Dynamic covalent templated-synthesis of [2]daisy chains†

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A couple of [2]daisy chains have been assembled in each case from four components in quantitative yields at room temperature in acetonitrile as a result of the self-templated clippings of their [24]crown-8 rings by reversible imine bond formation around secondary dialkylammonium recognition sites in their stalks.

Dynamic covalent chemistry1 (DCC) with its growing collection of thermodynamically controlled reactions has been widely employed2 in the preparation of mechanically interlocked molecules3 (MIMs). Common reactions employed in the syntheses of MIMs include metal–ligand coordination,4 olefin metathesis,5 and disulfide6 and imine7 bond formations. These reversible reactions have significant advantages over those occurring under kinetic control. The reason is that thermodynamically most stable products are obtained under equilibrium conditions as a result of a ‘proof-reading’ or ‘error-checking’ process which eventually eliminates undesired kinetically competitive intermediates. Imine bond formation, which has been developed7a–h as a powerful synthetic tool, is one of the best known and successful reactions employed in DCC.

One special class of [2]rotaxanes—dubbed [2]daisy chains—are of considerable interest7i on account of their mechanically interlocked structures which are reminiscent of molecular muscles and have the potential to convert external stimuli, i.e., acid–base,7h,i chemical,8 and light,7j into contraction–expansion type reversible mechanical movements. We have reported7b,c,d,h previously a clipping protocol based on imine bond formation, resulting in the quantitative formation of a [2]rotaxane7h and a series of [n]rotaxanes8 (n = 3–20) in excellent yields. We envisage the utilization of a similar approach as a facile and efficient way of building [2]daisy chains. Although different synthetic approaches, occurring under either kinetic or thermodynamic control, have been employed7d,h,i in [2]daisy chain synthesis to date, only a few examples10 exploit the use of DCC. Reversible imine bond formation could potentially allow the construction of [2]daisy chains by using the condensation of a diamino acyclic polyether precursor and a dialdehyde carrying a secondary amino group. This strategy, not only results in the formation of [2]daisy chains in high yields, but it also reduces vastly the formation of unwanted byproducts.

Herein, we report the power of the DCC approach in bringing about four-component self-assembly processes to afford (Fig. 1) the [2]daisy chains DC1-2CF3CO2 and DC2-2CF3CO2. We have prepared (Scheme 1) daisy chain precursors P1 and P2 composed of diformylpyridine derivatives containing a –CH2NHCH2–center and investigated the favourable thermodynamics of imine bond formation upon addition of trifluoroacetic acid (TFA) for the

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The synthesis (Scheme 1a) of target monomer P1 begins with the oxidation of the dimethyl-4-(hydroxymethyl)pyridine-2,6-dicarboxylate13, with 2-iodoxybenzoic acid (IBX) in refluxing CH₂Cl₂ to produce, in 95% yield, the aldehyde 2, which was condensed with 3,5-dimethoxybenzylamine, before the resulting imine, along with the methyl esters, were reduced with NaBH₄. The dialdehyde function in 3 was protected chemoselectively as its fluorenylmethyl carbamate. The diol 4 was subjected to another IBX oxidation to furnish the aldehyde 5, which was converted into the target monomer P1 in 30% yield upon reaction with morpholine in CH₂Cl₂ at room temperature. When the dialdehyde P1 and tetraethylene glycol bis(2-aminophenyl)ether14 (M) were mixed in equimolar proportions with 1.0 equiv of TFA in CD₃CN at room temperature, a golden yellow solution formed. The ¹H NMR spectrum (500 MHz, CD₃CN, 298K) was recorded after mixing 5 min, revealing (Fig. 2a) the quantitative formation of the [2]daisy chain DC1[2]CF₃CO₂.

The formation of DC1[2]CF₃CO₂ is evident in the spectrum from the appearance of a singlet (δ = 8.38 ppm) for the imine protons (Hₐ) of the [24]crown-8, and the complete disappearance of the singlet (δ = 9.98 ppm) corresponding to the formyl protons in the monomer P1. In comparison with other rotaxanes7b,10a,b formed by the analogous clipping protocol, addition of acid brings about [N⁺–H···X] hydrogen bonds, and [N⁺–C–H···X] (X = O or N) interactions. In contrast to these analogs with related binding motifs, [π···π] stacking interactions between the central pyridine rings and the dimethoxybenzyl stoppers are not possible because of the inherent kink of the [24]crown-8 ring as a result of daisy chain formation. However, [π···π] stacking interactions between the dimethoxybenzyl stoppers and one of the lateral imino phenyl rings result in upfield shifts of the resonances corresponding to Hₐ and Hₐ. The energy-minimized structure (Fig. 2b and S1, ESI†) of DC1[2]⁺, obtained by molecular modelling, reveals the presence of such interactions in a compact environment. Furthermore, high-resolution electrospray-ionization mass spectrometry (HR-ESI-MS) confirms the constitutional identity of DC1[2]CF₃CO₂ with intense base peaks at m/z 1309.8259 and 655.3133, corresponding to [DC1–2CF₃CO₂–H]⁺ and [DC1–2CF₃CO₂]⁺, respectively.

In order to demonstrate the general applicability of this strategy, another diformylpyridine derivative P2 (Scheme 1b) was prepared containing an additional phenylene unit. The mixture of 4-formylphenylboronic acid (6) and 3,5-dimethoxy-benzylamine was heated under reflux in PhMe, followed by reduction with NaBH₄ in EtOH to afford the boronic acid derivative 7 in 80% yield. Employing a Suzuki–Miyaura coupling reaction between 7 and 4-bromo-2,5-diformylpyridine resulted in the formation of the dialdehyde P2 in 50% yield. When the dialdehyde P2 and the diamine M were mixed in equimolar amounts in CD₃CN at room temperature, a golden yellow solution was obtained upon addition of 1.0 equiv of TFA. As in the case of DC1[2]CF₃CO₂, quantitative formation of DC2[2]CF₃CO₂ was observed (Fig. 3a) by ¹H NMR spectroscopy. The structure of DC2[2]CF₃CO₂ was confirmed by the broad singlet (δ = 9.95 ppm) for the –NH₂⁺ protons encircling the crown ether, a singlet that resonates at δ = 8.45 ppm for the imine protons (Hₐ) of the [24]crown-8 ring, and the complete disappearance of the singlet which resonates at δ = 9.98 ppm for the formyl protons of monomer P2. The upfield shifts of pyridyl (Hₐ), phenylene (Hₐ and Hₐ), and stopper (Hₐ and Hₐ) protons relative to the monomer P2 indicate the presence of stabilizing [π···π] stacking interactions as revealed by the energy-minimized structure

Fig. 2 (a) ¹H NMR spectrum of DC1[2]CF₃CO₂ in CD₃CN at 298 K recorded in 5 min after mixing P1, M, and TFA. (b) A side-on view of energy-minimized structure of DC1[2]⁺ using the Merck molecular force field (MMFF94).

Fig. 3 (a) ¹H NMR spectrum of DC2[2]CF₃CO₂ in CD₃CN at 298 K. (b) A side-on view of energy-minimized structure of DC2[2]⁺ employing MMFF94.
DC2\(^{2+}\). HR-ESI-MS also supports the formation of DC2\(2CF_3CO_2^-\) by the presence of intense base peaks at \(m/z\) 1575.6778 ([DC2\(2CF_3CO_2^-\)]\(^{1+}\)), 1461.6880 ([DC2\(2CF_3CO_2^-\)]\(^{2+}\)), and 751.3469 ([DC2\(2CF_3CO_2^-\)]\(^{3+}\)).

In conclusion, we have demonstrated that [2]daisy chains can be self-assembled quantitatively by imine condensations between a diformylpyridine derivative carrying a secondary amine appendage to serve, on protonation, as a self-template, and a diaminocrown ether. In these covalent dynamic templated syntheses, the protonation, on adding an equimolar amount of acid (TFA) into the reaction mixture, leads to an extremely efficient syntheses, the protonation, on adding an equimolar amount of acid (TFA) into the reaction mixture, leads to an extremely efficient self-templation when constructing [2]daisy chains by means of four-component self-assembly processes. It also represents a ‘green’ transformation in which no additional reagents are consumed. We believe that this approach has the potential to be highly efficient in the synthesis of two or three state switchable daisy chains, as well as their polymeric analogues following judicious design and facile syntheses of the monomers.

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Notes and references

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