Synthesis and Self-Association of 4-Pyrimidinones

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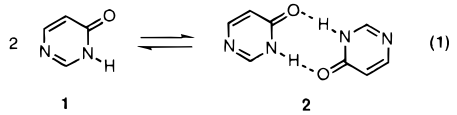
Crystallization of 4-pyrimidinone from $CHCl_3$ produced colorless needles that were shown by X-ray crystallography to consist of cyclic hydrogen-bonded dimers **2** of the 4(3*H*)-pyrimidinone tautomer **1**. Vapor-pressure osmometry established that a simple derivative, 5-(2-phenylethyl)-4(3*H*)-pyrimidinone (**5**), self-associates in solution with a value of K_a (220 ± 110 m^{-1} at 26 °C in CH_2Cl_2) close to that measured for 2-pyridinone under similar conditions. These observations suggest that 4-pyrimidinones and 2-pyridinones have similar modes and degrees of association and should be equally suitable for use as sticky functional groups that can be incorporated in complex molecules to make them associate in particular ways. This hypothesis was tested by synthesizing three dipyrimidinones (**12**, **16**, and **21**) designed to form strongly hydrogen-bonded dimers and by making a tetrapyrimidinone (**26**) designed to self-associate and to thereby generate a three-dimensional hydrogen-bonded network. In all cases, however, the compounds proved to have very low solubilities in organic solvents, and crystals suitable for X-ray diffraction could not be obtained despite intensive effort. It is possible that the simultaneous presence of multiple tautomers, all capable of strong intermolecular association, disfavors the sustained growth of single crystalline phases.

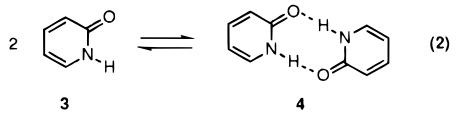
Introduction

A powerful strategy for the designed construction of new ordered materials is *molecular tectonics*,[2] which relies on the predisposition of sticky molecules called *tectons* to associate in particular ways.[3] An effective method for making tectons is to modify geometrically suitable molecules by attaching selected functional groups that are known to participate reliably in specific intermolecular interactions. Various interactions can be used to direct association, but hydrogen bonds have proven to be particularly suitable because of their strength, directionality, and specificity. As a result, molecules designed to associate by hydrogen bonding have been studied extensively as components for supramolecular assembly, and these molecules have incorporated a variety of groups chosen for their ability to form hydrogen bonds. Conspicuously uncommon in previous studies of this type are derivatives of 4(3*H*)-pyrimidinone (**1**) or its tautomers,[4,5] despite the critical biological role of closely related purines and pyrimidines in ensuring the self-association of nucleic acids. In this paper, we describe our efforts to use 4-pyrimidinone groups to direct intermolecular association. In particular, we describe the association of 4(3*H*)-pyrimidinone (**1**) itself in the solid state, the association of a simple derivative in solution, and the synthesis of more complex derivatives that incorporate multiple 4-pyrimidinone groups held in orientations designed to favor specific patterns of self-association.

Results and Discussion

Self-Association of 4(3*H*)-Pyrimidinone (1) in the Solid State. In the solid state and in solution, derivatives of 2(1*H*)-pyridinone (**3**) show a well-established tendency to self-associate and to form cyclic hydrogen-bonded dimers **4** (eq 2).[6] This preference has been used





effectively to control the association of more complex derivatives that incorporate multiple 2-pyridinone groups.[2] An analogous association of 4-pyrimidinones to give cyclic hydrogen-bonded dimers **2** (eq 1) is intrinsically more problematic because more tautomeric forms are present;[7] nevertheless, simple derivatives of dimer **2** have been observed in the solid state.[8] Surprisingly, however, no

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(2) (a) Brunet, P.; Simard, M.; Wuest, J. D. *J. Am. Chem. Soc.* **1997**, *119*, 2737. (b) Su, D.; Wang, X.; Simard, M.; Wuest, J. D. *Supramol. Chem.* **1995**, *6*, 171. (c) Wuest, J. D. In *Mesomolecules: From Molecules to Materials*; Mendenhall, G. D., Greenberg, A., Liebman, J. F., Eds.; Chapman & Hall: New York, 1995; p 107. (d) Wang, X.; Simard, M.; Wuest, J. D. *J. Am. Chem. Soc.* **1994**, *116*, 12119. (e) Simard, M.; Su, D.; Wuest, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 4696.

(3) For recent reviews of related work, see: Aakeröy, C. B. *Acta Crystallogr.* **1997**, *B53*, 569. Philp, D.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1154. Desiraju, G. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2311. Lawrence, D. S.; Jiang, T.; Levett, M. *Chem. Rev.* **1995**, *95*, 2229.

(4) Boucher, É.; Simard, M.; Wuest, J. D. *J. Org. Chem.* **1995**, *60*, 1408.

(5) For recent related work, see: Beijer, F. H.; Sijbesma, R. P.; Kooijman, H.; Spek, A. L.; Meijer, E. W. *J. Am. Chem. Soc.* **1998**, *120*, 6761. Branda, N.; Kurz, G.; Lehn, J.-M. *J. Chem. Soc., Chem. Commun.* **1996**, 2443. Liao, R.-F.; Lauher, J. W.; Fowler, F. W. *Tetrahedron* **1996**, *52*, 3153. Schall, O. F.; Gokel, G. W. *J. Chem. Soc., Chem. Commun.* **1992**, 748.

(6) For references, see: Gallant, M.; Phan Viet, M. T.; Wuest, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 721.

(7) Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. *Adv. Heterocycl. Chem., Suppl. 1* **1976**, 1.

(8) For example, see: Harker, C. S. W.; Tiekink, E. R. T.; Whitehouse, M. W. *Inorg. Chim. Acta* **1991**, *181*, 23. Kawai, T.; Yosuoka, N.; Kasai, N.; Kakudo, M. *Cryst. Struct. Commun.* **1973**, *2*, 663.

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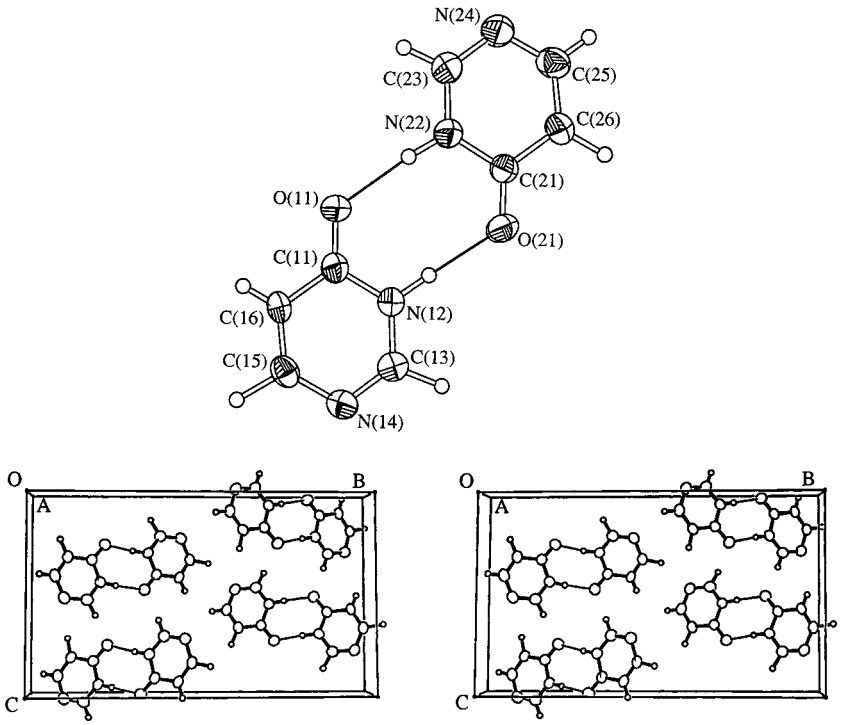


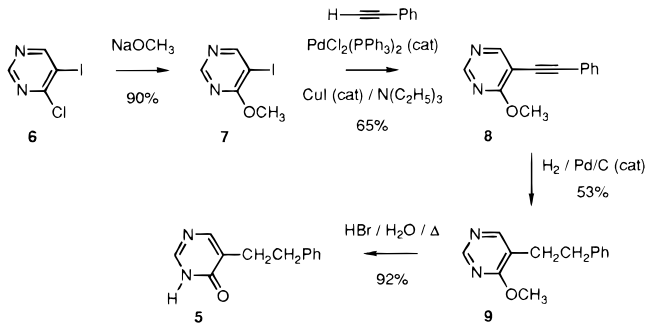
Figure 1. ORTEP views of the structure of the cyclic hydrogen-bonded dimer **2** of 4(3*H*)-pyrimidinone (**1**). The upper figure shows the atomic numbering, and the lower figure provides a stereoview of the unit cell along the *a* axis. Non-hydrogen atoms are represented by ellipsoids corresponding to 50% probability, hydrogen atoms are shown as spheres of arbitrary size, and hydrogen bonds are drawn using narrow lines.

crystal structure of 4(3*H*)-pyrimidinone (**1**) or a tautomer has ever been reported. We have found that slow evaporation of a saturated solution of 4-pyrimidinone in $CHCl_3$ produces colorless needles suitable for X-ray crystallographic study. The results of this study, summarized in Figure 1, confirm that the heterocycle is present as cyclic hydrogen-bonded dimers **2** of the 4(3*H*)-pyrimidinone tautomer **1**. Bond lengths and angles in this structure have normal values. In particular, the average N−H···O angle is 173(4)°, and the corresponding average N−O distance is 2.791(8) Å.

Self-Association of a Typical 4-Pyrimidinone in Solution. We then measured the self-association of a typical 4-pyrimidinone in solution by vapor-pressure osmometry. A derivative with adequate solubility in suitable organic solvents, 5-(2-phenylethyl)-4(3*H*)-pyrimidinone (**5**),[9] was prepared by the route summarized in Scheme 1. Treatment of 4-chloro-5-iodopyrimidine (**6**)[10] with $NaOCH_3$ provided a 91% yield of 5-iodo-4-methoxypyrimidine (**7**), which was subjected to palladium-catalyzed coupling with phenylacetylene to give derivative **8** in 67% yield. Hydrogenation then provided a 51% yield of 4-methoxy-5-(2-phenylethyl)pyrimidine (**9**), which was converted into the required 4-pyrimidinone **5** in 92% yield by treatment with aqueous HBr.

Studies of the self-association of 4-pyrimidinone **5** were carried out by vapor-pressure osmometry in CH_2Cl_2 at 26 °C using four dilute solutions with molal concentrations ranging from 7.4×10^{-3} to 15×10^{-3} *m*. These studies revealed a concentration-dependent association

Scheme 1



that we suggest is due to dimerization for the following two reasons: (1) dimerization is observed in the solid state, and (2) the low concentrations used disfavor the formation of higher oligomers. The observed value of K_a, 220 ± 110 m^{-1}, is closely similar to the value measured for 2-pyridinone in $CDCl_3$ at 25 °C (150 m^{-1}).[11] Together, our structural and colligative data indicate that 4-pyrimidinones and 2-pyridinones have similar modes and degrees of association and should be equally suitable as sticky groups designed to induce complex molecules to associate in particular ways.

Synthesis of Complex Molecules Containing Multiple 4-Pyrimidinone Groups. To test this hypothesis, we decided to synthesize a dipyrimidinone analogous to dipyridinone **10**,[12] which is known to self-associate in the solid state and in solution to form the strongly hydrogen-bonded dimer **11** (eq 3). Analogous dipyrimidinone **12**[9] was synthesized by the route summarized in Scheme 2. Palladium-catalyzed coupling of 2-ethynyl-4-methoxypy-

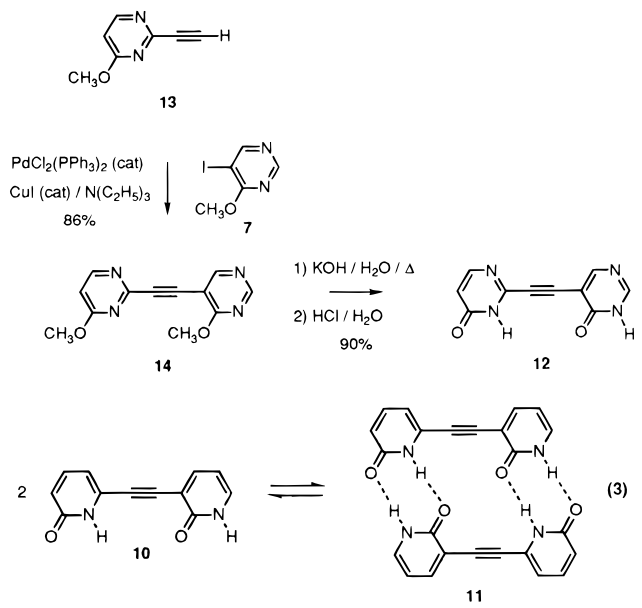
(9) For simplicity, all such structures in this paper are represented solely by the 4(3*H*)-pyrimidinone tautomer, even when other tautomers are undoubtedly present.

(10) Sakamoto, T.; Kondo, Y.; Watanabe, R.; Yamanaka, H. *Chem. Pharm. Bull.* **1986**, *34*, 2719.

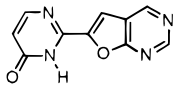
(11) Hammes, G. G.; Lillford, P. J. *J. Am. Chem. Soc.* **1970**, *92*, 7578.

(12) Ducharme, Y.; Wuest, J. D. *J. Org. Chem.* **1988**, *53*, 5787.

Scheme 2



rimidine (**13**)[4] with 5-iodo-4-methoxypyrimidine (**7**) gave an 86% yield of dipyrimidine **14**, which was converted into target **12** in 90% yield by treatment with KOH and subsequent neutralization. Unfortunately, the very low solubility of dipyrimidinone **12** in organic solvents, its facile rearrangement to furopyrimidine **15**[9] by a formal

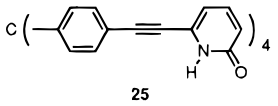


5-*endo-dig* cyclization,[4,13] and other factors prevented us from obtaining crystals suitable for X-ray diffraction and from studying its self-association in solution.

We then turned to the related dipyrimidinone **16**,[9] which was prepared according to Scheme 3. Palladium-catalyzed coupling of 5-iodo-4-methoxypyrimidine (**7**) with (trimethylsilyl)acetylene yielded pyrimidine **17**,[14] which was deprotected to give 5-ethynyl-4-methoxypyrimidine (**18**) in 42% overall yield. Palladium-catalyzed coupling of 2-ethynyl-4-methoxypyrimidine (**13**)[4] with 1-bromo-4-iodobenzene gave a 91% yield of pyrimidine **19**. Subsequent palladium-catalyzed coupling of compound **19** with the chlorozinc acetylide derived from 5-ethynyl-4-methoxypyrimidine (**18**) then provided a 52% yield of dipyrimidine **20**, which was converted into target **16** in 71% yield by sequential treatment with KOH and HCl. Again, however, the predisposition of dipyrimidinone **16** to undergo 5-*endo-dig* cyclization, its poor solubility, and other factors prevented us from crystallizing it and studying its self-association in solution.

To eliminate the possibility of cyclization, we decided to link two 4-pyrimidinones without using an ethynyl spacer at the 5-position. Compound **21**,[9] in which the 4-pyrimidinone rings are connected directly without a spacer, was synthesized by the novel route summarized in Scheme 4. The reaction of 4-chloro-6-methoxypyrimidine (**22**)[15] with LDA (0.5 equiv), followed by the addition of CH_3COOH (0.5 equiv) and DDQ (2 equiv), gave a 20% yield of bipyrimidine **23**.[16] Hydrogenolysis then converted compound **23** into 4,4′-dimethoxy-2,5′-bipyrimidine (**24**) in 53% yield, and target **21** was obtained in 65% yield by standard deprotection. Unfortunately, the solubility of bipyrimidinone **21** proved to be particularly low, and we were unable to obtain crystals suitable for X-ray diffraction or to study its self-association in solution.

In a final attempt to characterize the self-association of a molecule incorporating multiple 4-pyrimidinone groups, we decided to synthesize a tetrapyrimidinone analogous to the known tetrapyridinone **25**.[2e] Crystal-



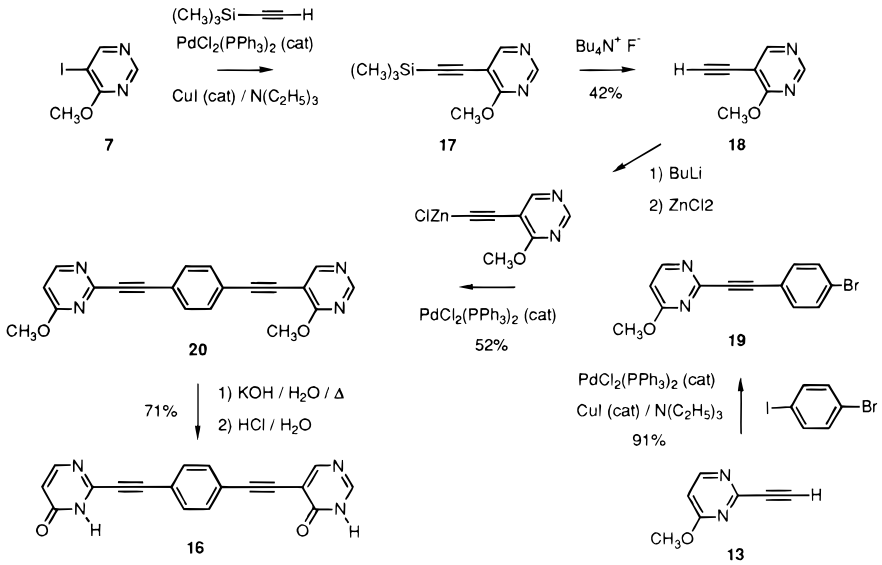
lization of tecton **25** is directed by normal pairwise hydrogen bonding of its four tetrahedrally oriented 2-pyridinone groups with those of four neighbors, thereby producing a remarkable structure in which interpenetrating diamondoid networks define significant spaces for the inclusion of guests. Analogous tetrapyrimidinone **26**[9] was prepared according to Scheme 5. Treatment of 2-ethynyl-4-methoxypyrimidine (**13**)[4] with BuLi (1 equiv) and $ZnCl_2$ (1 equiv), followed by palladium-catalyzed coupling of the resulting chlorozinc acetylide with tetrakis(4-iodophenyl)methane (**27**),[2e,17] gave tetrapyrimidine **28** in 34% yield. Without extensive purification, compound **28** was converted into tetrapyrimidinone **26** in 56% yield by normal deprotection. Once again, however, the solubility of this compound was extremely low, and we were not able to prepare crystals suitable for X-ray diffraction.

Conclusions

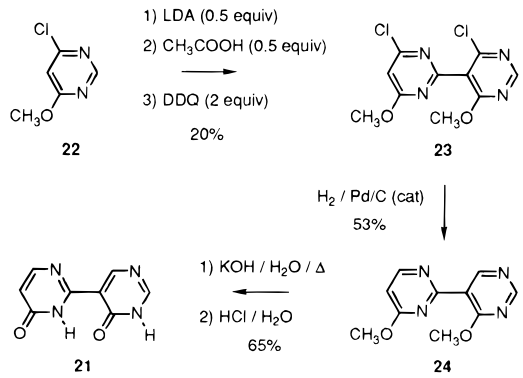
Our results establish that 4(3*H*)-pyrimidinone (**1**) self-associates in the solid state to form the cyclic hydrogen-bonded dimer **2** and simple derivatives also self-associate in solution with values of K_a similar to those measured for 2-pyridinones. These observations suggest that 4-pyrimidinones and 2-pyridinones can both be used effectively in molecular tectonics as sticky groups that predispose more complex molecules to which they are attached to associate in particular ways. In addition, our efficient syntheses of the potentially self-complementary dipyrimidinones **12**, **16**, and **21**, as well as our preparation of the self-complementary tetrapyrimidinone **26**, demonstrate that it is easy to make tectons with multiple 4-pyrimidinone groups held in orientations designed to favor specific patterns of self-association. In fact, the synthesis of complex pyrimidinones can be easier than that of analogous pyridinones, because a variety of appropriate pyrimidine precursors are readily and economically available and special methods developed for

(13) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
(14) For related reactions, see: Sakamoto, T.; Shiraiwa, M.; Kondo, Y.; Yamanaka, H. *Synthesis* **1983**, 312.
(15) Isbecque, D.; Promel, R.; Quinaux, R. C.; Martin, R. H. *Helv. Chim. Acta* **1959**, *42*, 1317.
(16) For related observations, see: Plé, N.; Turck, A.; Bardin, F.; Queguiner, G. *J. Heterocycl. Chem.* **1992**, *29*, 467. Radinov, R.; Chanev, C.; Haimova, M. *J. Org. Chem.* **1991**, *56*, 4793. Harden, D. B.; Mokrosz, M. J.; Strekowski, L. *J. Org. Chem.* **1988**, *53*, 4137.
(17) Su, D.; Menger, F. M. *Tetrahedron Lett.* **1997**, *38*, 1485. The detailed procedure for the synthesis of tetrakis(4-iodophenyl)methane that appears in this paper was actually taken from the Ph.D. thesis of D. Su, Université de Montréal, 1995.

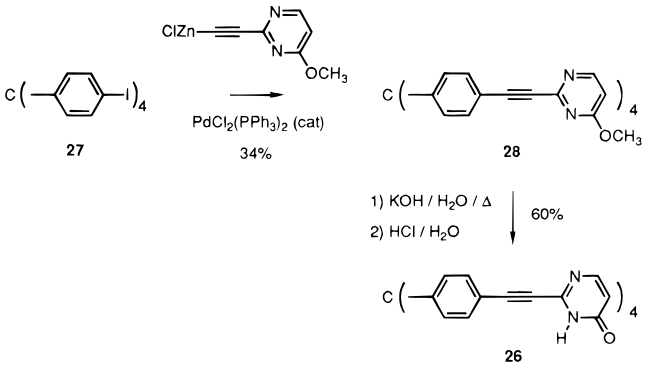
Scheme 3



Scheme 4



Scheme 5



the synthesis of pyrimidines, such as those that yield dipyrimidinone **21**, cannot be used to make the corresponding pyridines.

Unfortunately, our results also suggest that compounds with multiple 4-pyrimidinone groups will be difficult to use in molecular tectonics for two reasons: (1) they tend to have very low solubilities in organic solvents, and (2) they appear to be particularly hard to crystallize. Despite determined effort, we were unable to grow single crystals of complex 4-pyrimidinones **12**, **16**, **21**, and **26** suitable for structural studies using X-ray diffraction, even though we have successfully used X-ray crystallography to solve the structures of many closely analogous 2-pyridinones. Our repeated failures to crystallize the corresponding 4-pyrimidinones undoubtedly have complex origins. However, one likely cause is the simultaneous presence of numerous tautomers, all capable of strong intermolecular association, which may disfavor the sustained growth of a single crystalline phase. Compounds with multiple 2-pyrimidinone groups that are symmetrically substituted will have smaller numbers of tautomers and may therefore prove to be more useful in molecular tectonics.

Experimental Section

Tetrahydrofuran (THF) was dried by distillation from the sodium ketyl of benzophenone, triethylamine and diisopropylamine were dried over KOH, and CH_3OH was dried by treating it with Mg and a catalytic amount of I_2. $PdCl_2(PPh_3)_2$ was prepared in the normal way.[18] All other reagents were commercial products that were used without further purification. Flash chromatography was performed in the usual manner.[19]

X-ray Crystallographic Study of 4(3*H*)-Pyrimidinone (1).[20] Crystals of 4(3*H*)-pyrimidinone (**1**) belong to the monoclinic space group $P2_1$ with $a = 3.7166(3)$ Å, $b = 19.8584(13)$ Å, $c = 11.6816(3)$ Å, $\beta = 94.272(4)°$, $V = 859.77(9)$ Å^3, $D_{calcd} = 1.485$ g cm^{-3}, and $Z = 8$. Data were collected at 295 K, and the structure was refined to $R_f = 0.053$, $R_w = 0.056$ for 1408 reflections with $I > 1.96\sigma(I)$.

5-Iodo-4-methoxypyrimidine (7). A stirred solution of 4-chloro-5-iodopyrimidine (0.839 g, 3.49 mmol)[10] in CH_3OH (15 mL) was treated with a solution of $NaOCH_3$ (0.80 mL, 25 wt % in CH_3OH, 3.5 mmol), and the resulting mixture was stirred at 25 °C for 24 h. Volatiles were then removed by evaporation under reduced pressure, H_2O (10 mL) was added to the residue, and the mixture was extracted with $CHCl_3$. The extracts were combined and dried, volatiles were removed by evaporation under reduced pressure, and the residue was crystallized from hexane to give 5-iodo-4-methoxypyrimidine (**7**) as analytically pure colorless needles (0.746 g, 3.16 mmol, 91%): mp 88.0−89.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (s, 3H), 8.66 (s, 1H), 8.75 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ

(18) Hartley, F. R. *Organomet. Chem. Rev., Sect. A* **1970**, *6*, 119.
(19) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(20) The authors have deposited X-ray crystallographic data, a description of the structure determination, and tables of atomic coordinates and isotropic thermal parameters, bond lengths and angles, anisotropic thermal parameters, and refined and calculated hydrogen atom coordinates with the Cambridge Crystallographic Data Centre. The data can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

55.0, 79.9, 157.2, 163.7, 167.0. Anal. Calcd for $C_5H_5IN_2O$: C, 25.45; H, 2.14; N, 11.87. Found: C, 25.51; H, 2.11; N, 11.96.

4-Methoxy-5-(phenylethynyl)pyrimidine (8). A stirred solution of 5-iodo-4-methoxypyrimidine (**7**; 2.12 g, 8.98 mmol) in $N(C_2H_5)_3$ (4 mL) was treated with phenylacetylene (1.08 g, 10.6 mmol), $PdCl_2(PPh_3)_2$ (0.145 g, 0.207 mmol), and CuI (0.064 g, 0.34 mmol), and the mixture was heated at reflux for 24 h. The resulting mixture was then cooled, diluted with H_2O, and extracted with CH_2Cl_2. Volatiles were removed from the combined extracts by evaporation under reduced pressure, and the residue was purified by sublimation (65 °C/0.8 Torr) to give 4-methoxy-5-(phenylethynyl)pyrimidine (**8**; 1.27 g, 6.04 mmol, 67%) as a colorless solid. Resublimation provided a purified sample: mp 72.5−75.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (s, 3H), 7.26 (m, 3H), 7.48 (m, 2H), 8.53 (s, 1H), 8.65 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.0, 80.2, 97.0, 106.4, 122.0, 128.0, 128.5, 131.3, 156.2, 158.9, 167.9; MS (FAB, 3-nitrobenzyl alcohol) *m/e* 211. Anal. Calcd for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.33. Found: C, 74.71; H, 4.80; N, 12.83.

4-Methoxy-5-(2-phenylethyl)pyrimidine (9). A suspension prepared by treating 4-methoxy-5-(phenylethynyl)pyrimidine (**8**; 95 mg, 0.45 mmol) in C_2H_5OH (4 mL) with 5% Pd/C (190 mg) was shaken at 25 °C under H_2 (1 atm) for 24 h. The suspension was then filtered, and solvent was removed from the filtrate by evaporation under reduced pressure. This yielded a residue of 4-methoxy-5-(2-phenylethyl)pyrimidine (**9**; 49 mg, 0.23 mmol, 51%) as a colorless oil, which was used without purification in the following step: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.86 (m, 4H), 4.00 (s, 3H), 7.17 (m, 3H), 7.28 (m, 2H), 8.13 (s, 1H), 8.65 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 28.9, 34.5, 53.4, 121.1, 125.8, 128.1, 128.1, 140.6, 155.4, 156.1, 167.2; MS (FAB, 3-nitrobenzyl alcohol) *m/e* 215; HRMS (FAB, 3-nitrobenzyl alcohol) calcd for $C_{13}H_{14}N_2O$ + H *m/e* 215.1184, found 215.1179.

5-(2-Phenylethyl)-4(3*H*)-pyrimidinone (5). A stirred solution of 4-methoxy-5-(2-phenylethyl)pyrimidine (**9**; 155 mg, 0.723 mmol) in aqueous HBr (2.5 mL, 48 wt %) was heated at reflux for 3 h. The mixture was cooled and made basic by adding saturated aqueous Na_2CO_3. The basified mixture was then extracted with $CHCl_3$, the combined extracts were dried, and volatiles were removed by evaporation under reduced pressure. This provided a residue of 5-(2-phenylethyl)-4(3*H*)-pyrimidinone (**5**; 133 mg, 0.664 mmol, 92%) as a colorless solid: mp 169−171 °C; IR (KBr) 3400−2300, 1671, 1652 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80 (t, 2H), 2.93 (t, 2H), 7.19 (m, 3H), 7.27 (m, 2H), 7.76 (s, 1H), 8.12 (s, 1H), 11.6 (bs, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 29.4, 34.0, 126.1, 128.3, 128.4, 128.4, 140.8, 146.8, 152.3, 164.0; MS (FAB, 3-nitrobenzyl alcohol) *m/e* 201; HRMS (FAB, 3-nitrobenzyl alcohol) calcd for $C_{12}H_{12}N_2O$ + H *m/e* 201.1028, found 201.1036.

Vapor-Pressure Osmometric Study of the Self-Association of 5-(2-Phenylethyl)-4(3*H*)-pyrimidinone (5). An Hitachi−Perkin−Elmer Model 115 molecular weight apparatus was used to evaluate the self-association of 5-(2-phenylethyl)-4(3*H*)-pyrimidinone (**5**). The instrument was calibrated at 26 °C by using solutions of benzil in CH_2Cl_2, and the association of pyrimidinone **5** in CH_2Cl_2 at 26 °C was then measured using four standard solutions of concentrations 7.4 $\times$ 10^{-3} *m*, 9.8 $\times$ 10^{-3} *m*, 12 $\times$ 10^{-3} *m*, and 15 $\times$ 10^{-3} *m*.

4-Methoxy-2-[(4-methoxy-5-pyrimidinyl)ethynyl]pyrimidine (14). A stirred solution of 2-ethynyl-4-methoxypyrimidine (**13**; 269 mg, 2.01 mmol)[4] and 5-iodo-4-methoxypyrimidine (**7**; 399 mg, 1.69 mmol) in $N(C_2H_5)_3$ (2 mL) was treated with $PdCl_2(PPh_3)_2$ (40 mg, 0.057 mmol) and CuI (20 mg, 0.11 mmol), and the mixture was heated at reflux for 16 h. The resulting mixture was then cooled, diluted with H_2O, and extracted with $CHCl_3$. Volatiles were removed from the combined extracts by evaporation under reduced pressure, and the residue was purified by flash chromatography (silica, ethyl acetate) to give 4-methoxy-2-[(4-methoxy-5-pyrimidinyl)ethynyl]pyrimidine (**14**; 353 mg, 1.46 mmol, 86%) as a colorless solid, which was further purified by crystallization from acetone/hexane: mp 155.5−156.5 °C; IR (KBr) 2223 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (s, 3H), 4.11 (s, 3H), 6.72 (d, 1H, ^3J = 5.8 Hz), 8.45 (d, 1H, ^3J = 5.8 Hz), 8.73 (s, 1H), 8.78 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.9, 54.4, 77.7, 95.1, 105.1, 107.9, 151.5, 156.9, 157.4, 160.3, 168.7, 169.1; MS (EI) *m/e* 242; HRMS (EI) calcd for $C_{12}H_{10}N_4O_2$ + H *m/e* 243.0882, found 243.0889.

2-[(3,4-Dihydro-4-oxo-5-pyrimidinyl)ethynyl]-4(3*H*)-pyrimidinone (12). A stirred suspension of 4-methoxy-2-[(4-methoxy-5-pyrimidinyl)ethynyl]pyrimidine (**14**; 49 mg, 0.20 mmol) in 1 M aqueous KOH (2 mL) was heated at reflux for 20 min, and the resulting homogeneous solution was then cooled. Acidification with 3 M aqueous HCl caused the precipitation of a colorless solid, which was separated by centrifugation and washed with H_2O, acetone, and CH_2Cl_2. This yielded a pure sample of 2-[(3,4-dihydro-4-oxo-5-pyrimidinyl)ethynyl]-4(3*H*)-pyrimidinone (**12**; 38 mg, 0.18 mmol, 90%): mp 240 °C dec; IR (KBr) 3500−2100, 2234, 1636 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.39 (d, 1H, ^3J = 6.7 Hz), 7.97 (d, 1H, ^3J = 6.7 Hz), 8.34 (s, 1H), 8.36 (s, 1H); MS (EI) *m/e* 214; HRMS (EI) calcd for $C_{10}H_6N_4O_2$ *m/e* 214.0491, found 214.0482.

4-Methoxy-5-[(trimethylsilyl)ethynyl]pyrimidine (17). A stirred solution of 5-iodo-4-methoxypyrimidine (**7**; 1.02 g, 4.32 mmol) in $N(C_2H_5)_3$ (5 mL) was treated with $PdCl_2(PPh_3)_2$ (0.084 g, 0.12 mmol), CuI (0.052 g, 0.27 mmol), and (trimethylsilyl)acetylene (0.51 g, 5.2 mmol). The resulting mixture was heated at 60 °C for 18 h, and volatiles were then removed by evaporation under reduced pressure. The residue was dissolved in a mixture of CH_2Cl_2 (25 mL) and ethyl acetate (100 mL), the solution was passed through a short column of silica, and volatiles were removed from the eluent by evaporation under reduced pressure. Kugelrohr distillation (80 °C/0.03 Torr) of the residue gave 4-methoxy-5-[(trimethylsilyl)ethynyl]-pyrimidine (**17**; 0.853 g, 4.13 mmol, 96%) as a pale yellow liquid, which was used immediately in the following step: IR (liquid film) 2158 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.19 (s, 9H), 3.97 (s, 3H), 8.46 (s, 1H), 8.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.7, 53.9, 95.5, 103.1, 106.1, 156.3, 159.6, 168.1.

5-Ethynyl-4-methoxypyrimidine (18). A solution of 4-methoxy-5-[(trimethylsilyl)ethynyl]pyrimidine (**17**; 1.07 g, 5.19 mmol) in THF (6 mL) was treated with CH_3COOH (0.36 g, 6.0 mmol) and with a solution of tetrabutylammonium fluoride (6.0 mL, 1.0 M in THF, 6.0 mmol), and the mixture was stirred at 25 °C for 30 min. The resulting mixture was then diluted with H_2O and extracted with CH_2Cl_2. Volatiles were removed from the combined extracts by evaporation under reduced pressure, and the residue was purified by flash chromatography (silica, hexane (85%)/ethyl acetate (15%)). Further purification was achieved by sublimation (25 °C/0.2 Torr), which provided 5-ethynyl-4-methoxypyrimidine (**18**; 0.483 g, 2.30 mmol, 44%) as an analytically pure colorless solid: mp 55.7−56.4 °C; IR (KBr) 3288, 3193 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.47 (s, 1H), 4.09 (s, 3H), 8.58 (s, 1H), 8.74 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 54.1, 74.7, 85.4, 105.2, 156.7, 158.8, 168.5. Anal. Calcd for $C_7H_6N_2O$: C, 62.68; H, 4.51. Found: C, 62.34; H, 4.59.

2-[(4-Bromophenyl)ethynyl]-4-methoxypyrimidine (19). A solution of 2-ethynyl-4-methoxypyrimidine (**13**; 0.967 g, 7.21 mmol)[4] and 1-bromo-4-iodobenzene (2.04 g, 7.21 mmol) in $N(C_2H_5)_3$ (20 mL) was treated with $PdCl_2(PPh_3)_2$ (0.148 mg, 0.211 mmol) and CuI (146 mg, 0.767 mmol), and the resulting mixture was stirred at 25 °C for 24 h. Volatiles were then removed by evaporation under reduced pressure, and the residue was purified by flash chromatography (silica, hexane (80%)/ethyl acetate (20%)) to give 2-[(4-bromophenyl)ethynyl]-4-methoxypyrimidine (**19**; 1.90 g, 6.57 mmol, 91%) as a colorless solid. A purified sample was prepared by recrystallization from hexane/$CHCl_3$: mp 125.5−126.5 °C; IR (KBr) 2222 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (s, 3H), 6.70 (d, 1H, ^3J = 5.9 Hz), 7.52 (m, 4H), 8.42 (d, 1H, ^3J = 5.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.7, 85.2, 88.8, 107.3, 120.0, 123.7, 131.3, 133.5, 151.8, 156.7, 168.8; MS (EI) *m/e* 290, 288. Anal. Calcd for $C_{13}H_9BrN_2O$: C, 54.00; H, 3.14; N, 9.69. Found: C, 54.46; H, 3.07; N, 9.69.

4,4′-Dimethoxy-2,5′-(1,4-phenylenedi-2,1-ethynediyl)-bispyrimidine (20). A solution of 5-ethynyl-4-methoxypyrimidine (**18**; 35.0 mg, 0.261 mmol) in THF (1 mL) was stirred

at −78 °C under dry N_2 and treated dropwise with a solution of butyllithium (104 μL, 2.5 M in hexane, 0.26 mmol). The resulting mixture was kept at −78 °C for 30 min, the temperature was subsequently allowed to rise to 0 °C, and then a solution of $ZnCl_2$ (42.3 mg, 0.310 mmol) in THF (1 mL) was added slowly. After 30 min, 2-[(4-bromophenyl)ethynyl]-4-methoxypyrimidine (**19**; 76.3 mg, 0.264 mmol) and $PdCl_2(PPh_3)_2$ (11.2 mg, 0.0160 mmol) were added, and the mixture was heated at reflux for 20 h. The resulting mixture was cooled, treated with 5% aqueous $NaHCO_3$, and extracted with CH_2Cl_2. Volatiles were removed from the combined extracts by evaporation under reduced pressure, and the residue was purified by flash chromatography (silica, hexane (40%)/ethyl acetate (60%)) to give 4,4′-dimethoxy-2,5′-(1,4-phenylenedi-2,1-ethynediyl)bispyrimidine (**20**; 46.4 mg, 0.136 mmol, 52%) as a pale yellow solid: mp 163.1−164.5 °C; IR (KBr) 2220 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.03 (s, 3H), 4.09 (s, 3H), 6.69 (d, 1H, ^3J = 5.9 Hz), 7.55 (d, 2H, ^3J = 8.6 Hz), 7.65 (d, 2H, ^3J = 8.6 Hz), 8.42 (d, 1H, ^3J = 5.9 Hz), 8.60 (s, 1H), 8.72 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 54.0, 54.4, 82.8, 86.1, 89.8, 96.6, 106.4, 107.6, 121.8, 123.4, 131.5, 132.4, 152.1, 156.8, 157.1, 159.3, 168.2, 169.2; MS (EI) *m/e* 342. HRMS (EI) calcd for $C_{20}H_{14}N_4O_2$ *m/e* 342.1117, found 342.1130.

2,5′-(1,4-Phenylenedi-2,1-ethynediyl)bis[4(3*H*)-pyrimidinone] (16). A stirred mixture of 4,4′-dimethoxy-2,5′-(1,4-phenylenedi-2,1-ethynediyl)bispyrimidine (**20**; 35.3 mg, 0.103 mmol) in 1 M aqueous KOH (1.2 mL) and C_2H_5OH (1.5 mL) was heated at reflux for 5 h, and the resulting homogeneous solution was then cooled. Acidification with 3 M aqueous HCl caused the precipitation of a solid, which was separated by centrifugation and washed with H_2O and acetone. This yielded 2,5′-(1,4-phenylenedi-2,1-ethynediyl)bis[4(3*H*)-pyrimidinone] (**16**; 22.9 mg, 0.0729 mmol, 71%) as a pale yellow solid: mp 268 °C dec; IR (KBr) 3600−2300, 2214, 1684 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 6.40 (d, 1H, ^3J = 6.4 Hz), 7.61 (d, 2H, ^3J = 8.5 Hz), 7.69 (d, 2H, ^3J = 8.5 Hz), 7.97 (d, 1H, ^3J = 6.4 Hz), 8.28 (s, 1H), 8.29 (s, 1H), 13.2 (bs, 2H); MS (EI) *m/e* 314; HRMS (EI) calcd for $C_{18}H_{10}N_4O_2$ *m/e* 314.0804, found 314.0800.

4,4′-Dichloro-6,6′-dimethoxy-2,5′-bipyrimidine (23). A solution of diisopropylamine (0.26 g, 2.6 mmol) in THF (1 mL) was stirred at 0 °C under dry N_2 and treated dropwise with a solution of butyllithium (1.2 mL, 2.2 M in hexane, 2.6 mmol). After 30 min, the resulting mixture was cooled to −78 °C and treated dropwise with a solution of 4-chloro-6-methoxypyrimidine (**22**; 0.746 g, 5.16 mmol)[15] in THF (3 mL). After 1h at −78 °C and 1h at −30 °C, the mixture was treated with CH_3COOH (0.16 g, 2.7 mmol). The temperature was then allowed to rise to 25 °C, and a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 1.29 g, 5.68 mmol) in THF (3 mL) was added. After 5 min, the resulting mixture was poured into 1.5 M aqueous NaOH (20 mL), and the product was extracted with CH_2Cl_2. Volatiles were removed from the combined extracts by evaporation under reduced pressure, and the residue was purified by flash chromatography (silica, hexane (85%)/ethyl acetate (15%)) to give 4,4′-dichloro-6,6′-dimethoxy-2,5′-bipyrimidine (**23**; 0.148 g, 0.515 mmol, 20%) as a colorless solid. Further purification was achieved by crystallization from hexane: mp 70.5−72.5 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.99 (s, 3H), 4.00 (s, 3H), 6.80 (s, 1H), 8.63 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 54.8, 55.0, 106.6, 118.7, 157.3, 158.4, 160.5, 160.7, 167.7, 170.8; MS (FAB, 3-nitrobenzyl alcohol) *m/e* 289, 287; HRMS (FAB, 3-nitrobenzyl alcohol) calcd for $C_{10}H_8{}^{35}Cl_2N_4O_2$ *m/e* 287.0102, found 287.0095.

4,4′-Dimethoxy-2,5′-bipyrimidine (24). A solution of 4,4′-dichloro-6,6′-dimethoxy-2,5′-bipyrimidine (**23**; 160 mg, 0.557 mmol) in CH_3OH (2 mL) was treated with 10% Pd/C (163 mg) and MgO (326 mg), and the resulting suspension was stirred at 25 °C under H_2 (1 atm) for 72 h. The mixture was then filtered, and volatiles were removed from the filtrate by evaporation under reduced pressure. Purification of the residue by flash chromatography (silica, ethyl acetate) provided 4,4′-dimethoxy-2,5′-bipyrimidine (**24**; 64.4 mg, 0.295 mmol, 53%) as a colorless solid. Further purification was achieved by crystallization from hexane: mp 113.0−113.5 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 4.05 (s, 3H), 4.12 (s, 3H), 6.71 (d, 1H, ^3J = 5.8 Hz), 8.57 (d, 1H, ^3J = 5.8 Hz), 8.85 (s, 1H), 9.10 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 53.7, 54.3, 106.7, 119.7, 157.2, 158.5, 158.5, 161.3, 166.8, 169.3; MS (FAB, 3-nitrobenzyl alcohol) *m/e* 219; HRMS (FAB, 3-nitrobenzyl alcohol) calcd for $C_{10}H_{10}N_4O_2$ + H *m/e* 219.0882, found 287.0874.

[2,5′-Bipyrimidine]-4,4′(3*H*,3′*H*)-dione (21). A stirred mixture of 4,4′-dimethoxy-2,5′-bipyrimidine (**24**; 18 mg, 0.082 mmol) in 1 M aqueous KOH (3 mL) was heated at reflux for 1 h, and the resulting homogeneous solution was then cooled. Acidification with 2 M aqueous HCl caused the precipitation of a solid, which was separated by centrifugation and washed with H_2O, CH_3OH, and CH_2Cl_2. This yielded [2,5′-bipyrimidine]-4,4′(3*H*,3′*H*)-dione (**21**; 10 mg, 0.053 mmol, 65%) as a colorless solid: mp > 300 °C dec; IR (KBr) 3600−2300, 1655 cm^{-1}; ^1H NMR (400 MHz, CF_3COOD) δ 7.09 (d, 1H, ^3J = 7.0 Hz), 8.51 (d, 1H, ^3J = 7.0 Hz), 9.24 (s, 1H), 9.57 (s, 1H). Because of the very low solubility and volatility of this compound, satisfactory ^{13}C NMR and mass spectra could not be obtained.

2,2′,2″,2‴-[Methanetetrayltetrakis(4,1-phenylene-2,1-ethynediyl)]tetrakis[4-methoxypyrimidine] (28). A solution of 2-ethynyl-4-methoxypyrimidine (**13**; 1.22 g, 9.10 mmol)[4] in THF (25 mL) was stirred at −78 °C under dry N_2 and treated dropwise with a solution of butyllithium (5.7 mL, 1.6 M in hexane, 9.1 mmol). The resulting mixture was kept at −78 °C for 30 min, and then a solution of $ZnCl_2$ (1.49 g, 10.9 mmol) in THF (20 mL) was added slowly. The temperature was subsequently allowed to rise to 0 °C. After 30 min, tetrakis(4-iodophenyl)methane (**27**; 1.25 g, 1.52 mmol)[2e,17] and $PdCl_2(PPh_3)_2$ (0.195 g, 0.278 mmol) were added, and the mixture was heated at reflux for 12 h. The resulting mixture was cooled, and volatiles were removed by evaporation under reduced pressure. The residue was treated with 5% aqueous $NaHCO_3$, and the mixture was extracted with CH_2Cl_2. Volatiles were removed from the combined extracts by evaporation under reduced pressure, and the residue was purified by adsorbing it on a bed of Florisil, washing the bed with CH_2Cl_2, and then desorbing the product with ethyl acetate. This provided 2,2′,2″,2‴-[methanetetrayltetrakis(4,1-phenylene-2,1-ethynediyl)]tetrakis[4-methoxypyrimidine] (**28**; 0.434 g, 0.511 mmol, 34%) as a colorless solid, which was used in the following step without further purification: IR (KBr) 2221 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.02 (s, 12H), 6.67 (d, 4H, ^3J = 5.8 Hz), 7.21 (d, 8H, ^3J = 8.5 Hz), 7.59 (d, 8H, ^3J = 8.5 Hz), 8.41 (d, 4H, ^3J = 5.8 Hz).

2,2′,2″,2‴-[Methanetetrayltetrakis(4,1-phenylene-2,1-ethynediyl)]tetrakis[4(3*H*)-pyrimidinone] (26). A stirred mixture of 2,2′,2″,2‴[methanetetrayltetrakis(4,1-phenylene-2,1-ethynediyl)]tetrakis[4-methoxypyrimidine] (**28**; 120 mg, 0.14 mmol) in 1 M aqueous KOH (3 mL) and dioxane (6 mL) was heated at reflux for 18 h, and the resulting mixture was then cooled and filtered. Acidification of the filtrate with 2 M aqueous HCl caused the precipitation of a solid, which was separated by centrifugation and washed with CH_3OH, CH_2Cl_2, and acetone. This yielded 2,2′,2″,2‴-[methanetetrayltetrakis-(4,1-phenylene-2,1-ethynediyl)]tetrakis[4(3*H*)-pyrimidinone] (**26**; 67 mg, 0.084 mmol, 60%) as a colorless solid: mp 264 °C dec; IR (KBr) 3600−2500, 2221, 1670 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 6.39 (d, 4H, ^3J = 6.4 Hz), 7.30 (d, 8H, ^3J = 8.6 Hz), 7.65 (d, 8H, ^3J = 8.6 Hz), 7.95 (d, 4H, ^3J = 6.4 Hz), 13.2 (bs, 4H). Because of the very low solubility and volatility ofthis compound, satisfactory ^{13}C NMR and mass spectra could not be obtained.

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Supporting Information Available: Tables of atomic coordinates and isotropic thermal parameters, complete bond lengths and angles, anisotropic thermal parameters, hydrogen atom coordinates and thermal parameters, and distances to weighted least-squares planes for the dimer **2** of 4(3*H*)-pyrimidinone and NMR spectra for compounds **5**, **17**, **21**, **26**, and **28** (23 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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