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Two-component self-assembly of a Tetra-Guanidiniocarbonyl Pyrrole Cation and Na₄EDTA: Formation of pH switchable supramolecular networks

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The guanidiniocarbonyl pyrrole (GCP) cation forms stable H-bond associated ion pairs with carboxylates even in aqueous solutions. A tetra GCP cation 1 undergoes efficient two-component self-assembly with Na₄EDTA, a tetra-carboxylate, leading to 3D supramolecular networks. These networks show dual pH responsiveness and reversibly dissociate back into monomers either upon addition of acid or base.

Two-component self-assembly to form supramolecular aggregates and polymers attracts a lot of interest nowadays as this endows new areas of research such as chiral amplification, energy transfer, end-capping, and the preparation of supramolecular block copolymers. On the one side, this approach is more complex and challenging than self-assembly of a single molecule, as it requires to balance noncovalent interactions between two individual molecules to ensure a sufficient degree of polymerization. On the other side, it allows to regulate the microscopic structure and macroscopic properties by altering the molar ratio of the two components. Furthermore, each of the components might possess functionalities that respond to external stimuli such as temperature, metal ions, light, pH, or solvent which might allow for switching back and forth between different types of nanostructures. Accordingly, different types of two-component self-assembly systems have been reported in the literature.

In this context we present a flexible tetra guanidiniocarbonyl pyrrole cation 1 which efficiently undergoes two-component self-assembly with Na₄EDTA to form supramolecular networks. The guanidiniocarbonyl pyrrole cation is a highly efficient anion binding site with an estimated binding constant for carboxylates of 10³ M⁻¹ in aqueous DMSO. We reasoned that a molecule possessing four of these GCP cations should strongly interact with a complementary tetra-anion such as Na₄EDTA to form a 3D crosslinked supramolecular network. Furthermore, since the guanidiniocarbonyl pyrrole cation has a pKₐ value of approximately 6–7, ion-pair formation with a carboxylic acid (pKₐ ca. 3–5) can only occur in a narrow pH range around neutral pH. This restriction offers the possibility to deliberately turn the ion-pair formation on or off by simply changing the pH from neutral to acidic (pH < 4) or basic (pH > 8). Therefore, any supramolecular aggregate formed should exhibit dual pH responsiveness. It should reversibly transform back into the individual monomers by the addition of either acid or base, respectively (Scheme 1).

Scheme 1. Two-component self-assembly of 1 and Na₄EDTA leads to 3D supramolecular networks which exhibit dual pH responsiveness.
The synthesis of the tetra guanidinocarbonyl pyrrole cation 1 is shown in Scheme 2. N,N,N',N'-tetraaminopropyl-1,2 ethylene diamine 2 was synthesized according to literature procedures.\textsuperscript{19} Compound 2 was then coupled with the Boc-protected guanidinocarbonyl pyrrole carboxylic acid\textsuperscript{17} 3 using HCTU in a mixture of DMF and MeOH as the coupling reagent (48 % yield). The Boc group was cleaved with TFA to produce the tetra cation 1 (74% yield).

Two-component self-assembly of 1 with Na\textsubscript{4}EDTA was studied with dynamic light scattering (DLS) measurements. We first measured the hydrodynamic diameters of both individual compounds 1 and Na\textsubscript{4}EDTA (1 mM) in DMSO and 10% H\textsubscript{2}O/DMSO, respectively (Figure 1A). None of them formed any larger aggregates in solution. However, in a 1:1-mixture of both compounds (v/v = 50/50, 0.5 mM each) immediately after mixing large aggregates are present which further increase in size upon aging (e.g. from ca. 70 nm diameter after mixing to more than 3800 nm after 57 h). Most likely initially smaller oligomers are formed, which rearrange into larger networks with time. As explained above self-assembly between 1 and Na\textsubscript{4}EDTA depends on the complementary charges of both compounds. Therefore, neither in acidic nor in basic solution supramolecular aggregation occurs (Figure 1B). However, the supramolecular aggregates were restored upon neutralization of the excess of acid or base.

Complex formation between these two components could also be proven by NMR titration. Upon the addition of aliquots of a stock solution of Na\textsubscript{4}EDTA (6 mM) in 10% H\textsubscript{2}O/DMSO to a solution of 1 (1 mM), significant complexation-induced shift changes of the amide NHs, guanidinio NHs and the pyrrole CHs were observed, indicating ion pair formation between the GCP cation and the carboxylates (Figure S9).\textsuperscript{20} A fluorescence titration provided a binding constant of $K$ ca. 950 M$^{-1}$ following the decrease of the fluorescence signal at $\lambda = 382$ nm upon addition of Na\textsubscript{4}EDTA to a solution of 1 (assuming a 1:1 stochiometry). This is in good agreement with the reported affinity of the GCP cation for carboxylates in aqueous DMSO.\textsuperscript{18,20}

Further evidence for the formation of a supramolecular network between 1 and Na\textsubscript{4}EDTA was obtained from concentration dependent viscosity measurements (Figure 3). The viscosity of solutions of both 1 and Na\textsubscript{4}EDTA alone only slightly increased with increasing concentrations. However, the viscosity of the corresponding 1:1-solutions significantly increased indicating the formation of 3D supramolecular networks at higher concentrations. Furthermore, the viscosity of the solutions reversibly dropped by adding TFA (10 equiv).
To further investigate the morphology of the supramolecular network we used atomic force microscopy (AFM) and transmission electron microscopy (TEM). Samples were prepared either by drying under ambient conditions or under vacuum by spin-coating on freshly cleaved mica surface. AFM samples were analysed in tapping-mode. No specific morphologies for either compound were revealed a densely entangled supramolecular network (Figure 3B), larger agglomerates are present. TEM images also revealed a densely entangled supramolecular network (Figure 3C).

In conclusion, we have designed and synthesized a flexible tetra guanidino carbonyl pyrrole cation which efficiently underwent a two component self-assembly with Na₂EDTA based on H-bond assisted ion pair formation, but only at neutral pH. Experimental evidence is provided for the formation of supramolecular networks which could be reversibly switched between network and monomers by adding either aid or base.

Notes and references
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