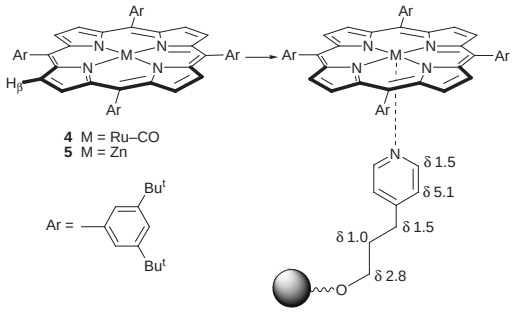


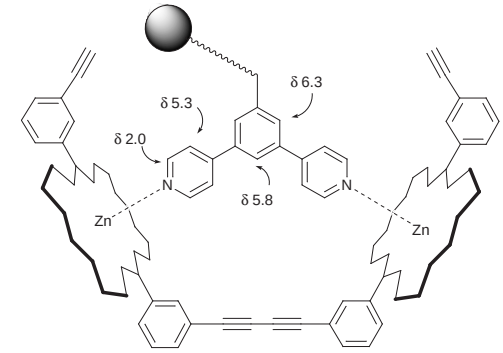
Fig. 1 400 MHz gel phase MAS ^{1}H NMR spectra: (*a*) CPMG spectrum of functionalised beads showing resonances due to **2** and **3**; (*b*) the same beads complexed to porphyrin **4**; (c) non-CPMG spectrum of the beads in (*a*) in the presence of excess porphyrin **5**; (*d*) CPMG spectrum of same sample as in (*c*)



Scheme 2

Scheme 1. The gel phase NMR spectrum of the beads allowed characterisation of the supported bidentate ligand, and again demonstrated formation of enol ether **3**. Treatment of these beads with a flexible porphyrin dimer in CH_2Cl_2 gave the corresponding complex **6** as dark purple beads that did not leach colour on washing, which is consistent with an expected binding constant of more than 10^6 M^{-1}. The one-dimensional and NOESY spectra of these beads allowed assignment of all the bound aromatic resonances of **6** and confirmed that the chemical shifts of ligand and host were essentially identical to the corresponding solution-state complex.

Finally, the bipyridyl beads were treated with our symmetrical Zn_3-butadiyne-linked cyclic porphyrin trimer.[5] Again the bound chemical shifts were as expected, but now all resonances including the enol ether were somewhat broadened. The implication of this result is that overall polymer mobility is reduced, even in chains that are not directly bound to host. We tentatively assign this observation to cross-linking of separate



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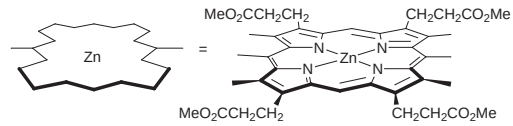

ligand chains *via* binding to the same trimer molecule within bead cavities. As expected, this is reversible: virtually all colour is removed from the beads by addition of the strongly-binding tri-functional ligand tripyridyltriazine.

We have shown that gel phase MAS ^{1}H NMR spectroscopy allows the study of non-covalent interactions between hosts and tethered guests. A wide range of two-dimensional techniques is available, and use of CPMG sequences of variable length should give access to subtle molecular mobility information. Furthermore this powerful technique holds out the prospect of studying the kinetics of molecular penetration into, and exit from, the interior of beads, and of characterising non-covalent cross-linking of ligand chains.

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Notes and References

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‡ NMR spectra were acquired at room temperature on a Varian Unity 400 MHz spectrometer using a 'NanoNMR' MAS probe. Sample tubes contained 40 μl of a $CDCl_3$ suspension of beads (*ca*. 1 mg = 0.4 μmol bound molecules), and were spun at 3 kHz. One-dimensional spectra were obtained typically with 32 scans, in *ca* 10 min. The CPMG sequence contained 2000 π-pulses with a repetition time of 2 ms.

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