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Pyrrole β-amides: Synthesis and characterization of a dipyrrinone carboxylic acid and an *N*-Confused fluorescent dipyrrinone

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ABSTRACT

Pyrrole β-amides are useful building blocks for the preparation of novel molecular architectures that can be used in supramolecular chemistry and sensor development. Under basic conditions, pyrrole β-amides with an α-aldehyde produce different condensation products when reacted with pyrrolinones depending on the amide substitution. Secondary amides form the expected dipyrrinones, but unexpectedly undergo a subsequent trans-amidation with the pyrrolinone nitrogen to produce an unsymmetrical imide (an *N*-confused fluorescent dipyrrinone). Under the same conditions, tertiary amides produce the expected dipyrrinone carboxylic acids, which have been shown to have strong self-association properties as determined by vapor pressure osmometry measurements, NMR studies, and X-ray crystal structure determination. Furthermore, an *N*-confused fluorescent dipyrrinone was produced from the same trans-amidation reaction during attempts to decarboxylate a dipyrrinone amide with a 9-carboxylic moiety.

1. Introduction

Molecular recognition driven by hydrogen bonding[1–3] has been extensively studied over the years and is frequently found in organic and biochemistry systems with amides and carboxylic acids being among the most essential functional groups incorporated into the hydrogen bonding interactions.[4,5] Amide-to-amide hydrogen bonding (Fig. 1A) has been recognized and studied for decades with typical self-association constants, K_A, on the order of $10^2\ M^{-1}$ in hydrogen bond-promoting solvents such as carbon tetrachloride and chloroform.[3]

Carboxylic acid to carboxylic acid hydrogen bonding (Fig. 1B) has also been investigated over the years.[1–4] Hydrogen bonded carboxylic acid dimers have been shown to exhibit even larger K_A's ($\sim10^3\ M^{-1}$) for self-association in hydrogen bond promoting solvents.[2–4] In contrast, the mixed type, amide-to-carboxylic acid hydrogen bonding (Fig. 1C) has received far less attention except in co-crystal formation,[5] and usually in connection with molecular recognition/self-assembly studies. By utilizing a combination of computational and experimental techniques, Rebek determined the order of dimerization energy to be carboxylic homodimer > amide-carboxylic dimers > amide homodimers. This dimerization energy order was also determined by computational methods to be the same in the gas phase, in carbon tetrachloride and in *N,N*-dimethylformamide solutions, as well as in molecular capsules.[6]

Dipyrrinones are well known participants in hydrogen bonding, and have been shown to be effective receptors for carboxylic acids[7–10] (Fig. 1E). The hydrogen bonding pocket of the dipyrrinone unit is composed of pyrrole and lactam N–H and a lactam C=O. There are numerous examples of dipyrrinones participating in hydrogen bonding via self-association[11–14] and with other species in a host-guest type interaction, such as anions (Cl^-, HSO_4^-, etc.) and benzoic acid.[15] For self-association, the traditional hydrogen bonding motif has the two dipyrrinone units held together by a network of four intermolecular hydrogen bonds showing amide-to-amide hydrogen bonding involving the lactam rings as well as the pyrroles N–H to lactam C=O hydrogen bonding (Fig. 1F).[8] When

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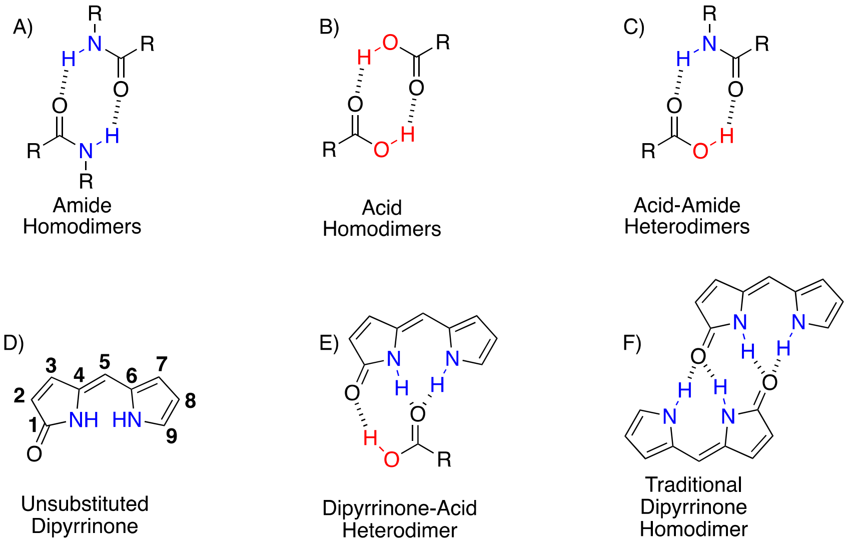

Fig. 1. A) Amide-to-amide homodimer hydrogen bonds. B) Carboxylic acid to carboxylic acid homodimer hydrogen bonds. C) Amide-to-carboxylic acid heterodimer hydrogen bonds. D) Backbone of unsubstituted dipyrrinones. E) Dipyrrinones-to-carboxylic acids heterodimer hydrogen bonds. F) Dipyrrinone homodimer displaying acid-to-amide hydrogen bonding as well as a third hydrogen bond between the pyrrole NH and the acid C=O.

hydrogen bonding to carboxylic acids, the complex displays acid-to-amide hydrogen bonding as well as a third hydrogen bond between the pyrrole N–H and the acid C=O, Fig. 1E.[7,9,16]

Interestingly, dipyrrinones have been shown to prefer the acid-to-amide hydrogen bonding interactions.[17,18] For example, dipyrrinones with a long alkyl linker between the dipyrrinone and the carboxylic acid located at the C(9) position of the dipyrrinone were found to prefer the intramolecular hydrogen bonded state with acid-to-amide hydrogen bonding over a self-associated dimer which would have displayed the amide-to-amide hydrogen bonding motif.[17] With a carboxylic acid at C(8) of the dipyrrinone, intramolecular acid-to-amide hydrogen bonding is not possible. Dipyrrinone analogs with a carboxylic acid at C(8) were found to adopt a self-associated state with the acid-to-amide hydrogen bonding pattern, again over the traditional hydrogen bonding pattern found in dipyrrinones without carboxylic acids.[19]

In our current study, we prepared new dipyrrinone analogs to further the understanding of dipyrrinones as receptors for carboxylic acids. The target compounds contain a carboxylic acid at C(9) with no linker and an amide at C(7) (Fig. 2) which should provide flexibility for adjusting solubility as well as an attachment point for incorporating the dipyrrinone moiety into larger supramolecular architectures. In the course of preparing the target compounds, we encountered unexpected reactivity in these new 7-amidodipyrrinones, which will also be discussed.

2. Results and discussion

2.1. Synthesis and characterization

Synthesis of the target molecules began with the Knorr pyrrole preparation of the β-amide pyrrole esters **2** and **3** from their corresponding acetoacetamide derivatives and ethyl acetoacetate in reasonable yields (Scheme 1).[20,21] Ceric ammonium nitrate oxidation of the pyrrole α-methyl to the corresponding aldehyde afforded pyrroles **4** and **5** in 55–75% yield.[22] Condensation of the tertiary amide derivative **5** with 3-ethyl-4-methylpyrrolin-2-one under basic conditions, KOH, provided target **6** in 83% yield. Hydrolysis of the ester was observed under the reaction conditions producing the dipyrrinone 9-carboxylic acid derivative **6**, rather than preserving the ester of the pyrrole. Attempts to decarboxylate **6** using standard methods failed to yield the desired α-free dipyrrinone analog. Instead, the *N*-confused fluorescent dipyrrinone **7** was isolated in 84% yield. This product was formed from an intramolecular *trans*-amidation reaction involving the 7-amide substituent and the pyrrolinone N–H moieties of the dipyrrinone resulting in the imide. Similar reactions to form this ring system have been observed with 7-ester dipyrrinone analogs, but never with amides.[23] Decarboxylation of the 9-carboxylic acid did take place, but it was not possible to determine which reaction occurred first, trans-amidation or decarboxylation.

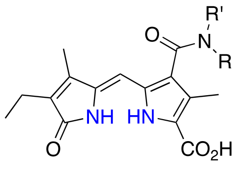

Fig. 2. 7-Aminodipyrrinone targets.

Condensation of the secondary amide derivative **4** with 3-ethyl-4-methylpyrrolin-2-one under basic conditions with KOH failed to produce the desired dipyrrinone carboxylic acid targets. Interestingly, the reaction of *N*-phenyl amide **4** under the same basic conditions as **5** produced the *N*-confused fluorescent dipyrrinone carboxylic acid **8**. As observed with **6**, hydrolysis of the ester was found to provide the carboxylic acid product **8**. The use of DBU as a non-nucleophilic base also produced the *N*-confused fluorescent dipyrrinone, but as the ester **9** rather than the carboxylic acid. Apparently, the secondary amide unit is more reactive in the trans-amidation reaction conditions than the tertiary amide. All attempts to condense the secondary amide pyrrole aldehydes with the pyrrolinone resulted in either the *N*-confused fluorescent dipyrrinone or the isolation of the starting material. Previously known *N*-confused fluorescent dipyrrinones were prepared from pyrrole aldehydes with a β-ester moiety and were shown to be highly fluorescent with λ_{max} for emission at ~500 nm in methanol.[23] Samples **7**, **8**, and **9** are also fluorescent. The λ_{max} for emission of **9** in acetonitrile was 578 nm with a quantum yield of 0.55. The emission λ_{max} for **8** in acetonitrile was 480 nm with quantum yield of 0.15. Sample **7** has an emission λ_{max} of 500 nm in