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Ureidopyrimidinones Incorporating a Functionalizable *p*-Aminophenyl Electron-Donating Group at C-6

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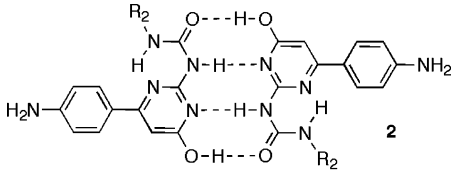
Received October 8, 2004



DADA dimeric array in DMSO

2-Ureido-4-[1*H*]-pyrimidinones have been reported to dimerize via quadruple hydrogen bonding systems with dimerization constants $>10^6$ M^{-1} in $CDCl_3$. The dimerization constant, K_{dim}, is dependent on the solvent as well as the ring-substituents present, where previously alkyl (e.g., R_1 = Me) and aromatic moieties (e.g., $R_1 = p\text{-}NO_2C_6H_4$, $R_1 = C_6H_2(OC_{13}H_{27})_3$) have been incorporated at the C-6 position. To assess the influence of alternative, functionalizable, electron-donating groups on the dimerization motif and tautomeric distribution of isomers, the synthesis of compounds possessing aminophenyl functionality at the C-6 position has been achieved. NMR spectroscopy chemical shift analysis revealed that compound **2** ($R_1 = p\text{-}NH_2C_6H_4$, $R_2 = C_6H_{13}$) existed as the 2-ureido-4-pyrimidinol dimeric DADA array in DMSO-d_6, where a dimerization constant of 46 M^{-1} was determined. This is the first time that a ureidopyrimidinone quadruple hydrogen bonding DADA array has been observed in pure DMSO, a highly polar solvent. The azo-derivative **5** of compound **2** was prepared which also adopted the pyrimidin-4-ol form in DMSO-d_6. Compounds **7**, **10** and **11** were then synthesized containing a more hydrophilic PEG unit in the lateral chain and the tautomeric distributions were determined.

Introduction

The design of supramolecular arrays based on noncovalent interactions, particularly hydrogen bonds, holds significant potential for the synthesis of new materials. The strength, reversibility and directionality of hydrogen bonds has led to widespread use in supramolecular structures.[1] In DNA, the three hydrogen-bonding motifs in base-pairs are well-known between purines and pyrimidines. Synthetic triply hydrogen-bonded arrays have been reported by a number of groups, in particular Zimmerman who has synthesized several acceptor (A) and donor (D) combinations including AAA·DDD arrays with association constants greater than 10^5 M^{-1}.[2] To further enhance the dimerization constant, arrays containing four hydrogen-bonds have also emerged including acetylated triazines,[3] pyrimidines,[4] and ureido naphthyridines.[5,6] Notably, Meijer reported the synthesis of stable dimers of ureidopyrimidinones, readily synthesized from commercially available starting materials.[4,6−8] These could be dimerized in a self-complimentary array of four hydrogen bonds, comprised of two donors (DD) and two acceptors (AA) with a dimerization constant (K_{dim}) for the

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† AWE. Aldermaston, Reading, Berkshire, RG7 4PR, UK.

(1) *Introduction to Hydrogen-Bonding*; Oxford University Press: Oxford, 1997.

(2) Zimmerman, S. C.; Corbin, P. S. *Struct. Bonding* **2000**, *96*, 63−94. Murray, T. J.; Zimmerman, S. C.; *J. Am. Chem. Soc*. **1992**, *114*, 4010−4011. Fenlon, E. E.; Murray, T. J.; Baloga, M. H.; Zimmerman, S. C. *J. Org. Chem*. **1993**, *58*, 6625−6628.

(3) Beijer, F. H.; Sijbesma, R. P.; Vekemans, J. A. J. M.; Meijer, E. W.; Kooijman, H.; Spek, A. L. *J. Org. Chem.* **1996**, *61*, 6371−6380.

(4) Beijer, F. H.; Kooijman, H.; Spek, A. L.; Sijbesma, R. P.; Meijer, E. W. *Angew. Chem., Int. Ed.* **1998**, *37*, 75−78.

(5) Corbin, P. S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9710−9711. Corbin, P. S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2000**, *122*, 3779−3780.

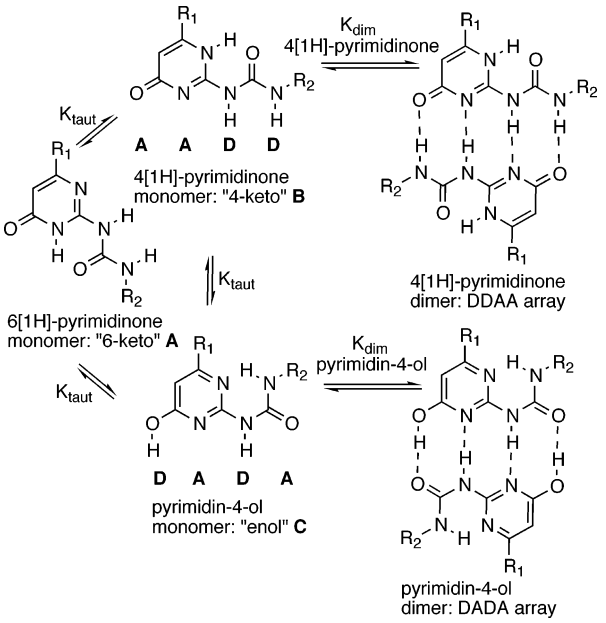
(6) Sijbesma, R. P.; Meijer, E. W. *J. Chem. Soc., Chem. Commun.* **2003**, 5−16.

(7) Beijer, F. H.; Sijbesma, R. P.; Kooijman, H.; Spek, A.; Meijer, E. W. *J. Am. Chem. Soc.* **1998**, *120*, 6761−6769.

(8) Söntjens, S. H. M.; Sijbesma, R. P.; van Genderen, M. H. P.; Meijer, E. W. *J. Am. Chem. Soc.* **2000**, *122*, 7487−7493.

10.1021/jo048223l CCC: $30.25
Published on Web 03/09/2005

SCHEME 1. Three Tautomeric Forms of Ureidopyrimidinones

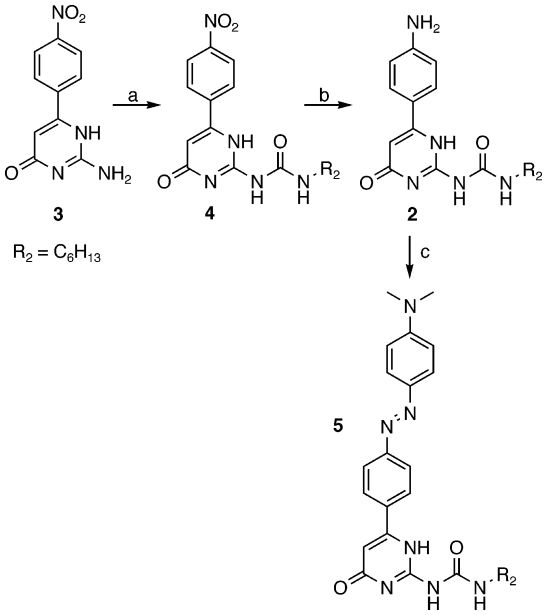


DDAA unit of approximately 10^7 M^{-1} in $CDCl_3$. Functionalization of various materials, using copolymers such as ethylene oxide-propylene oxide (PEO/PPO) with the 2-ureido-4[1*H*]-pyrimidinone building block, was then used to generate supramolecular polymers with a high degree of polymerization and interesting thermal and mechanical properties.[9−11]

Although the synthetic accessibility and strong hydrogen bonding arrays generated highlights the advantages of using ureidopyrimidinones, a less attractive but important feature is the presence of up to three tautomeric forms in solution (Scheme 1).[6]

Depending on the solvent and concentration used as well as the substituents (R_1 and R_2) these three forms are in equilibrium. In the polar aprotic solvent DMSO the ureidopyrimidinones were reported to exist in the 6[1*H*]-pyrimidinone monomeric form **A** (6-keto), whereas in less polar solvents, such as $CDCl_3$ or toluene, as a mixture of the 4[1*H*]-pyrimidinone form **B** (4-keto) and pyrimidin-4-ol **C** (enol) that can both dimerize via a DDAA and DADA array, respectively.[6−8] The DADA array is less stable than the DDAA array due to repulsive secondary interactions; however, high dimerization constants were still observed.[7] Investigations into the effect of the substituent at the 6-position (R_1) revealed that electron-withdrawing groups such as *p*-nitrophenyl- or trifluoro- (and $R_2 = n\text{-}C_{18}H_{37}$, $n\text{-}C_4H_9$) favored the pyrimidin-4-ol form **C** in chloroform as well as in toluene, but the monomeric tautomer **A** in DMSO-d_6.[7] However, when R_1 was the aryl electron donating moiety $C_6H_2\text{-}(OC_{13}H_{27})_3$ (and $R_2 = n\text{-}C_4H_9$), the 4[1*H*]-pyrimidinone **B** predominated (87:13 **B/C**) in $CDCl_3$. The presence of alkyl groups at R_1 (e.g., Me and $R_2 = n\text{-}C_4H_9$) led to an even stronger preference for tautomer **B** (>99%) in $CDCl_3$ and for this reason has been the substituent selected for the synthesis of most self-assembled materials.[9]

SCHEME 2. Synthesis of Novel Ureidopyrimidinones Containing a *p*-$NH_2C_6H_4$ or Azo Electron-Donating Group at the C-6 Position[a]



[a] Reagents and conditions: (a) $C_6H_{13}NCO$, pyridine, reflux 18 h, 88%; (b) $SnCl_2$, HCl, EtOH, reflux 1 h, 55%; (c) $NaNO_2$, $C_6H_5NMe_2$, 20%.

The DADA and DDAA templates have numerous applications in materials chemistry, including use as reversible polymers that respond to changes in temperature or solvent and enhance processability.[12] In addition, a functionalizable group present in the motif can lead to enhanced structural diversity. Our aim was therefore to synthesize ureidopyrimidinones with a functionalizable group and we selected an aryl electron-donating group at the C-6 position with the expectation that from previous work this might lead to the generation of a DDAA dimeric array. Herein we describe synthetic approaches to ureidopyrimidinones possessing *p*-aminophenyl groups at C-6, and an alkyl or hydrophilic side chain at R_2, as well as an azo-derivative. Studies investigating the tautomeric distributions of the compounds prepared are also presented.

Results and Discussion

The synthesis of 6-(*p*-aminophenyl)isocytosine **2** was performed as shown in Scheme 2 via the nitro derivative. Products are represented in the 4[1*H*]-pyrimidinone form. Ethyl *p*-nitrobenzoyl acetate was reacted with guanidinium carbonate to give the 6-substituted isocytosine **3** as previously reported.[7] Subsequent coupling with hexyl isocyanate gave **4** in 88% yield.[7] Reduction of the nitro group in **4** was initially attempted under hydrogenation conditions, but no reaction was observed, probably due to the low solubility of **4** in the reaction solvent. Alternatively, the prior reduction of ethyl *p*-nitrobenzoyl

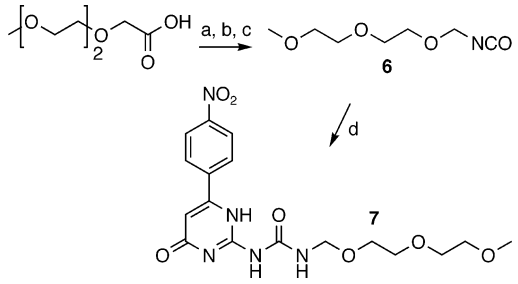
(9) Sijbesma, R. P.; Beijer, F. H.; Brunsveld, L.; Folmer, B. J. B.; Hirschberg, J. H. K. K.; Lange, R. F. M.; Lowe, J. K. L.; Meijer, E. W. *Science* **1997**, *278*, 1601−1604.

(10) Lange, R. F. M.; van Gurp, M.; Meijer, E. W. *J. Polymer Sci: Part A* **1999**, *37*, 3657−3670.

(11) Bosman, A. W.; Brunsveld, L.; Folmer, B. J. B.; Sijbesma, R. P.; Meijer, E. W. *Macromol. Symp.* **2003**, *201*, 143−154.

(12) Bosman, A. W.; Sijbesma, R. P.; Meijer, E. W. *Materials Today* **2004**, 34−40.

SCHEME 3. Synthesis of Novel Ureidopyrimidinone Incorporating the PEG Isocyanate 6[a]



[a] Reagents and conditions: (a) $SOCl_2$; (b) NaN_3, acetone; (c) toluene, heat; (d) **3**, pyridine, 28%.

acetate was considered, however when this was attempted reduction of the β-keto moiety was also observed. Therefore, other reduction methods for **4** were investigated and the use of tin (II) chloride in acidified ethanol[13] successfully gave **2** in 54% isolated yield. The synthesis of a derivative of **2**, containing an azo moiety as an alternative electron-donating group, was then carried out.

Formation of the azo derivative **5** was achieved reacting **2** with sodium nitrite and *N*,*N*-dimethylaminobenzene. Unfortunately, compound **2** had low solubility in the reaction solvent, and the isolated yield of compound **5** was 20%.

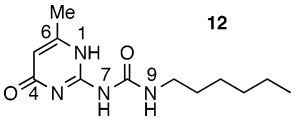
The solubilities of compounds **2** and **5** were low in a range of solvents. Therefore the introduction of a hydrophilic side chain at R_2 was investigated to enhance solubilities and assess the effect of a hydrophobic versus hydrophilic side chain at R_2 on the tautomeric distribution. The incorporation of defined PEG groups via the use of an alternative isocyanate moiety was initially explored.

There are few reports describing the synthesis of PEG-isocyanates despite the utility of such compounds as linkers in chemical biology applications. However, Strazewski et al. have reported the preparation of PEG-diisocyanates in five steps from the alcohol, using triphosgene in the final step.[14] We investigated a more direct route for the synthesis of the novel isocyanate **6**, commencing from 2-[2-(2-methoxyethoxy)ethoxy]ethanoic acid (Scheme 3). Formation of the acid azide, via the acid chloride, and conversion to the isocyanate using the Curtius rearrangement gave **6** which was directly reacted with 6-(*p*-nitrophenyl)isocytosine **3** to give **7** in 28% yield.

Unfortunately, attempts to reduce the nitro-group in **7** under acidic conditions led to cleavage of the PEG group, presumably due to the close proximity of the urea and PEG oxygen moiety. Therefore, an alternative novel isocyanate was prepared incorporating a benzyl spacer adjacent to the urea, which would be more stable to the acidic reducing conditions required (Scheme 4).

Reaction of methyl-4-hydroxyphenylethanoate with 1-(2-bromoethoxy)-2-(2-methoxyethoxy)ethane[15] and potassium carbonate in acetonitrile gave **8** in 60% yield. Hydrolysis of the ester, formation of the acid chloride, then acid azide under aqueous conditions and rearrangement, gave the isocyanate **9**. Reaction with 6-(*p*-nitrophenyl)isocytosine **3** gave **10** in 81% yield. Reduction to the corresponding amine **11** was successfully achieved again using tin (II) chloride in acidified ethanol,[13] with retention of the PEG chain, in 63% yield. Compound **11** had improved solubility in chloroform compared to **2** and **5**. Attempts to convert the amine **11** into the corresponding azo derivative led to formation of an inseparable mixture of compounds.

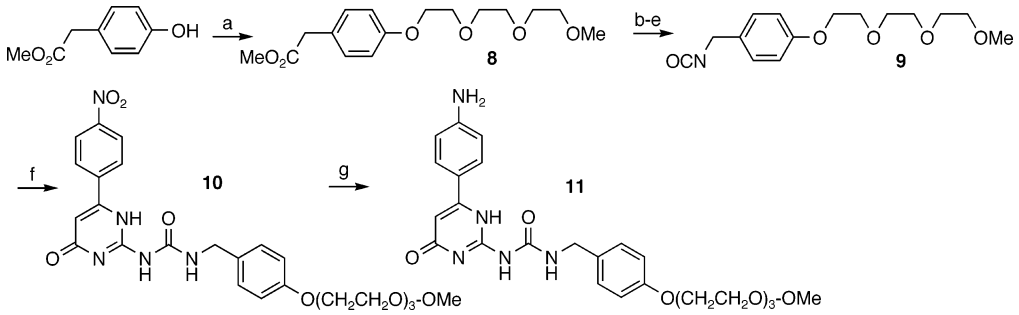
Initial tautomeric studies were carried out on the amine **2** (R_1 = *p*-$NH_2C_6H_4$, R_2 = C_6H_{13}) together with **4** (R_1 = *p*-$NO_2C_6H_4$, R_2 = C_6H_{13}) and **12** (R_1 = Me, R_2 = C_6H_{13}) as controls, since studies have been reported on closely related analogues of the later two pyrimidinones.[7,16]



The solubility of **2** was poor in $CDCl_3$, and only trace signals were observed. Nevertheless, ^1H chemical shifts were measured for a very dilute solution at 55 °C and key signals which indicate the tautomer adopted in $CDCl_3$ are given in Table 1.

From the comparison of these shifts with those reported by Meijer et al.[7] it is clear that **2** exists as the dimeric DDAA tautomer **B** in $CDCl_3$. For a more detailed NMR study, DMSO-d_6 was used as an alternative solvent. This solvent is expected to strongly interfere with the hydrogen bonds of ureidopyrimidinone dimers, but nevertheless it provides us with additional means of assessing the strength and nature of the hydrogen bonding, and indeed, whether a C-6 functionalized ureidopyrimidinones can be identified that would exist as a quadruple hydrogen bonded dimer even in a DMSO solution. The ^1H NMR spectroscopic data for the H-bonding protons (1-H, 7-H, 9-H) as well as for the vinylic

SCHEME 4. Synthesis of Novel Ureidopyrimidinones Incorporating the PEG Isocyanate 9[a]



[a] Reagents and conditions: (a) $Br(CH_2CH_2O)_3OMe$, K_2CO_3, MeCN, reflux 2 d, 60%; (b) NaOH 1 N, MeOH, reflux, 70%; (c) $SOCl_2$, 100%; (d) NaN_3, acetone; (e) toluene, heat; (f) **3**, pyridine, 81%; (g) $SnCl_2$, HCl, EtOH, reflux 1 h, 63%.

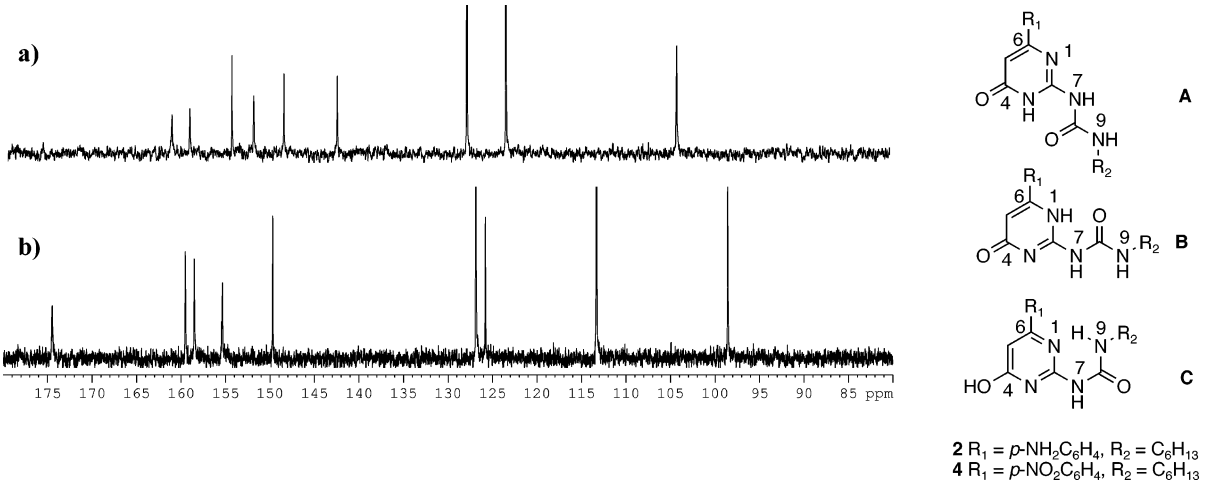


FIGURE 1. ^{13}C NMR spectra for (a) $R_1 = p$-$PhNO_2$ (**4**) and (b) $R_1 = p$-$PhNH_2$ (**2**).

TABLE 1. ^1H NMR Chemical Shifts (δ/ppm) of 2 in $CDCl_3$ at 55 °C and 2 and 4 in DMSO-d_6 at 25 °C

proton[a]	**2** ($CDCl_3$)	**2** (1.8 mM DMSO-d_6)	**2** (25 mM DMSO-d_6)	**2** (saturated DMSO-d_6)	**4** (saturated DMSO-d_6)
1-H (NH)	13.72				
3-H (NH in **A**)					12.05
5-H	6.22	5.74	5.83	5.88	6.66
7-H (NH)	12.00	7.39	7.78	8.01	10.04
9-H (NH)	10.17	10.33	10.19	10.13	7.38

[a] Chemical shifts of protons that shift significantly, depending on the tautomer present, are included. For comparison, ^1H NMR chemical shifts of **4** in DMSO-d_6 are also shown.

proton (5-H) in **2**, **4**, and **12** were assessed. Notably, the ^1H NMR spectra were very similar for compounds **4** and **12**, but compound **2** gave rise to significantly different chemical shifts, suggesting a different tautomeric form may be present. Meijer et al. have reported that analogues of **4** and **12**, where $R_1 = p$-$NO_2C_6H_4$, $R_2 = C_{18}H_{37}$ and R_1 = Me, $R_2 = C_4H_9$, existed in DMSO-d_6 as the monomeric 6-keto form **A**.[7] Comparison of the chemical shift data suggested that **4** and **12** indeed adopted the monomeric tautomeric form **A** in DMSO-d_6, but that **2** interestingly existed as tautomers **B** or **C**.

^{13}C NMR spectral analysis of **2**, **4**, and **12** also highlighted key differences in chemical shifts, and the region 80−180 ppm for compounds **4** and **2** is shown in Figure 1. It has been reported that the vinylic carbon at C-5 has a specific chemical shift of ∼104 ppm in tautomer **A** and 106 ppm in tautomer **B**, but for the enol form **C** an upfield shift is observed due to the aromatic ring.[7] The chemical shift of C-5 in **2** was observed at 98.6 ppm, suggesting that the pyrimidin-4-ol DADA **C** was present. Similarly C-4 is normally observed at ∼161 ppm in the keto form **A**, but for **2** was observed at 174.5 ppm, supporting the existence of a dimeric form in DMSO.

Since the number of protonated nitrogens in the enol form **C** is different from that in tautomers **A** and **B**, we use dipolar-dephased ^{15}N CPMAS experiments with **2** to identify the tautomeric form present in the solid-state.[17] Two tertiary N signals were observed at −164.5 and −178.5 ppm, attributable to N-1 and N-3, respectively. Resonances around −250 ppm are characteristic for secondary amide signals and corresponded to N-7 and N-9 at −260.4 and −280.5 ppm.[16] The primary amine was observed at −324.9 ppm. Comparison of the ^{13}C MAS spectrum of **2** with the ^{13}C NMR data in DMSO-d_6, showed that there were no significant differences in the chemical shifts confirming that the dimeric enolic form **C** was present in both cases. For example, C-5 and C-6 were observed at 98.6 ppm and 159.5 in DMSO-d_6 and 98.3 and 159.3 by solid-state NMR.

Selective NOE measurements were performed for **2** using an excitation sculpting technique, which allows detection of transient NOEs.[18] On selective inversion of the signal due to the aromatic ortho protons on the *p*-aminophenyl ring, negative enhancements of −2% for proton 9-H, −9% for the meta protons on the *p*-aminophenyl ring, and −6% for 5-H were measured. Considering the high viscosity of the solvent used and well-established relationship between the molecular weight (viz. motional correlation times) and sign of the NOE, the negative sign of the enhancements observed for **2** suggested a dimeric array was present.[19] By comparison, in selective NOE experiments of the related nitro-derivative **4** which is in the monomeric 6-keto form **A**, all enhancements were positive.

From previous results reported by Meijer et al. and our data presented here, it follows that at ambient temper-

(13) Bellamy, F. D.; Ou, K. *Tetrahedron Lett.* **1984**, *25*, 839−842.
(14) Gunzenhauser, S.; Biala, E.; Strazewski, P. *Tetrahedron Lett.* **1998**, *39*, 6277−6280.
(15) Brockmann, T. W.; Tout, J. M. *J. Am. Chem. Soc.* **1995**, *117*, 4437−4447.
(16) Sontjens, S. H. M.; van Genderen, M. H. P.; Sijbesma, R. P. *J. Org. Chem.* **2003**, *68*, 9070−9075.
(17) Opella, S. J.; Frey, M. H. *J. Am. Chem. Soc.* **1979**, *101*, 5854−5856.
(18) Stott, K.; Stonehouse, J.; Keeler, J.; Hwang, T. L.; Shaka, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 4199−4200.
(19) Neuhaus, D.; Williamson, M. P. *The Nuclear Overhauser effect in Structural and Conformational Analysis*, 2nd ed.; Wiley-VCH: New York, 2000.

atures the dimerization process is fast, whereas the tautomeric equilibrium between dimers is slow on the NMR time scale. Hence, whenever two or more tautomeric dimers coexist in a given solvent, different sets of peaks are observed for each tautomer and the relative population of each form can be determined by integration. In the case of fast dimerization, however, only one set of peaks is observed and the measured chemical shifts (either ^{1}H or ^{13}C) reflect exchange averaged values: these are intermediate between those for the monomer and dimer and their position is determined by the monomer/dimer population ratio. As the extent of dimerization is concentration dependent, variable concentration measurements of either chemical shifts or diffusion coefficients can be used to derive a number of parameters, such as chemical shifts or diffusion coefficients for boundary forms, or relative populations of both forms. Details of the relevant techniques for the nonlinear analysis of variable concentration data can be found in a recent review by Fielding.[20] Here we have used diffusion NMR for dimerization constant measurement, since the diffusion coefficient is molecular weight dependent. However, diffusion coefficients cannot be used for distinguishing different tautomeric forms since, for example, the monomeric tautomers **A**, **B** and **C** of a given ureidopyrimidinone are expected to have similar diffusion rates. Thus, the concentration dependence of ^{1}H chemical shifts has been used when identification of the tautomer involved in the dimerization is of interest.

In particular, the above comparison of solid-state and solution NMR data revealed that compound **2** is predominantly the dimeric tautomer **C** in concentrated solutions of DMSO-d_6. However, dilution experiments with **2** in DMSO-d_6 indicated a strong dependence between concentration and chemical shift for 7-H, consistent with a hydrogen bonded array, since an increase in population of the dimers occurs at higher concentrations. Notably, experiments revealed an upfield shift for 7-H: a signal at 8.01 ppm in a saturated solution; 7.78 ppm at 25 mM, and 7.39 ppm at 1.8 mM (Table 1). Conversely, the chemical shift of 9-H was unaffected at approximately 10.2 ppm, consistent with the presence of tautomer **C** where there is an intramolecular hydrogen bond. Thus it is clear that there is a dimer−monomer equilibrium and that the population of dimer decreases on dilution.

The upfield shift for 7-H on dilution is also in favor of monomeric enol **C**. To further establish the tautomeric state of the monomeric form in DMSO-d_6 the chemical shift changes of the vinylic proton (5-H) were assessed. The C−H protons are preferable in this regard, as N−H protons could be affected by a possible intermolecular proton exchange. The chemical shift of 5-H in tautomer **A** of the nitro derivative **4** is 6.67 ppm, which is significantly higher than 5.88 ppm measured for the saturated solution of **2**. Hence, if the monomeric form in the dimerization equilibrium were tautomer **A**, then an increase of the vinylic proton shift would be expected on dilution. From our measurements, the chemical shift of 5-H slightly decreases (Table 1). This suggests that both dimeric and monomeric forms exist as enols (tautomer **C**). The evidence based on the changes of proton shifts was further supported by $^1J_{CH}$ couplings for C-5, which were measured from the ^{13}C satellites in ^{1}H spectra. In particular, from the analysis of a number of ureidopyrimidinones, we have found two distinct values of $^1J_{CH}$ in keto and enol forms: 160 Hz in tautomer **C** and 170 Hz in tautomers **A** and **B**. The values measured for saturated, 25 mM and 1.8 mM concentrations were 160.9, 160.2 and 159.5 (±0.3) Hz. By comparison, $^1J_{CH}$ was 169.6 Hz for tautomer **A** of **4** in DMSO-d_6. Based on these results, we consider a simple two-site mono-enol/dimer-enol exchange for **2** in DMSO-d_6, rather than a possible three-site equilibrium which also includes the monomeric form **A**.

Diffusion experiments were then performed on compounds **2**, **4**, and **12** in DMSO-d_6, as previously described.[21] As expected, no change in diffusion was observed for solutions of **4** and **12** as they adopt the monomeric tautomer **A**.[7] With compound **2**, the results were in accordance with the presence of the DADA dimer, since a change of diffusion was observed upon decreasing the concentration of the solution, suggesting the presence of dimeric species in solution in equilibrium with monomers. The concentration of **2** in DMSO was varied from 1.8 to 25 mM at 25 °C, and overall seven different concentrations were studied. From the analysis of diffusion experiments using the nonlinear least-squares method,[20,22,23] the diffusion coefficients for pure dimer and monomer were derived, which then were used to calculate the ratio of dimer/monomer in DMSO-d_6: 13:87 at 1.8 mM, 54:46 at 25 mM and 95:5 in saturated solution. The relative error in these % contents was estimated to be ±10%. Calculations using the nonlinear least-squares method[22,23] lead to a dimerization constant close to 46 M^{-1} for compound **2**, the low value reflecting the high polarity of DMSO which decreases the strength of hydrogen-bonding in the DADA motif. However, unlike other ureidopyrimidinones studied both in this work and by Meijer et al,[7,8] the high polarity of DMSO is not sufficient to completely dissociate the quadruple hydrogen bonding. Such high stability for the DADA dimer may be explained by the fact that the $-C_6H_4NH_2$ substituent at C-6 significantly stabilizes the enolic tautomer **C**, which then dimerizes on increasing concentration. In the case of other ureidopyrimidinones with different substituents at C-6 such stabilization is absent and monomeric 6[1H]-pyrimidinone (tautomer **A**) is observed.

Meijer et al. have reported that pyrimidinones possessing electron-withdrawing groups at C-6 favor the pyrimidin-4-ol form **C** in $CDCl_3$ and monomer **A** in DMSO-d_6, while alkyl or ether electron-donating groups adopt the DDAA array predominantly in $CDCl_3$ and again the monomer **A** in DMSO-d_6.[7] Interestingly we have determined that the amine derivative **2** has led for the first time to a DADA dimeric array in DMSO suggesting an enhanced dimerization constant for this tautomeric form in DMSO.

We also synthesized as outlined above a derivative of **2** with an electron-donating group, compound **5**, and

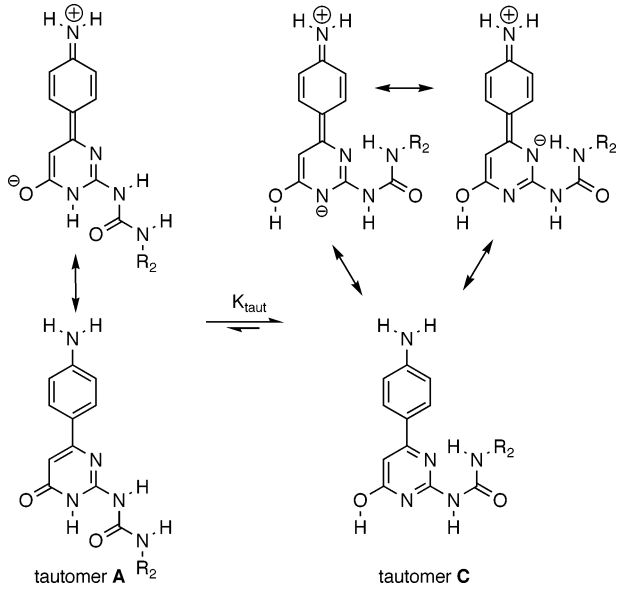
(20) Fielding, L. *Tetrahedron* **2000**, *56*, 6151−6170.

(21) Atkinson, C. E.; Aliev, A. E.; Motherwell, W. B. *Chem. Eur. J.* **2003**, *9*, 1714−1723.

(22) Carcanague, D. R.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 769−771.

(23) Peterson, B. R.; Wallimann, P.; Carcanague, D. R.; Diederich, F. *Tetrahedron* **1995**, *51*, 401−421.

SCHEME 5. Tautomerism of A and C



analogues with hydrophilic side chains. Analysis of the azo compound **5** by NMR spectroscopy indicated, from chemical shift data, that in DMSO-d_6 the pyrimidinol tautomer **C** was also exclusively present. By analogy with **2**, the low-frequency shift of 5-H on dilution (from 6.13 ppm at 35 mM to 6.05 ppm at 5 mM) indicated a fast mono-enol/dimer-enol exchange, but no tautomeric equilibrium either for mono- or dimeric enol. Thus, the tautodimeric behavior of **5** was similar to that of **2**.

The *p*-nitrophenyl derivatives **7** and **10** were not soluble in chloroform, and were analyzed by NMR in DMSO-d_6. Both compounds adopted the monomeric tautomer **A**, which was consistent with other reported *p*-nitrophenyl analogues. This also suggested that the presence of a more hydrophilic side chain did not effect the tautomeric distribution of the ureidopyrimidinones.[7] The behavior of **11** in DMSO-d_6 was studied by NMR and comparison of the chemical shift data with **2** indicated that the pyrimidin-4-ol form **C** was present. NMR studies in $CDCl_3$ revealed the existence of a mixture of the 4[1H]-pyrimidinone monomer **B** and pyrimidin-4-ol **C** at (60 ± 5)% and (40 ± 5)% at 298 K; ^{1}H NMR chemical shifts were observed for **B** at 13.7, 12.2 and 10.9 ppm, for 1-H, 7-H and 9-H respectively, with a second set of signals for the pyrimidin-4-ol **C** at 13.2, 11.4 and 10.2 ppm, for 4-H, 7-H and 9-H, respectively.

The presence of the DADA array in DMSO-d_6 for compounds **2**, **5**, **11** and a high proportion (40%) of pyrimidin-4-ol in $CDCl_3$ for compound **11** is extremely interesting, particularly since previous reports have indicated that the presence of an electron donating group at C-6 results in the formation of the DDAA array in high ratios in $CDCl_3$, and the monomeric tautomer **A** in DMSO-d_6. However, DMSO is a strong hydrogen-bonding acceptor and has the capability of forming stabilizing hydrogen bonds with the NH protons of the amine group, and this may enhance formation of the DADA array with compounds **2** and **11**. Other tautomeric systems possessing amines or amides groups have also been reported where solvation in DMSO has resulted in formation of the most polar tautomer.[24,25] Solvation of the amine in DMSO through hydrogen-bonding enhances the polarization of the π-electron density away from the amine nitrogen, thus enhancing the basicity of the oxygen atom and N1 and N3 of the pyrimidinone moiety (as indicated in the zwitterionic mesomeric representations in Scheme 5). The preferred formation of tautomer **C**, rather than **A**, for **2** and **11** may therefore be due to a combination of several factors: higher basicity of the oxygen atom with respect to N1 and N3; a more pronounced aromatic stabilization of the pyrimidin-4-ol with respect to the pyrimidinone moiety, and a favorable intramolecular hydrogen-bond between the urea side chain and N1 (Scheme 5). A similar rational can be invoked with compound **5**, the azo derivative.

Conclusions

Several ureidopyrimidinones have been synthesized possessing electron-donating moieties at R_1. The existence of the dimeric DADA array in DMSO and solid state for compound **2** has been established using NMR experiments. The azo derivative **5** similarly adopted the pyrimidin-4-ol tautomer **C** in DMSO-d_6. The PEG-substituted derivative of **2**, compound **11**, also adopted the pyrimidin-4-ol tautomer **C** in DMSO-d_6, however, in $CDCl_3$, a mixture of the 4[1H]-pyrimidinone monomer **B** and pyrimidin-4-ol **C** was observed, in a ratio of 60:40 at 298 K. Furthermore, the introduction of a more hydrophilic side chain into **2** did not influence the tautomeric distributions generated in DMSO. These results are particularly important for the construction of functionalizable quadruple H-bonding motifs in polar solvents.

Experimental Section

General Methods. Compound **3**, 6-(*p*-nitrophenyl)isocytosine, was prepared as previously reported.[7]

***N*-Hexyl-*N*′-(1,4-dihydro-4-oxo-6-*p*-aminophenyl-2-pyrimidinyl)urea (2)**. Tin(II) chloride (1.88 g, 8.30 mmol) was added to a solution of **4** (0.50 g, 1.39 mmol) in concd HCl (15 mL) and absolute ethanol (7 mL). After stirring the mixture at rt for 15 min, the solution was heated at reflux for 1 h. Upon cooling to rt, the product precipitated out of solution. The product was collected by filtration and washed with 5 N NaOH (5 mL) and water (5 mL) to give **2** as a yellow solid (0.25 g, 55%): mp >300 °C; IR (KBr) 3380, 3196, 2920, 2864, 1677, 1595 cm^{-1}; (pyrimidin-4-ol DADA tautomer **C**) ^{1}H NMR δ (500 MHz; DMSO-d_6) 10.13 (1H, s, NHCON*H*CH$_2$), 8.01 (1H, s, N*H*CONHCH$_2$), 7.51 (2H, d, *J* 8.4 Hz, 2′−H), 6.57 (2H, d, *J* 8.4 Hz, 3′−H), 5.87 (1H, s, 5-H), 5.34 (2H, s, NH$_2$), 3.20 (2H, m, CONHC*H*$_2$), 1.51 (2H, m, NHCH$_2$C*H*$_2$), 1.35 (2H, m, NH(CH$_2$)$_2$C*H*$_2$), 1.28 (4H, m, NH(CH$_2$)$_3$C*H*$_2$C*H*$_2$), 0.85 (3H, m, CH$_3$); ^{13}C NMR δ (125 MHz; DMSO-d_6) 174.5 (C-4), 159.5 (C-6), 158.5 (C-2), 155.4 (NH*C*ONH), 149.7 (C-4′), 126.9 (C-2′), 125.8 (C-1′), 113.3 (C-3′), 98.6 (C-5), 38.8 (CONH*C*H$_2$), 31.1 (NH(CH$_2$)$_3$*C*H$_2$), 29.6 (NHCH$_2$*C*H$_2$), 26.3 (NH(CH$_2$)$_2$*C*H$_2$), 22.1 (NH(CH$_2$)$_4$*C*H$_2$), 13.9 (CH$_3$); ^{13}C CPMAS δ 176.4 (C-4), 159.3 (C-6), 157.2 (NH*C*ONH), 146.5 (C-4′), 130.0 (C-1′), 129.0 (C-2′), 115.0 (C-3′), 98.5 (C-5), 41.7 (CONH*C*H$_2$), 33.1 (NH(CH$_2$)$_3$*C*H$_2$), 28.0 (NHCH$_2$*C*H$_2$), 24.5 (NH(CH$_2$)$_2$*C*H$_2$), 23.9 (NH(CH$_2$)$_4$*C*H$_2$), 16.0 (CH$_3$); ^{15}N CPMAS δ −164.6 (N-3), −178.3 (N-1), −260.3 (N-7), −280.5 (N-9), −324.0 (NH$_2$); *m/z*

(24) Lei, Y. X.; Cerioni, G.; Rappoport, Z. *J. Org. Chem.* **2001**, *66*, 8397−8394.

(25) Sinkkonen, J.; Ovcharenko, V.; Zelenin, K. N.; Bezhan, I. P.; Chakchir, B. A.; Al-Assar, F.; Pihlaja, K. *Eur. J. Org. Chem.* **2002**, 2046−2053.

HRMS calcd for $C_{17}H_{24}O_2N_5$ $(MH)^+$ 330.19299, found 330.19288; *m/z* (ES+) 352 ($[MNa]^+$, 100).

1-{6-[4-(4-Dimethylaminophenylazo)phenyl]-4-oxo-1,4-dihydropyrimidin-2-yl}-3-hexylurea (5). The amino compound **2** (0.10 g, 0.30 mmol) was dissolved in a mixture of acetic acid (2 mL) and concd HCl (0.7 mL). The solution was then cooled to 5 °C. To this was added a solution of sodium nitrite (0.03 g, 0.03 mmol) in water (0.6 mL) at 0 °C, resulting in the formation of a yellow solution. The reaction was stirred for 15 min at 0 °C. A solution of *N,N*-dimethylaniline (0.036 g, 0.30 mol) in acetic acid (0.1 mL) at 0 °C was then added to give a red solution, and the mixture was stirred for 30 min at rt. A saturated sodium acetate solution was then added to the mixture in order to increase the pH close to 6, resulting in the precipitation of the azo compound. Recrystallization from methanol afforded **5** (0.030 g, 20%): (pyrimidin-4-ol DADA tautomer **C**) ^{1}H NMR δ (400 MHz; DMSO-d_6) 10.21 (1H, s, N*H*CONHCH$_2$), 7.96 (2H, d, *J* 7.9 Hz, 2′−H, 6′−H), 7.80 (2H, d, *J* 9.1 Hz, NMe$_2$Ar 2-H 6-H), 7.78 (2H, d, *J* 7.9 Hz, 3′−H, 5′−H), 6.83 (2H, d, *J* 9.1 Hz, NMe$_2$Ar 3-H 5-H), 6.04 (1H, s, 5-H), 3.18 (2H, m, NHC*H*$_2$CH$_2$), 3.06 (6H, s, NMe$_2$), 1.51 (2H, m, NHCH$_2$C*H*$_2$), 1.34 (2H, m, NH(CH$_2$)$_2$C*H*$_2$), 1.26 (4H, m, NH-(CH$_2$)$_3$C*H*$_2$C*H*$_2$), 0.82 (3H, m, CH$_2$C*H*$_3$); ^{13}C NMR δ (75 MHz; DMSO-d_6) 175.5 (C-4), 159.5 (C-6), 158.7 (C-2), 155.8 (NHCONH), 153.0, 152.97, 143.1, 140.1, 127.1, 125.1, 122.2, 112.0, 102.0 (C-5), 39.0 (NHCH$_2$), 30.0, 26.7, 22.4, 14.2 (CH$_2$*C*H$_3$); *m/z* (ES+) 484 ($[MNa]^+$, 100), 461 (MH^+, 30).

1-[2-(2-Methoxyethoxymethyl]-3-(1,4-dihydro-4-oxo-6-*p*-nitrophenyl-2-pyrimidinyl)urea (7). A suspension of 6-(*p*-nitrophenyl)isocytosine **3** (150 mg, 0.645 mmol) and **6** (2.80 mmol) in dry pyridine (10 mL) and DMF (15 mL) was heated at 90 °C for 16 h. The solvent was removed in vacuo and the product purified using flash silica chromatography (chloroform/methanol, 35:1) to give **7** as a solid (32 mg, 28%): ^{1}H NMR (6[1*H*]-pyrimidinone monomeric **A**) δ (300 MHz; DMSO-d_6) 11.92 (1H, s, 3-H), 10.30 (1H, s, N*H*CONHCH$_2$), 8.32 (2H, d, *J* 9.1 Hz, 3′-H), 8.23 (2H, d, *J* 9.1 Hz, 2′-H), 7.86 (1H, br s, CON*H*CH$_2$), 6.72 (1H, s, 5-H), 4.67 (2H, d, *J* 6.6 Hz, NHC*H*$_2$O), 3.48−3.55 (6H, m, CH$_2$O), 3.42 (2H, m, CH$_2$O), 3.21 (3H, s, OCH$_3$); ^{13}C NMR δ (100 MHz; DMSO-d_6) 164.6 (C-4), 155.2 (NH*C*ONH), 148.5 (C-4′), 142.4 (C-1′), 128.1 (C-2′), 123.8 (C-3′), 104.8 (C-5), 74.6 (NH*C*H$_2$O), 71.3, 69.7, 69.6, 67.0, 58.0 (OCH$_3$); *m/z* (ES+) 430 ($[MNa]^+$, 90), 408 (MH^+, 10).

1-(4-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}benzyl)-3-[6-(4-nitrophenyl)-4-oxo-1,4-dihydropyrimidin-2-yl]-urea (10). The isocyanate **9** (3.30 mmol) was added to a solution of the amine **3** (0.255 g, 1.10 mmol) in dried pyridine (10 mL). The mixture was then heated at reflux for 18 h. The product was precipitated by the addition of hexane, and filtration afforded **10** as a colorless solid (0.469 g, 81%): mp 238−240 °C (hexane); IR (KBr) 3216, 3133, 3079, 2931, 2876, 1667, 1613, 1559 cm^{-1}; (6[1*H*]-pyrimidinone tautomer **A**) ^{1}H NMR δ (400 MHz; DMSO-d_6) 11.92 (1H, s, 3-H), 10.07 (1H, s, N*H*CONHCH$_2$), 8.25 (2H, d, *J* 8.8 Hz, 3′-H), 8.13 (2H, d, *J* 8.8 Hz, 2′-H), 7.74 (1H, br s, CON*H*CH$_2$), 7.26 (2H, d, *J* 8.5 Hz, CH$_2$Ar 2-H, 6-H), 6.93 (2H, d, *J* 8.5 Hz, CH$_2$Ar 3-H, 5-H), 6.67 (1H, s, 5-H), 4.31 (2H, d, *J* 5.4 Hz, CONHC*H*$_2$), 4.06 (2H, m, CH$_2$OAr), 3.73 (2H, m, CH$_2$O), 3.56 (2H, m, CH$_2$O), 3.51 (4H, m, 2 × CH$_2$O), 3.42 (2H, m, CH$_2$O), 3.35 (3H, s, OCH$_3$); ^{13}C NMR δ (125 MHz; DMSO-d_6) 161.6 (C-4), 159.1 (C-6), 157.7 (CH$_2$Ar C-4), 154.5 (NHCONH), 152.1 (C-2), 148.4 (C-4′), 142.3 (C-1′), 130.7 (CH$_2$Ar C-1), 128.9 (CH$_2$Ar C-2, C-6), 127.9 (C-2′, C-6′), 123.7 (C-3′, C-5′), 114.5 (CH$_2$Ar C-3, C-5), 104.2 (C-5), 71.3 (CH$_2$OAr), 69.9, 69.8, 69.6, 68.9, 67.1, 58.1 (OCH$_3$), 42.4 (NHCH$_2$Ar); *m/z* HRMS calcd for $C_{25}H_{29}N_5O_8Na$ 550.19083, found 550.19059; *m/z* (+FAB) 550 ($[MNa]^+$, 10).

1-(4-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}benzyl)-3-[6-(4-aminophenyl)-4-oxo-1,4-dihydropyrimidin-2-yl]urea (11). Tin(II) chloride (0.857 g, 3.80 mmol) was added to a solution of **9** (0.334 g, 0.634 mmol) in concd HCl (7.5 mL) and absolute ethanol (3.75 mL). The solution was heated at 90 °C for 2 h. The yellow solution was then poured into ice and the pH adjusted to 8−9 by addition of sodium hydrogen carbonate. The aqueous layer was then extracted with chloroform (5 × 10 mL) and the organic phase washed with saturated sodium chloride solution (10 mL) and dried ($MgSO_4$). The solvents were evaporated in vacuo, and the product was purified using flash silica chromatography (chloroform/methanol, 7:1) to give **11** as an oil (200 mg, 63%): IR (KBr) 3448, 3363, 3219, 2937, 2879, 1693, 1667, 1623, 1600, 1573, 1512 cm^{-1}; (4[1*H*]-pyrimidinone tautomer **B**) ^{1}H NMR δ (500 MHz; $CDCl_3$) 13.66 (1H, s, 1-H), 12.17 (1H, s, N*H*CONHCH$_2$), 10.89 (1H, s, CON*H*CH$_2$), 7.45 (2H, d, *J* 7.3 Hz, CH$_2$Ar 2-H, 6-H), 7.31 (2H, d, *J* 8.2 Hz, 2′−H), 6.87 (2H, d, *J* 7.3 Hz, CH$_2$Ar 3-H, 5-H), 6.73 (2H, d, *J* 8.2 Hz, 3′−H), 6.21 (1H, s, 5-H), 4.46 (2H, s, CONHC*H*$_2$), 4.16−3.44 (12H, m, CH$_2$O), 3.36 (3H, s, OMe); (pyrimidin-4-ol DADA tautomer **C**) ^{1}H NMR δ (400 MHz; $CDCl_3$) 13.24 (1H, s, OH), 11.41 (1H, s, N*H*CONHCH$_2$), 10.19 (1H, s, CON*H*CH$_2$), 7.37 (2H, d, *J* 8.2 Hz, 2′−H), 7.13 (2H, d, *J* 7.4 Hz, CH$_2$Ar 2-H, 6-H), 6.96 (2H, d, *J* 7.4 Hz, CH$_2$-Ar 3-H, 5-H), 6.54 (1H, s, 5-H), 6.35 (2H, d, *J* 8.2 Hz, 3′−H), 4.43 (2H, s, CONHCH$_2$), 4.16−3.44 (12H, m, CH$_2$O), 3.41 (3H, s, OMe); (4[1*H*]-pyrimidinone tautomer **B**) ^{13}C NMR δ (125 MHz; $CDCl_3$) 173.1 (C=O), 157.9 (CH$_2$Ar C-4), 157.0 (NHCONH), 149.7 (C-4′), 131.3 (CH$_2$Ar C-1), 128.7 (CH$_2$Ar C-2, C-6), 127.1 (C-2′, C-6′), 120.0 (C-1′), 115.2 (C-3′, C-5′), 114.6 (CH$_2$Ar C-3, C-5), 101.7 (C-5), 67.4−71.9 (signal overlap), 38.7−60.4 (several signals not assignable to each tautomer); (pyrimidin-4-ol DADA tautomer **C**); ^{13}C NMR δ (100 MHz; DMSO-d_6) 165.5 (COH), 161.0 (C-6), 157.7 (CH$_2$Ar C-4), 154.6 (NHCONH), 153.2 (C-2), 151.0 (C-4′), 131.0 (CH$_2$Ar C-1), 129.0 (CH$_2$Ar C-2, C-6), 127.7 (C-2′, C-6′), 123.2 (C-1′), 114.5 (CH$_2$-Ar C-3, C-5), 113.3 (C-3′, C-5′), 98.0 (C-5), 71.3, 67.0, 69.8, 69.6, 69.0, 67.2, 58.1 (OCH$_3$), 42.6 (NH*C*H$_2$); *m/z* HRMS calcd for $C_{15}H_{22}O_6$ $(MH)^+$ 498.23471, found 498.23376.

Acknowledgment. We thank the AWE for a studentship to V.G.H.L. Dr. B. R. Peterson (Pennsylvania State University) is thanked for providing the Associate program used in this work for the analysis of the concentration-dependent diffusion rates.

Supporting Information Available: Experimental procedures and spectral data for compounds **4**, **6**, **8**, **9**, and **12** and copies of NMR spectra for compounds **2**, **4**, **5**, **7**, **8**, and **10**−**12** (and intermediates). This material is available free of charge via the Internet at http://pubs.acs.org.

JO048223L