Scheme III

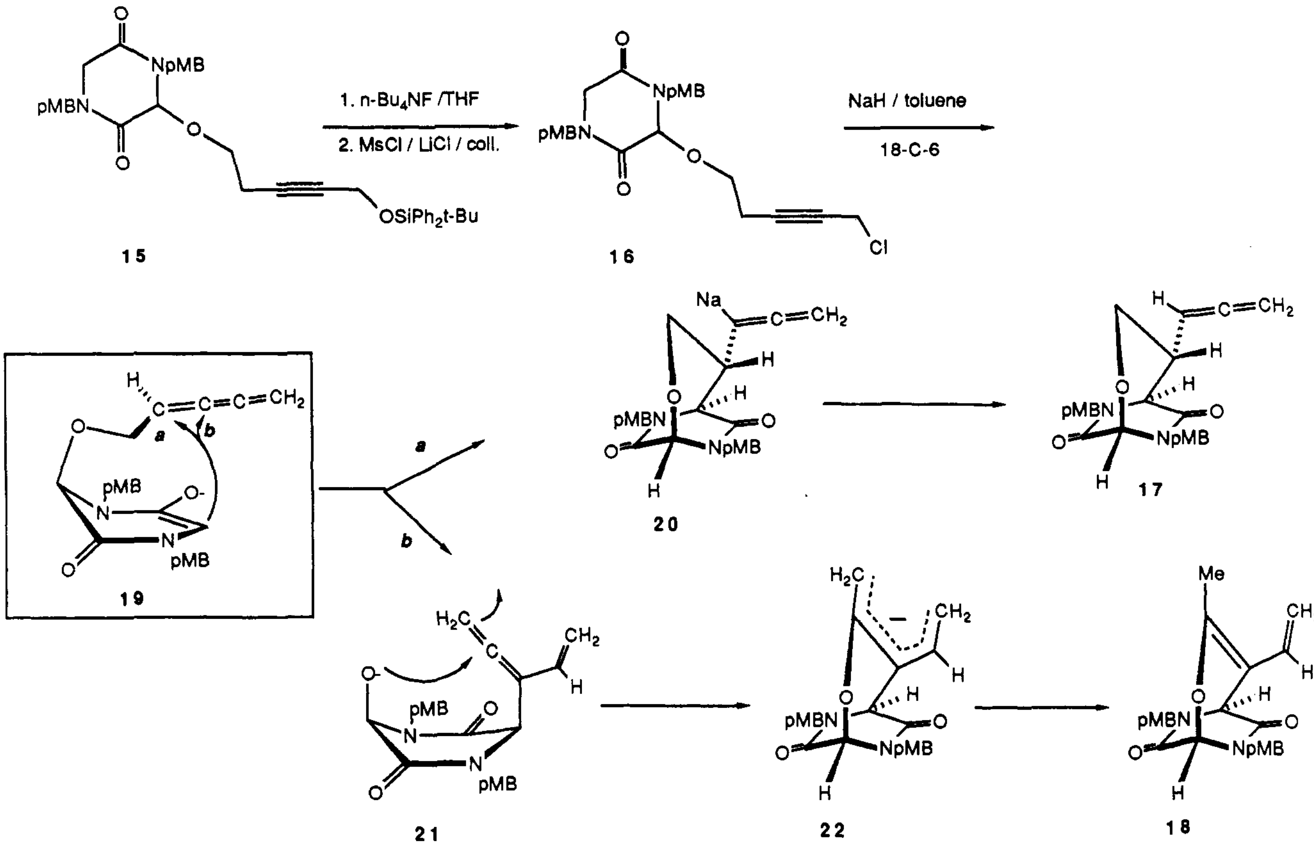
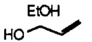
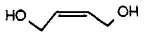
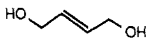
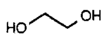


Table I. Cyclization of 10 → 11

ENTRY	SOLVENT / BASE	ALCOHOL (ROH)	YIELD %
1	MeOH / NaOMe Δ	MeOH	60
2	EtOH / KOt-Bu Δ	EtOH	74
3	THF / KOt-Bu 0°		73
4	THF / KOt-Bu 25°		54
5	THF / KOt-Bu Δ		57
6	THF / KOt-Bu Δ		61
7	THF / KOt-Bu Δ		46
8	DMF / KOt-Bu 0°		67
9	THF / NaH 0°		50
10	DMF / KOt-Bu 0°		67
11	DMF / KOt-Bu 0°		66

actions must be determined empirically and seems intimately related to the reactivity of the electrophilic tether. Under no set of reaction conditions was it possible to detect a product resulting from intramolecular S_N2' cyclization (a bicyclo[4.2.2] *exo*-allene derivative).

A mechanism for the formation of these interesting substances is depicted in Scheme III. Base-induced elimination of HCl from **16** would furnish the cumulene **19**. Subsequent enolate addition via path a furnishes the metalloallene **20**, which protonates to furnish **17**. It is also of interest that the enolate addition to the cumulene appears to proceed stereospecifically since a single diastereomer of **17** was isolated with the relative stereochemistry depicted.[8]

Alternatively, enolate addition via an intramolecular S_N2' (pathway b) reaction furnishes the alkoxy ene–allene **21**, which suffers intramolecular readdition of the alkoxide across the allene moiety resulting in the highly delocalized anion **22**, which protonates to furnish **18**. In spite of the modest yields in the formation of **17** and **18**, these reactions provide the shortest, most direct routes for constructing unsaturated bicyclic piperazinediones. It is expected that the methodology described herein will open numerous new pathways to monosubstituted and new bicyclic piperazinediones that have heretofore been inaccessible or tedious to prepare.

Acknowledgment. We thank the National Institutes of Health (AIGM 18957) for support of this research.

Supplementary Material Available: Spectroscopic and analytical data for all new compounds (7 pages). Ordering information is given on any current masthead page.

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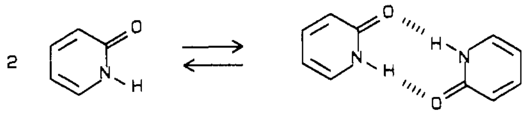
Use of Hydrogen Bonds To Control Molecular Aggregation. Extensive, Self-Complementary Arrays of Donors and Acceptors

Summary: Strong new hydrogen-bonding motifs can be created by using rigid spacers to link 2-pyridones in series. Asymmetric dipyridones like acetylene **5** have self-complementary arrays of hydrogen-bond donors and acceptors and therefore form strong dimers in $CHCl_3$ ($-\Delta G° > 6.5$

kcal/mol) and in the solid state. In contrast, symmetric dipyridones like acetylene 6 are not self-complementary and therefore form polymeric aggregates.

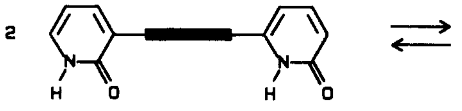
Sir: Nature uses hydrogen bonds to help regulate the association of biological molecules,[2] and chemists have begun to take advantage of the characteristic strength and directionality of these bonds to create nonbiological aggregates with novel properties.[3] Unfortunately, few hydrogen-bonding motifs are strong and specific enough to force complex interacting molecules to form predictable aggregates.[4] In this paper, we show how to amplify the strength of one of the most reliable motifs, the cyclic dimer of lactams like 2-pyridone (eq 1), and how to create new motifs containing extensive, self-complementary arrays of hydrogen-bond donors and acceptors.



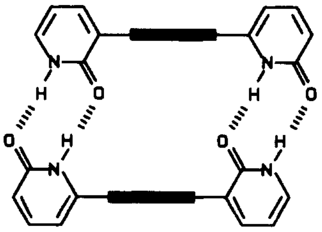
(1)

1 2

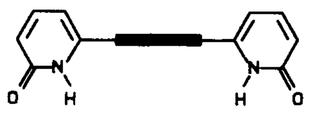
Crystalline 2-pyridones typically exist as hydrogen-bonded dimers,[5] and dimerization is also distinctly favored in aprotic solvents with small dielectric constants.[6,7] For example, ultrasonic studies indicate that the thermodynamic parameters for eq 1 are $\Delta G° = -2.7$ kcal/mol, $\Delta H° = -5.9$ kcal/mol, and $\Delta S° = -10.7$ eu in $CHCl_3$ at 25 °C.[7d] Molecules incorporating two or more 2-pyridones rigidly linked by appropriate spacers should therefore associate strongly, and the precise mode of aggregation should depend critically on the pattern of hydrogen-bond donors and acceptors. Self-complementary asymmetric dipyridones 3 should be able to dimerize (eq 2), whereas symmetric isomers 4 should be forced to polymerize.



3

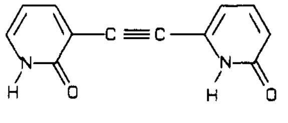


(2)



4

An asymmetric dipyridone 5[8] incorporating an acetylenic spacer could be prepared without difficulty by coupling[9] 2-(benzyloxy)-6-bromopyridine[10] with (trimethylsilyl)-acetylene ($N(C_2H_5)_3$, 3 mol % $Pd(PPh_3)_4$, 5 mol % CuI, 97%), desilylating (KOH, CH_3OH, 95%), coupling[11] the resulting monosubstituted acetylene with 2-(benzyloxy)-3-bromopyridine[12] (n-BuLi, $ZnCl_2$, 6 mol % $Pd(PPh_3)_4$, 79%), and deprotecting the dibenzyl ether (CF_3COOH, 72 °C, 94%).[14] Symmetric isomer 6[8] was synthesized in two efficient steps by coupling[15] 2-(benzyloxy)-6-bromo-



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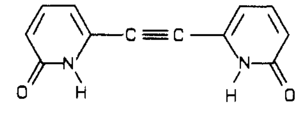

6

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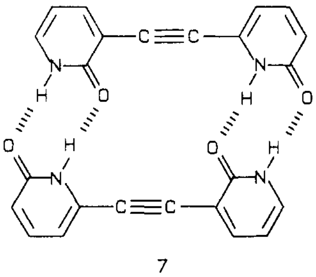
pyridine[10] with acetylene ($N(C_2H_5)_3$, 3 mol % $Pd(PPh_3)_4$, 1 mol % CuI, 79%), followed by deprotecting the resulting dibenzyl ether (93%).[14]

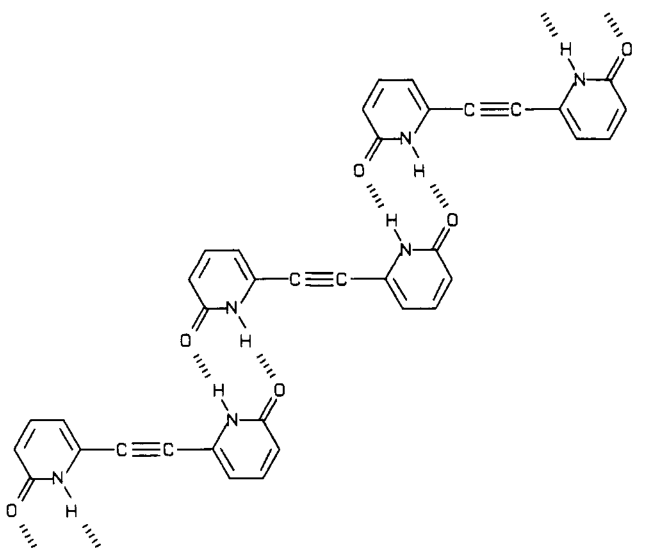
Vapor-pressure osmometric studies at 41 °C confirmed that both acetylenic dipyridones **5** and **6**, like 2-pyridone itself, exist as solvated monomers in CH_3OH and other strongly hydrogen-bonding polar solvents. In $CHCl_3$, however, all three compounds are associated. The ratio of absorbances at 1672 cm^{-1} (monomer) and 1654 cm^{-1} (dimer) in the infrared spectrum of 2-pyridone at 25 °C indicates about 20% dimerization at 1.1×10^{-3} M, and the behavior of symmetric dipyridone **6** is similar. In contrast, asymmetric dipyridone **5** is almost exclusively dimeric (>90%) even at distinctly lower concentrations (3.6×10^{-4} M). We attribute the particularly strong association of self-complementary dipyridone **5** to the formation of dimer **7** with $-\Delta G° > 6.5$ kcal/mol at 25 °C.



7

X-ray crystallographic studies established that dipyridones **5** and **6** also have different modes of aggregation in the solid state. As expected, asymmetric isomer **5** exists as discrete dimers **7**, and symmetric isomer **6** adopts the planar polymeric motif **8**.[16] Dimer **7** is distinctly nonplanar; in each dipyridone subunit **5** the average planes of the pyridone rings make an angle of 29°, presumably to minimize repulsion of the carbonyl oxygens directed toward the interior of the dimer.[17] Otherwise, the bond lengths and angles in each structure are closely similar to those of related molecules.[5,19]

Our strategy for amplifying the strength of simple hydrogen-bonding motifs can clearly be extended to produce self-complementary arrays with even lower free energies of aggregation. Creative incorporation of these sticky subunits in larger molecules may produce the elements of a molecular Lego construction set that allows chemists to make predictably ordered supramolecular aggregates with useful properties.



8

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Registry No. 5, 117068-69-6; 6, 117068-70-9; 2-(benzyloxy)-6-bromopyridine, 117068-71-0; (trimethylsilyl)acetylene, 1066-54-2; acetylene, 74-86-2; 2-(benzyloxy)-3-bromopyridine, 52200-49-4.

Supplementary Material Available: Spectroscopic and analytic data and atomic positional and thermal parameters for 5 and 6 (5 pages). Ordering information is given on any current masthead page.

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[16] (a) Ducharme, Y.; Simard, M.; Wuest, J. D., unpublished results. (b) Crystals of the asymmetric dipyridone **5** belong to the monoclinic space group $P2_1/c$ with a = 8.930 (9) Å, b = 13.299 (9) Å, c = 10.781 (9) Å, β = 126.08 (9)°, and V = 1034.8 $Å^3$. An Enraf-Nonius CAD-4 diffractometer was used to collect a set of intensity data at 220 K ($2\theta \leq 140.0°$, Cu Kα, 1614 nonzero reflections). The structure was solved by direct methods and refined by full-matrix least-squares calculations to R = 0.044, Rw = 0.054, and goodness-of-fit ratio = 1.94. (c) Crystals of the symmetric dipyridone **6** belong to the same space group with a = 4.900 (3) Å, b = 13.184 (5) Å, c = 8.989 (3) Å, β = 115.97°, and V = 522.1 $Å^3$. Similar collection and treatment of the data led to R = 0.12, Rw = 0.098, and goodness-of-fit ratio = 3.40 for 652 nonzero reflections. The atomic positional and thermal parameters for both structures are included in the supplementary material.

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General Approach to Highly Functionalized Benzylic Organometallics of Zinc and Copper

Summary: A general synthesis of highly functionalized benzylic zinc organometallics is described. The corresponding copper derivatives, formed by a transmetalation with CuCN·2LiCl, react in high yields with allylic halides, enones, acyl chlorides, and aldehydes.

Sir: Benzylic lithium and magnesium compounds are often difficult to prepare by conventional methods. When metal-halogen exchange reactions are used, there is often formation of cross-coupling products[1] even at low temperature, and thus special reaction conditions[2] had to be developed. Direct metalation[3] requires the use of strong

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