

## Self-Assembly



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# Hydrogen-Bond-Mediated Self-Assembly of Aminopyrazolones: Macrocyclic Quartets—Single and Stacked One-Dimensional Motifs\*\*

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A broad goal of modern research resides in the development of selective protocols for the organization of matter across length scales.<sup>[1]</sup> Toward this end, the self-assembly of molec-

ular components has garnered considerable success as a procedure for the spontaneous generation of well-defined discrete and recurrent architectures.<sup>[2,3]</sup> Hydrogen-bond-mediated self-assembly has proven especially effective,<sup>[3]</sup> largely because of the design of tailored recognition elements in the form of hydrogen-bond donor–acceptor arrays, which allows the free energy and “orthogonality” of recognition events to be tuned.<sup>[3c]</sup> The utility of hydrogen-bond recognition elements is highlighted by their application to the design of oligomers (foldamers) that adopt specific secondary structures,<sup>[4,5]</sup> molecular strands that engage in specific modes of intermolecular aggregation,<sup>[6]</sup> polymers possessing non-covalent main chains<sup>[7]</sup> and side chains,<sup>[8]</sup> as well as the self-assembly of dendritic macromolecules.<sup>[9]</sup>

We recently developed duplex molecular strands based on the aminotriazine and diaminopyridazine hydrogen-bonding motifs as part of a program concerning hydrogen-bond-mediated self-assembly.<sup>[10]</sup> These systems engage in high-affinity twofold self-association, as established by isothermal titration calorimetry (ITC), <sup>1</sup>H NMR dilution studies, vapor pressure osmometry (VPO), and single-crystal X-ray diffraction analysis. With the goal of developing synthetic strands that self-assemble to form transmembrane channels,<sup>[11]</sup> we sought oligomers incorporating recognition elements that direct fourfold self-association. While quadruplexes based on guanosine and their structural relatives are commonplace,<sup>[12]</sup> other heterocyclic molecules that participate in hydrogen-bond-mediated fourfold self-association are exceptionally uncommon.<sup>[13]</sup> 3,5-Disubstituted pyrazoles are known to form dimers **A**, as well as cyclic trimers **B** and tetramers **C**, in solution and in the solid state (Scheme 1).<sup>[14]</sup> It was postulated that the hitherto unexplored aminopyrazolones **1** should preferentially engage in fourfold self-association through heteromeric aggregation (amide–amide), as the quadruplex type arrangement is reinforced by four additional hydrogen bonds as in **1**<sub>4</sub>. However, homomeric association (amide–amide, amidine–amidine) of aminopyrazolone **1** may compete to provide 1-dimensional motif **1**<sub>n</sub>. Finally, because ditopic association is relatively weak, arrangements involving unrequited hydrogen-bond donor–acceptor sites are probable in the solid state.<sup>[15]</sup>

Aminopyrazolones **1a–1c** were synthesized according to a literature procedure.<sup>[16]</sup> Specifically, ethyl cyanoacetate was subjected to exhaustive alkylation followed by hydrazination to afford dibutylaminopyrazolone **1a**, didodecylaminopyrazolone **1b**, and dibenzylaminopyrazolone **1c**. Synthesis of the optically pure C<sub>2</sub>-symmetric bis(aminopyrazolone) **1d** was achieved through the alkylation of a chirally modified cyanoacetate ester based on (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisoborneol (Scheme 2).<sup>[17]</sup>

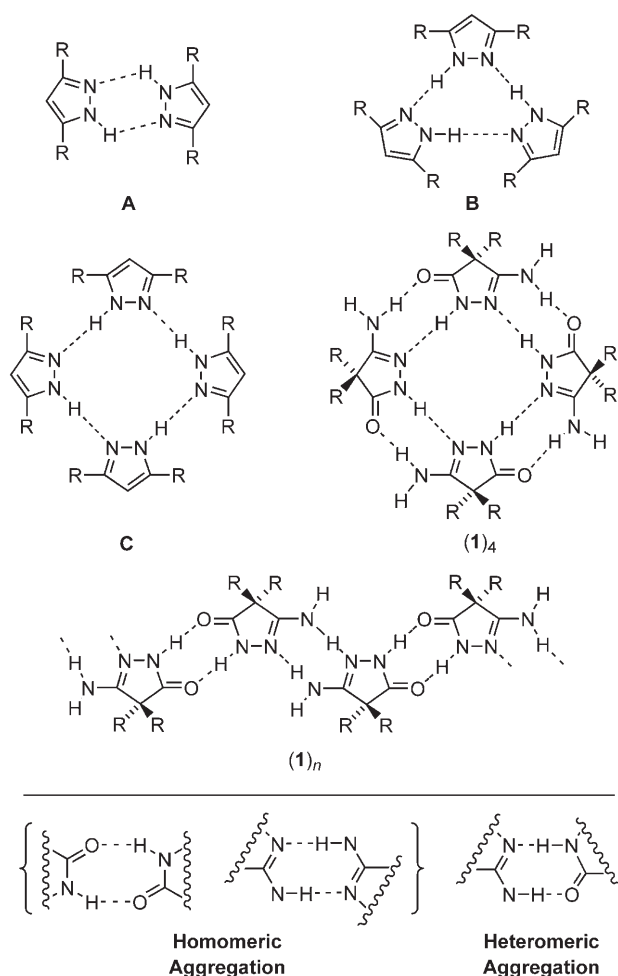
Single crystals of compounds **1a–1d** were obtained and subjected to X-ray diffraction analysis to determine the mode of assembly in the solid state. Analysis of crystals of dibutylaminopyrazolone **1a** obtained from ethyl acetate reveal a 1-dimensional hydrogen-bonding motif involving homomeric association of the ditopic hydrogen-bond donor–acceptor sites (amide–amide, amidine–amidine; Figure 1). The N–H⋯N and N–H⋯O hydrogen bonds in the linear aggregate (**1a**)<sub>n</sub> have equal lengths of 3.07 Å. In contrast, X-

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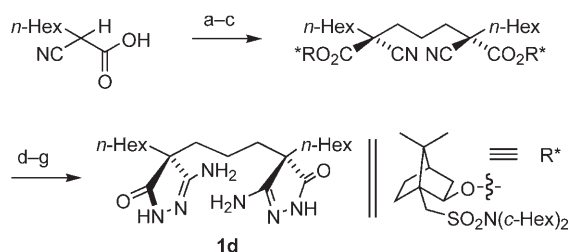
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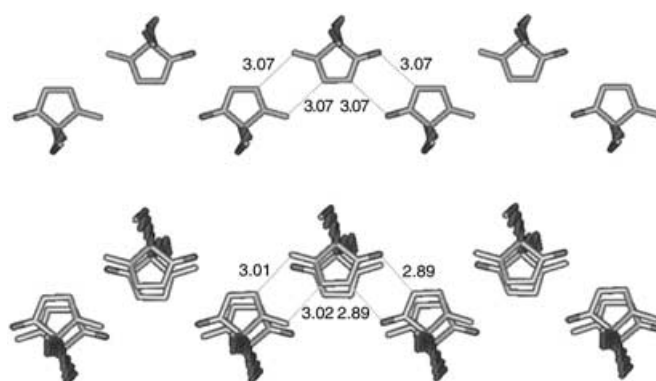


**Scheme 1.** Assembly modes established for 3,5-disubstituted pyrazoles and those proposed for aminopyrazolones **1**.

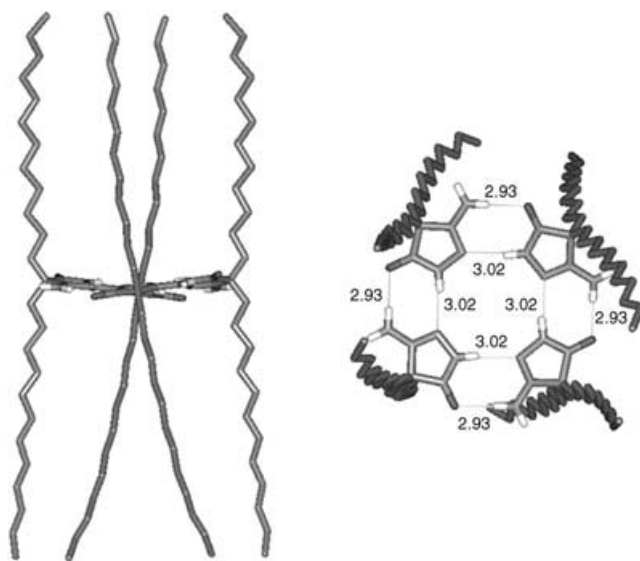


**Scheme 2.** Synthesis of bis(aminopyrazolone) **1d**. Reagents: a)  $\text{PCl}_5$  (100 mol %),  $\text{Et}_2\text{O}$  (0.3 M),  $25^\circ\text{C}$ . b)  $\text{R}^*\text{OH}$  (50 mol %),  $\text{AgCN}$  (75 mol %),  $\text{PhCH}_3$  (0.1 M),  $60^\circ\text{C}$ , 70 % over two steps. c) LDA (120 mol %), 1,3-diiodopropane (50 mol %), HMPA (150 mol %), THF (0.1 M),  $-78^\circ\text{C}$  to  $25^\circ\text{C}$ , 38 %. d)  $\text{LiOH}$  in MeOH (1.83 N, 1830 mol %),  $25^\circ\text{C}$ , 83 %. e)  $\text{PCl}_5$  (212 mol %),  $\text{Et}_2\text{O}$  (0.1 M). f) MeOH (excess),  $25^\circ\text{C}$ , 97 % over two steps. g)  $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$  (1000 mol %),  $105^\circ\text{C}$ , 70 %. LDA = lithium diisopropylamide, HMPA = hexamethyl phosphoramide.

ray diffraction analysis of crystals of didodecylaminopyrazolone **1b** obtained from 1,2-dichloroethane reveals the desired cyclic quartet structure (**1b**)<sub>4</sub> derived through heteromeric association (amide–amidine, amide–amidine; Figure 2). The  $\text{N}\cdots\text{H}$  and  $\text{N}\cdots\text{H}\cdots\text{O}$  hydrogen-bond lengths in the cyclic



**Figure 1.** Top: Solid-state structure of dibutylaminopyrazolone **1a**. Bottom: Solid-state structure of  $\text{C}_2$ -symmetric bis(aminopyrazolone) **1d**. Solvent is omitted for clarity.



**Figure 2.** Solid-state structure of didodecylaminopyrazolone **1b**.

aggregate are 3.02 Å and 2.93 Å, respectively. A pore size of approximately 2.6 Å is estimated when the van der Waals radii are taken into account; hence, the pore size is sufficiently large to accommodate lithium, sodium, and potassium ions. The solid-state structure of dibenzylaminopyrazolone **1c** reveals a non-coplanar arrangement of the aminopyrazolone rings.<sup>[18]</sup> The energetic driving force represented by the packing preferences of the phenyl moieties in **1c**, appears to supercede the free energy of hydrogen-bond formation, as only one of the four hydrogen-bond donor–acceptor sites forms a contact with another aminopyridazine molecule. Finally, X-ray diffraction analysis of a crystal of  $\text{C}_2$ -symmetric bis(aminopyrazolone) **1d** obtained from 1,3-dimethyl-2-imidazolidinone reveals a stacked 1-dimensional motif. In this stacked motif,  $\text{N}\cdots\text{H}$  and  $\text{N}\cdots\text{H}\cdots\text{O}$  hydrogen-bond lengths of 3.01/3.02 Å and 2.89 Å are observed, respectively.

In summary, initial studies on the hydrogen-bond-mediated self-assembly of aminopyrazolones have established that two primary modes of aggregation are evident for *n*-alkyl-substituted aminopyrazolones **1a**, **1b**, and **1d** in the solid

state. Homomeric aggregation (amide–amide, amidine–amidine) of aminopyrazolones **1a** and **1d** gives rise 1-dimensional architectures (**1**)<sub>n</sub>, while heteromeric aggregation (amide–amidine) generates the desired macrocyclic quartets (**1**)<sub>4</sub>. The self-assembly of aminopyrazolones in solution is currently under investigation. These studies suggest that suitably tailored aminopyrazolone oligomers may spontaneously assemble to form channel-type aggregates.

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