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COMMUNICATION

Cyclodextrin–phosphane possessing a guest-tunable conformation for aqueous rhodium-catalyzed hydroformylation†

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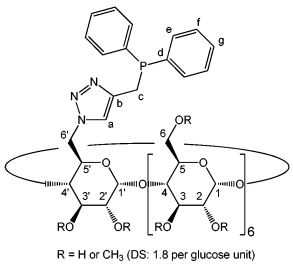
The inclusion of a guest inside the cavity of a new water-soluble cyclodextrin–phosphane allows controlling the natural conformation of this ligand leading to an inversion of the regioselectivity during aqueous hydroformylation reaction.

In the field of the design of new ligands for organometallic catalysis, an alternative approach has been recently highlighted to generate various ligands from supramolecular interactions.[1] As pioneering examples, the teams of Reek and Breit independently reported the elaboration of bidentate ligands by supramolecular interactions. Reek *et al.* developed a strategy based on the coordination ability[2] while Breit *et al.* focused their attention on blocks built by hydrogen bonding interactions.[3] This approach has then emerged as a powerful and flexible tool to build new catalytic systems in organic medium.[4] In aqueous medium, the formation of inclusion complexes between a water-soluble host and a guest by hydrophobic interactions has recently appeared as a smart way to access to supramolecular bidentate ligands for aqueous catalysis. More precisely, a triaryl-phosphane can be included in a mono-amino-β-cyclodextrin to build a water-soluble supramolecular bidentate P,N-ligand.[5] Associated to a platinum precursor, this ligand allowed performing hydrogenation reaction in aqueous medium. In this communication, we report that hydrophobic interactions can also be used to control the conformation of a water-soluble ligand. More precisely, we have found that the geometry of a CD modified by a diphenylphosphane group (Scheme 1; **1**) can be tuned by the inclusion of a guest inside the CD cavity. This supramolecular control allowed orienting the regioselectivity during the hydroformylation reaction catalyzed by rhodium complexes based on **1**.

The CD phosphane **1** was synthesized from borane-protected diphenylpropynylphosphane[6] and randomly methylated mono-6-azido-6-deoxy-β-CD[7] by Cu(I)-catalyzed azide–alkyne cycloaddition reaction followed by a borane-deprotection reaction (procedure in ESI†). To obtain a highly water-soluble compound, we have used a platform based on a randomly methylated CD (RameCD) since RameCDs are among the more water-soluble CDs.[8] The solubility of this CD phosphane in water was equal to 15 mM at 20 °C. Two-dimensional ^{1}H homonuclear NMR experiments based on the T-ROESY sequence were performed to evidence potential spatial proximities between the different protons of **1**, since CDs possessing a pendant group can exhibit a self-inclusion phenomenon (Fig. 1).[9] Only slight dipolar contacts were observed between the phenyl protons and the CD inner protons. Nevertheless, it was impossible to exactly distinguish the different protons due to the overlapped resonances. Indeed, **1** is not a well defined compound but a mixture of partially methylated CDs. However, it is possible to propose a schematic representation for **1** where the primary face of the CD is capped by one of the two phenyl groups. As this molecule possesses well-identified hydrophobic and hydrophilic parts, the behaviour of this CD phosphane was also investigated by surface tension measurements. The evolution of the surface tension (γ) *versus* the concentration of **1** in water is presented in Fig. 2. The surface tension gradually decreased until a break in the slope of the curve but no plateau was observed. This breaking point in the surface tension profile was identified as a critical aggregation concentration (CAC) and was equal to 11 μM. The formation of aggregates could be due to the association of the hydrophobic parts of **1** (*i.e.* phenyl groups). Indeed, in the case of Rame-β-CD, the decrease in surface tension was largely lower compared to **1** and only a hydrotropic behavior was observed. These results indirectly showed that the penetration of the phosphane moiety is not deep since the hydrophobic parts can aggregate.



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Scheme 1 Structure of **1**.

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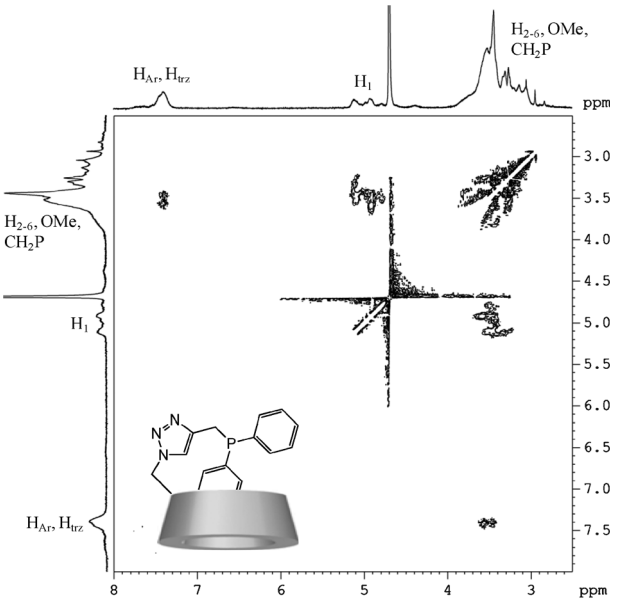


Fig. 1 2D TROESY NMR spectrum in D_2O (25 °C, 1.2 mM) and schematic representation of **1**.

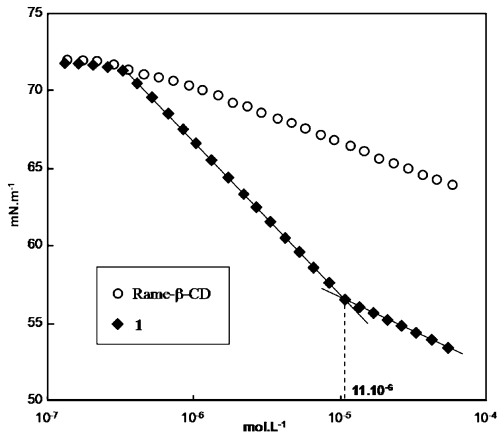


Fig. 2 Surface tension curve of aqueous solutions of **1** and Rame-β-CD at 25 °C.

To estimate inclusion capacity of **1**, attempts were made to include an external host in the cavity of **1**. 1-Adamantanecarboxylate sodium salt (ACNa) was selected because of its high affinity for the β-CD cavity.[10] The NMR continuous variation method (Job's plot) clearly showed that **1** formed a 1 : 1 inclusion complex with ACNa (see ESI†). 2D T-ROESY NMR experiments performed on a solution containing **1** and ACNa showed intense correlation peaks between the adamantyl protons and internal CD protons proving again the formation of inclusion complexes (Fig. 3). In addition, not only no cross peak was observed between the aromatic and adamantyl protons but also the correlation between the phenyl and internal CD protons observed in the case of **1** alone has disappeared (Fig. 1). These observations unambiguously proved that ACNa is able to fully expulse the included phenyl group. The schematic representation of this inclusion complex is depicted in Fig. 3. The association constant for this 1 : 1 inclusion complex was then determined by isothermal titration calorimetry (ITC). The value was found to be very high, equal to 46 600 M^{-1} (see ESI†). Indeed, for

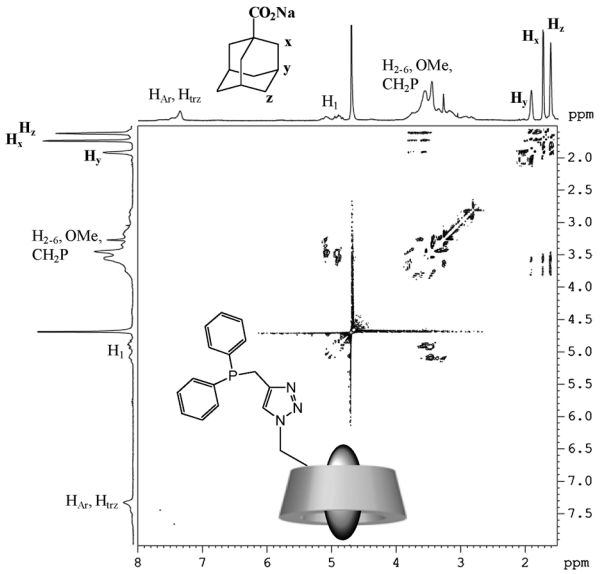
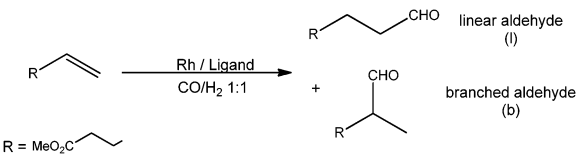


Fig. 3 2D TROESY NMR spectrum of a 1 : 1 mixture of $AdCO_2Na$/**1** in D_2O (25 °C, 6 mM/2 mM) and schematic representation of this inclusion complex.

comparison, the values obtained with β-CD and Trime-β-CD (a permethylated β-CD) are equal to 51 000 M^{-1} and 850 M^{-1}, respectively. This last result showed that although a capping phenomenon was observed, the CD cavity is able to deeply include a guest.

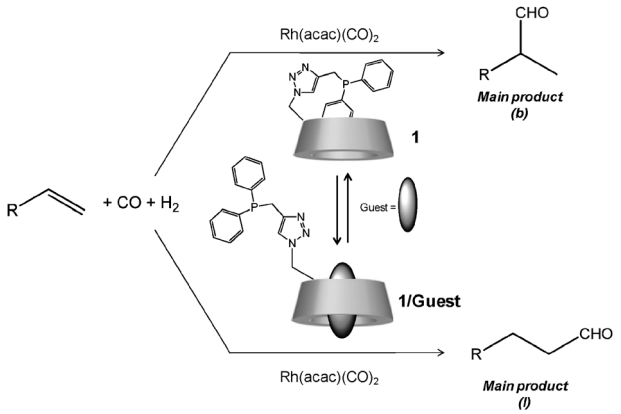
The catalytic behaviour of the combination between a rhodium species and **1** was investigated in hydroformylation reaction (Table 1). The experiments were performed with methyl 4-pentenoate (a water-soluble substrate). Note that NMR experiments showed that this substrate is not included in the CD cavity (see ESI†). When **1** was used as a ligand, total conversion was reached after 6 h with a linear to branched aldehyde ratio (l/b) equal to 40/60 (Table 1, entry 1). In order to determine if the catalytic activity and selectivity can be controlled by supramolecular interaction, the hydroformylation reaction was performed in the presence of ACNa (3 equivalents compared to **1**). At the chosen concentration, more than 99%

Table 1 Rhodium-catalyzed hydroformylation of methyl 4-pentenoate[a]



Entry	Ligand	Time/h	Guest	C[b] (%)	S[c] (%)	l/b[d]
1	**1**	6	(−)	99	99	40/60
2	**1**	6	ACNa	99	99	64/36
3	**1**	6	SD	98	99	65/35
4	TPPTS	2	(−)	98	99	64/36
5	TPPTS	2	ACNa	98	99	64/36
6	TPPTS	2	SD	98	99	64/36

[a] *Experimental conditions*: $Rh(acac)(CO)_2$ (1.94×10^{-3} mmol), ligand (7.76×10^{-3} mmol), H_2O (6 mL), substrate (0.97 mmol), ACNa or SD (23.3×10^{-3} mmol); 1500 rpm, *T*: 80 °C, *P*(CO/H_2: 1/1) = 50 bar. [b] Olefin conversion. [c] Aldehydes selectivity. [d] Ratio of linear to branched aldehyde products.



Scheme 2 Schematic representation of the mechanism leading to linear or branched products.

of the CD cavities are occupied by ACNa (see ESI† for calculation). The conversion and aldehydes selectivity are not different from the experiments performed without ACNa (compare entries 1 and 2). However, the regioselectivity was inverted moving from a l/b distribution of 40/60 to 64/36. In the presence of ACNa, the linear product becomes preponderant. In order to ensure that this interesting behaviour was not specific to the nature of ACNa, two types of control experiments were performed. At first, a supplementary experiment was performed with sodium dodecanoate (SD) as guest. SD forms an inclusion complex with **1** and it is also able to displace the included phenyl group (see ESI†). Expectedly, the l/b ratio was also inverted (compare entries 1 and 3). Other experiments were performed with trisulfonated triphenylphosphane (TPPTS) as ligand instead of **1**. The first was performed without a guest, the second with ACNa and the third with SD (Table 1; entries 4–6). In all cases, no change was observed in activity and selectivities. These three last results indicated that the increase in the l/b ratio was not due to the simple presence of an additional compound. This increase has been attributed to a modification of the conformation of **1** in the presence of a guest (Scheme 2). As an increase in steric crowding around the Rh metal center is known to promote the formation of a linear product, these results suggest that the **1**/guest ligand is bulkier than **1**.[11] So, **1** or **1**/guest possesses a specific bulkiness leading preferentially to branched or linear products.

To resume, we have successfully prepared a valuable water-soluble CD-phosphane for aqueous organometallic catalysis. Indeed, rhodium-catalyzed hydroformylation reaction can be performed in water by using this CD-phosphane as ligand. The conformation of this ligand is controllable by inclusion of a guest leading to a variation of the regioselectivity during hydroformylation reaction. By varying the nature of the guest, it will be possible to access to a library of new cyclodextrin–based supramolecular ligands with specific properties.

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