Self-Assembly

DOI: 10.1002/anie.200502539

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

*Hegui Gong and Michael J. Krische**

A broad goal of modern research resides in the development of selective protocols for the organization of matter across length scales.[1] Toward this end, the self-assembly of molecular components has garnered considerable success as a procedure for the spontaneous generation of well-defined discrete and recurrent architectures.[2,3] Hydrogen-bond-mediated self-assembly has proven especially effective,[3] 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.[3c] The utility of hydrogen-bond recognition elements is highlighted by their application to the design of oligomers (foldamers) that adopt specific secondary structures,[4,5] molecular strands that engage in specific modes of intermolecular aggregation,[6] polymers possessing non-covalent main chains[7] and side chains,[8] as well as the self-assembly of dendritic macromolecules.[9]

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.[10] These systems engage in high-affinity twofold self-association, as established by isothermal titration calorimetry (ITC), ^{1}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,[11] we sought oligomers incorporating recognition elements that direct fourfold self-association. While quadruplexes based on guanosine and their structural relatives are commonplace,[12] other heterocyclic molecules that participate in hydrogen-bond-mediated fourfold self-association are exceptionally uncommon.[13] 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).[14] It was postulated that the hitherto unexplored aminopyrazolones **1** should preferentially engage in fourfold self-association through heteromeric aggregation (amide–amidine), as the quadruplex type arrangement is reinforced by four additional hydrogen bonds as in $\mathbf{1}_4$. However, homomeric association (amide–amide, amidine–amidine) of aminopyrazolone **1** may compete to provide 1-dimensional motif $\mathbf{1}_n$. Finally, because ditopic association is relatively weak, arrangements involving unrequited hydrogen-bond donor–acceptor sites are probable in the solid state.[15]

Aminopyrazolones **1a**–**1c** were synthesized according to a literature procedure.[16] 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_2-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).[17]

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 $(\mathbf{1a})_n$ have equal lengths of 3.07 Å. In contrast, X-

[*] H. Gong, Prof. M. J. Krische
University of Texas at Austin
Department of Chemistry and Biochemistry
1 University Station–A5300
Austin, TX 78712-1167 (USA)
Fax: (+1) 512-471-8696
E-mail: mkrische@mail.utexas.edu

[**] Acknowledgment is made to the Research Corporation Cottrell Scholar Award (CS0927), the Alfred P. Sloan Foundation, the Dreyfus Foundation, and the NSF-CAREER Program.

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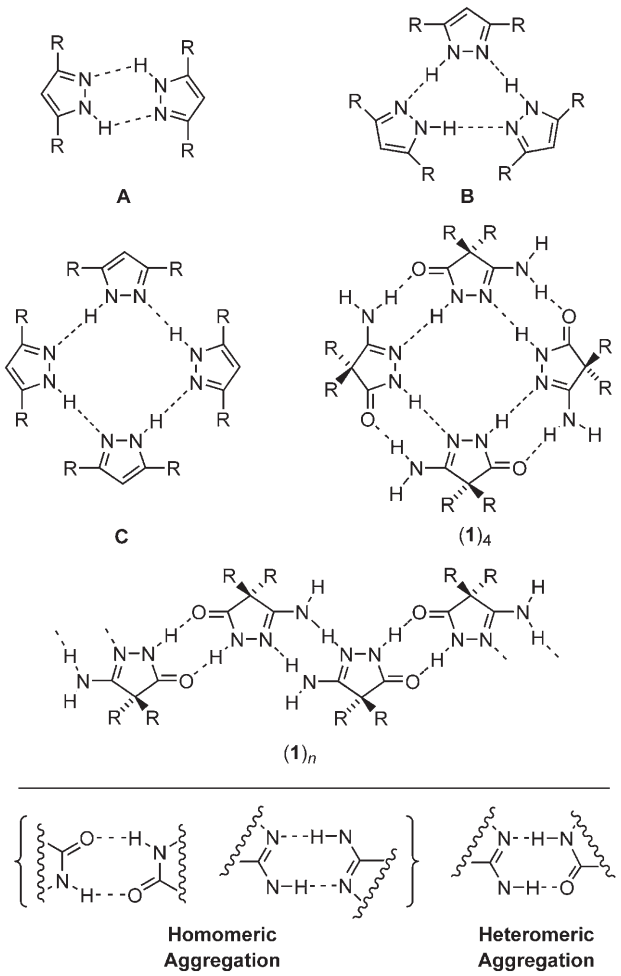
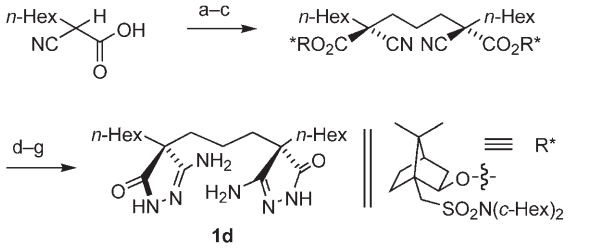


Scheme 1. Assembly modes established for 3,5-disubstituted pyrazoles and those proposed for aminopyrazolones **1**.



Scheme 2. Synthesis of bis(aminopyrazolone) **1d**. Reagents: a) PCl_5 (100 mol%), Et_2O (0.3 M), 25 °C. b) R*OH (50 mol%), AgCN (75 mol%), $PhCH_3$ (0.1 M), 60 °C, 70% over two steps. c) LDA (120 mol%), 1,3-diiodopropane (50 mol%), HMPA (150 mol%), THF (0.1 M), −78 °C to 25 °C, 38%. d) LiOH in MeOH (1.83 N, 1830 mol%), 25 °C, 83%. e) PCl_5 (212 mol%), Et_2O (0.1 M). f) MeOH (excess), 25 °C, 97% over two steps. g) NH_2NH_2-H_2O (1000 mol%), 105 °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 $(\mathbf{1b})_4$ derived through heteromeric association (amide–amidine, amide–amidine; Figure 2). The N–H···N and N–H···O hydrogen-bond lengths in the cyclic

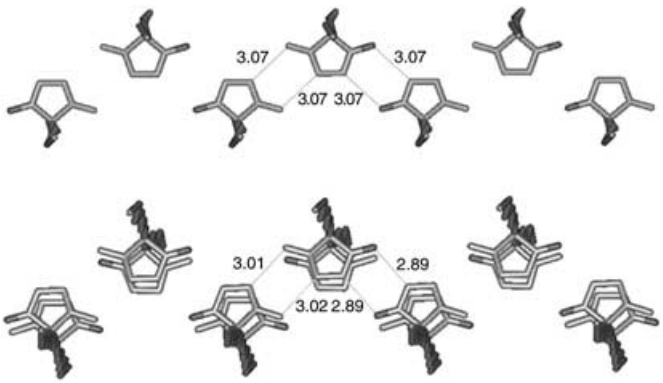


Figure 1. Top: Solid-state structure of dibutylaminopyrazolone **1a**. Bottom: Solid-state structure of C_2-symmetric bis(aminopyrazolone) **1d**. Solvent is omitted for clarity.

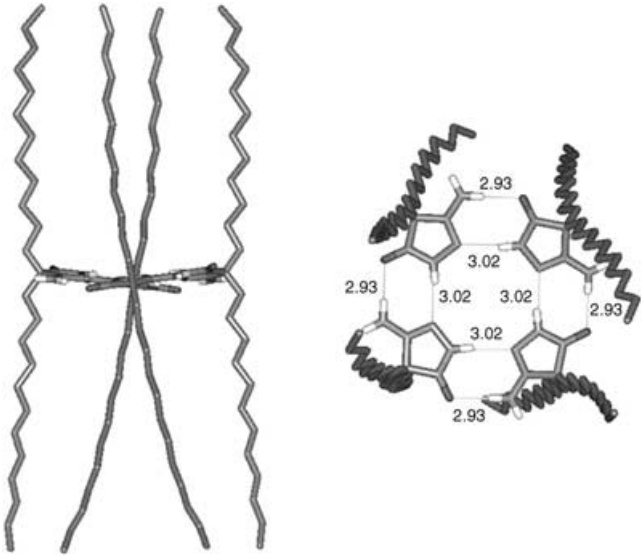


Figure 2. Solid-state structure of didodecylaminopyrazolone **1b**.

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.[18] 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 C_2-symmetric bis(aminopyrazolone) **1d** obtained from 1,3-dimethyl-2-imidazolidinone reveals a stacked 1-dimensional motif. In this stacked motif, N–H···N and N–H···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 $(\mathbf{1})_n$, while heteromeric aggregation (amide–amidine) generates the desired macrocyclic quartets $(\mathbf{1})_4$. 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.

Received: July 20, 2005
Published online: October 7, 2005

Keywords: donor–acceptor systems · host–guest systems · hydrogen bonds · noncovalent interactions · self-assembly

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[18] Detailed depictions of the solid-state structure of **1c** are provided in the Supporting Information.

