Synthesis and Binding Properties of Monomeric and Dimeric Guanine and Cytosine Amine Derivatives

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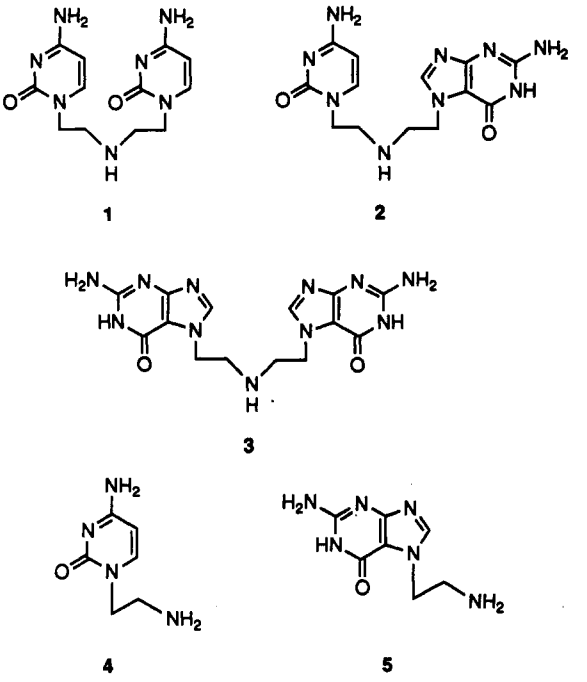
The syntheses of the N-protected forms of the cytosine homodimer **1**, the guanine cytosine heterodimer **2**, and the guanine homodimer **3** are described. Derivatization of these dimers, as well as the protected monomers corresponding to **4** and **5**, with ω-methoxypoly(ethylene glycol)-α-carboxylic acid **26** and subsequent deprotection formed the amides **29**, **31**, **33**, **35**, and **37**. The binding properties of these solubilized compounds in DMSO-d_6 were examined using ^{1}H NMR.

There is considerable current interest in the design of molecular receptors capable of hosting nucleic acid bases (hitherto "nucleobases"), presumably directed toward the eventual design of ligands which will bind to the natural nucleotide or polynucleotide substrates in some useful way.[1-10] An alternative inducement for studying the complexation properties of the nucleobases, however, involves their potential utility as binding components in artificial systems. In this case, recognition processes due to base pairing can be amplified several orders of magnitude by the choice of nonpolar media.[11-14] Such specific interactions may be utilized to impose proximity relationships between chromophores and/or to produce organized molecular aggregates having, e.g., photophysical interest, provided that the base components can be attached covalently.[15]

With this goal in mind the guanine/cytosine base pair in particular attracted our interest. This base pair has found relatively little application in recognition work, apparently as a result of the high insolubility in organic solvents of the cytosine and guanine heterocycles. Nonetheless, this property of the base pair belies its greater potential for association as compared to its corresponding adenine/thymine analogue. The exocyclic amino groups

Chart I



(1) (a) Rebek, J., Jr.; Askew, B.; Ballester, P.; Buhr, C.; Jones, S.; Nemeth, D.; Williams, K. *J. Am. Chem. Soc.* **1987**, *109*, 5033. (b) Rebek, J., Jr.; Askew, B.; Ballester, P.; Buhr, C.; Costero, A.; Jones, S.; Williams, K. *J. Am. Chem. Soc.* **1987**, *109*, 6866. (c) Rebek, J., Jr.; Williams, K.; Parris, K.; Ballester, P.; Jeong, K.-S. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1244. (d) Jeong, K.-S.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 3327. (e) Askew, B.; Ballester, P.; Buhr, C.; Jeong, K.-S.; Jones, S.; Parris, K.; Williams, K.; Benzing, T.; Tjivikua, T.; Wolfe, J.; Rebek, J., Jr. *Science* **1988**, *242*, 262. (f) Askew, B.; Ballester, P.; Buhr, C.; Jeong, K. S.; Jones, S.; Parris, K.; Williams, K.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 1082. (g) Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245. (h) Jeong, K. S.; Tjivikua, T.; Muehldorf, A.; Deslongchamps, G.; Famulok, M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 201. (i) Park, T. K.; Schroeder, J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 5125. (j) Park, T. K.; Schroeder, J.; Rebek, J., Jr. *Tetrahedron* **1991**, *47*, 2507.

(2) (a) Hamilton, A. D.; Van Engen, D. *J. Am. Chem. Soc.* **1987**, *109*, 5035. (b) Hamilton, A. D.; Pant, N.; Muehldorf, A. *Pure Appl. Chem.* **1988**, *60*, 533. (c) Mueldorf, A. V.; Van Engen, D.; Warner, J. C.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 6561. (d) Goswami, S.; Hamilton, A. D.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 3425. (e) Hamilton, A. D.; Muehldorf, A.; Chang, S. K.; Pant, N.; Goswami, S.; Van Engen, D. *J. Incl. Phenom.* **1989**, *7*, 27. (f) Hamilton, A. D.; Little, D. *J. Chem. Soc., Chem. Commun.* **1990**, 297. (g) Hirst, S. C.; Hamilton, A. D. *Tetrahedron Lett.* **1990**, *31*, 2401.

(3) (a) Chen, C.-W.; Whitlock, H. W., Jr. *J. Am.* Chem. *Soc.* **1978**, *100*, 4921. (b) Brienne, M.-J.; Gabard, J.; Lehn, J.-M.; Stibor, I. *J. Chem. Soc., Chem. Commun.* **1989**, 1868. (c) Lehn, J.-M.; Mascal, M.; DeCian, A.; Fischer, J. *J. Chem. Soc., Chem. Commun.* **1990**, 479. (d) Koert, U.; Harding, M. M.; Lehn, J.-M. *Nature* **1990**, *346*, 339. (e) Hosseini, M. W.; Blacker, A. J.; Lehn, J.-M. *J. Am. Chem. Soc.* **1990**, *112*, 3896. (f) Hosseini, M. W.; Lehn, J.-M. *J. Chem. Soc., Chem. Commun.* **1991**, 451.

(4) Constant, J. F.; Fahy, J.; L'homme, J.; Anderson, J. E. *Tetrahedron Lett.* **1987**, *28*, 1777.

(5) Kim, M.; Gokel, G. W. *J. Chem. Soc., Chem. Commun.* **1987**, 1686.

(6) (a) Zimmerman, S. C.; Wu, W. *J. Am. Chem. Soc.* **1989**, *111*, 8054. (b) Zimmerman, S. C.; Zeng, Z. *J. Org. Chem.* **1990**, *55*, 4789. (c) Zimmerman, S. C.; Wu, W.; Zeng, Z. *J. Am. Chem. Soc.* **1991**, *113*, 196.

(7) Adrian, J. C., Jr.; Wilcox, C. S. *J. Am. Chem. Soc.* **1989**, *111*, 8055.

(8) (a) Aoyama, Y.; Mizokami, K.; Toi, H. *Chem. Lett.* **1990**, 651. (b) Aoyama, Y.; Onishi, H.; Tanaka, Y. *Tetrahedron Lett.* **1990**, *31*, 1177. (c) Kurihara, K.; Ohta, K.; Honda, Y.; Kunitake, T. *J. Am. Chem. Soc.* **1991**, *113*, 5077.

(9) (a) Schmidtchen, F. P. *Tetrahedron Lett.* **1989**, *30*, 4493. (b) Galán, A.; Pueyo, E.; Salmerón, A.; De Mendoza, J. *Tetrahedron Lett.* **1991**, *31*, 1827.

(10) (a) Sessler, J. L.; Magda, D. J.; Hugdahl, J. *J. Incl. Phenomen.* **1989**, *7*, 19. (b) Sessler, J. L.; Magda, D. In *Inclusion Phenomena and Molecular Recognition*; Atwood, J. L., Ed.; Plenum Press: New York, 1989; p 17. (c) Furuta, H.; Magda, D.; Sessler, J. L. *J. Am. Chem. Soc.* **1991**, *113*, 978. (d) Furuta, H.; Furuta, K.; Sessler, J. L. *J. Am. Chem. Soc.* **1991**, *113*, 4706. (e) Furuta, H.; Cyr, J. M.; Sessler, J. L. *J. Am. Chem. Soc.* **1991**, *113*, 6677.

(11) Newmark, R. A.; Cantor, C. R. *J. Am. Chem. Soc.* **1968**, *90*, 5010.

(12) Petersen, S. B.; Led, J. J. *J. Am. Chem. Soc.* **1981**, *103*, 5308.

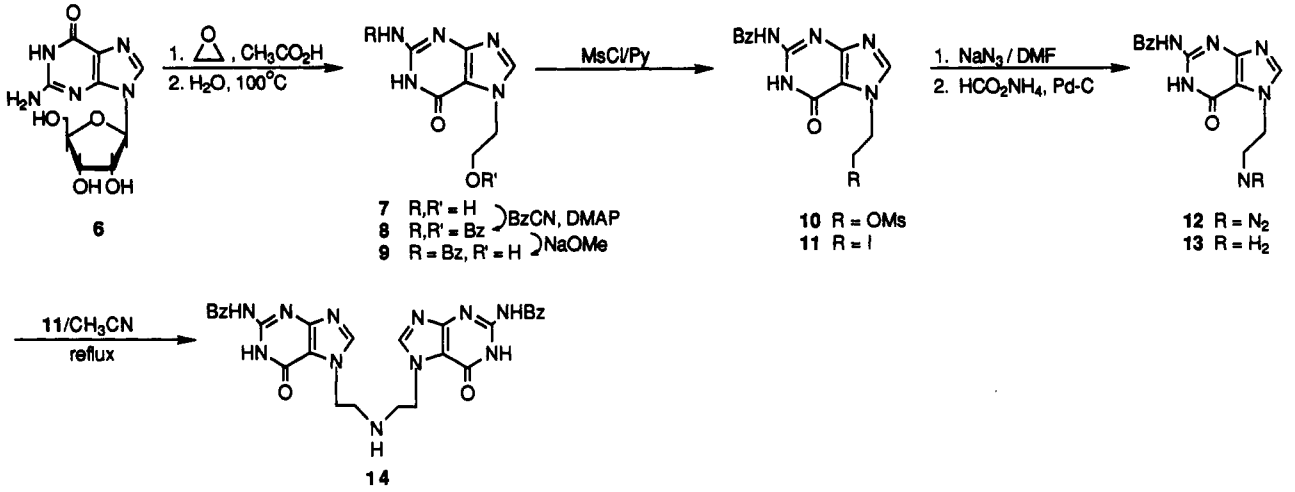
(13) Kyogoku, Y.; Lord, R. C.; Rich, A. *Biochim. Biophys. Acta* **1969**, *179*, 10.

(14) (a) Williams, L. D.; Chawla, B.; Shaw, B. R. *Biopolymers* **1987**, *26*, 591. (b) Williams, N. G.; Williams, L. D.; Shaw, B. R. *J. Am. Chem. Soc.* **1990**, *111*, 7205. (c) Williams, L. D.; Williams, N. G.; Shaw, B. R. *J. Am. Chem. Soc.* **1990**, *112*, 829.

(15) (a) Harriman, A.; Magda, D.; Sessler, J. L. *J. Chem. Soc., Chem. Commun.* **1991**, 345. (b) Harriman, A.; Magda, D.; Sessler, J. L. *J. Phys. Chem.* **1991**, *95*, 1530. (c) Harriman, A.; Kubo, Y.; Sessler, J. L. *J. Am. Chem. Soc.*, in press.

0022-3263/92/1957-0818$03.00/0

Scheme I



on both guanine and cytosine offer an additional difference which may be taken advantage of in order to protect and solubilize the compounds during synthesis.

We were also intrigued by the possibility of using "dimeric" base derivatives as recognition units, not only as an obvious approach to extending the degree of association of the monomers but also as a means of incorporating sequence specificity into the binding process. However, while naturally occurring dinucleotides such as NAD^+ are readily manipulated by enzymes, the flexibility due to the sugar and phosphate backbone connecting the two bases presents an obstacle to their effective use in artificial systems. In order to minimize degrees of conformational freedom and enhance the lipophilic nature of the binding units while maintaining the simplest synthetic system, it was decided to eliminate superfluous functionality and derive the simplest base-containing systems possible. Here, the idea was that a ribose-free system might be capable of adopting well-defined conformations not available to a ribophosphate-containing dimer.

Our initial synthetic targets were dinucleotide analogues in which ribose and phosphate moieties were replaced by short aliphatic chains and a nitrogen "linchpin" (Chart I). It was anticipated that we could compare the affinity of the complementary pairs for one another with the affinity of the monomeric analogues **4** and **5**. The nitrogen linchpin in this case can serve a dual purpose in that it not only provides a synthetically facile means of linking the two nucleobases but also may readily be functionalized to provide, e.g., a nonpolar character to the entire molecule or to attach a photoactive chromophore. The hydrogen bonding properties of individual nucleosides have previously been investigated in dimethyl sulfoxide (DMSO)[11,12] and chloroform[13,14] solutions; in this paper, we report upon the synthesis and base pairing interactions which occur between solubilized derivatives of the dimeric species **1–3** and monomeric species **4** and **5** in DMSO-d_6.

Results and Discussion

Our first attempts to obtain the simple acyclic analogue of guanosine, 9-(hydroxyethyl)guanine, by simple alkylation led to the production of complex mixtures of mono- and multialkylated products.[16] Although other methods had been developed[17] which allow for the formation of mixtures of 9- and 7-substituted products, the use of chromatography to separate these two products at this first step of synthesis seemed undesirable. Fortunately, it is possible to synthesize 7-substituted guanines regiospecifically via alkylation of guanosine with epoxides and subsequent hydrolysis.[18,19] Although this regioisomer differs from that found in DNA, it was expected on the basis of CPK models that Watson–Crick-type base pairing (to cytosine or its derivatives) would still be possible with these systems. Moreover, because position 7 would be blocked, no Hoogsteen or "back-side" base-pairing interactions would be expected to occur.

Due to the low solubility of guanine derivatives in organic solvents, it was determined that a lipophilic protective group on its exocyclic amino group would be needed in order to produce compounds amenable to normal synthetic procedures. The alkylation product of guanosine and ethylene oxide, 7-(hydroxyethyl)guanine (**7**), it was found, could be diacylated using benzoyl cyanide in pyridine to produce the ester/amide **8** (Scheme I). Monodeprotection using mildly basic conditions resulted in the nitrogen-protected hydroxyethyl guanine **9**. Activation of the hydroxyl group was achieved first by preparation of the mesylate **10** using methanesulfonyl chloride in pyridine, followed by conversion to the iodide **11** using sodium iodide in warm acetone. The mesylate **10** was found to react cleanly with sodium azide in DMF to produce the azide **12**. The aminoethylguanine monomer **13** was then obtained in crystalline form by catalytic transfer hydrogenation in ethanol with ammonium formate.

In order to obtain the guanine "homodimer" **14** (a precursor to **3**), compound **13** was alkylated with the iodoethylguanine derivative **11** by heating at reflux in CH_3CN for 48 h in the presence of K_2CO_3. Column chromatography proved difficult due to the low solubility of the guanine derivatives, but purification was readily achieved using acid/base extraction. This allowed the protected homodimer **14** to be obtained in ca. 30% yield based on **13**.

In order to prepare the pyrimidine analogues, cytosine was converted to its sodium salt and alkylated with ethylene carbonate[20] to produce the 1-hydroxyethyl heterocycle **16** (Scheme II). Selective benzoylation of the

(16) For a review of relevant synthetic methods, see: (a) Sessler, J. L.; Magda, D. J.; Lynch, V.; Schiff, G. M.; Bernstein, D. I. *Nucleosides, Nucleotides* **1989**, *8*, 431. (b) Kjellberg, J.; Johansson, N. G. *Nucleosides, Nucleotides* **1989**, *8*, 225 and references cited therein. (c) Reference 10c.

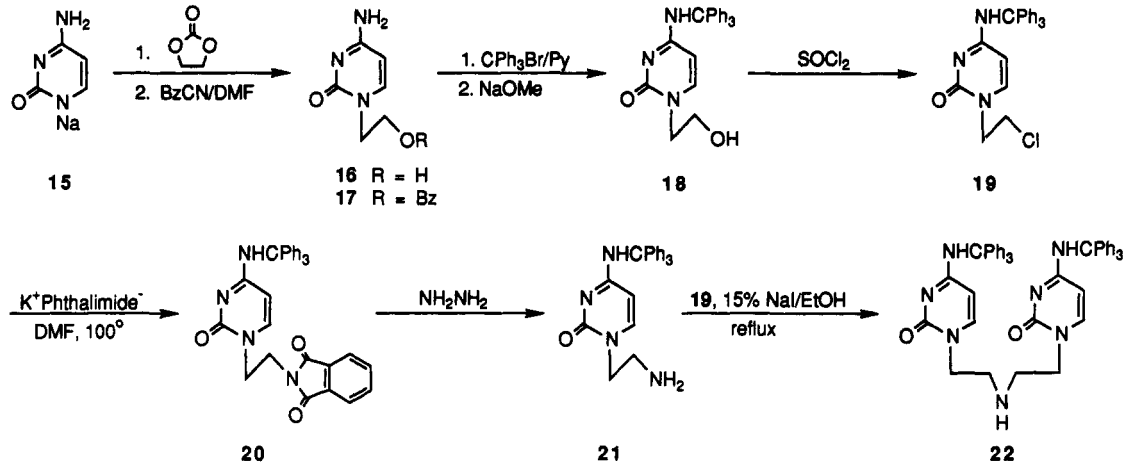
(17) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1988**, *53*, 1294.

(18) Brookes, P.; Lawley, P. D. *J. Chem. Soc.* **1961**, 3923.

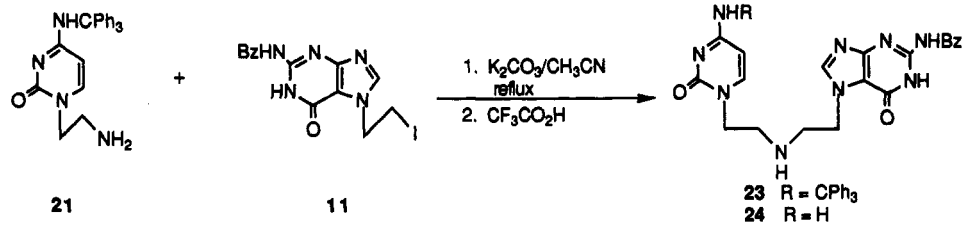
(19) Roe, R., Jr.; Paul, J. S.; Montgomery, P. O'B. *J. Heterocycl. Chem.* **1973**, *10*, 859.

(20) Ueda, N.; Kondo, K.; Kono, M.; Takemoto, K.; Imoto, M. *Makromol. Chem.* **1968**, *120*, 13.

Scheme II



Scheme III



2′-hydroxyl group was then effected using benzoyl cyanide in dimethylformamide (DMF). Tritylation of the resulting benzoic ester **17** could then be accomplished by heating with trityl bromide in pyridine at 100 °C for several hours. Stirring in 0.1 N NaOMe/MeOH released the trityl-protected hydroxyethylcytosine **18** in about 50% overall yield from **17**. Alcohol **18** was then converted to the chloride **19** in about 90% yield using thionyl chloride at reflux. Fortunately, this transformation proceeded without substantial loss of the trityl protective group (despite the acidic conditions involved). The chloride **19** could then be reacted readily with potassium phthalimide in DMF (97%). Following hydrazinolysis of the resulting phthalimide, the primary amine **21** was obtained in 99% yield. Coupling between **21** and the chloride **19** was carried out in the presence of sodium iodide in order to minimize competing intramolecular cyclization of **19**. The resulting homodimer **22** was thus obtained in ca. 62% yield.

The trityl-protected aminoethylcytosine **21** was also alkylated with the guanine electrophile **11** to afford the diprotected "mixed dimer" **23** (Scheme III). Unfortunately, yields to date have not exceeded 33% when both reagents are used on a equimolar basis: a roughly 5% yield of the diguanine monocytosine trimer is produced under normal reaction conditions, and substantial amounts of debenzoylated products are formed when the reaction is subjected to prolonged reflux.

The homodimers **14** and **22**, as well as heterodimer **23**, have been proven to be excellent nucleophiles in typical alkylation and acylation reactions. The protective groups lend favorable solubility characteristics to the dinucleotide analogues and may be selectively removed either before or after further functionalization. For instance, the trityl group in compound **23** may be hydrolyzed by stirring at reflux in trifluoroacetic acid for 0.5 h to produce the monoprotected dimer **24**, while 3 h at reflux in 0.1 N NaOMe/MeOH is sufficient to cleave the benzamide on guanine. The resultant deprotected "mixed dimer" **2** (Chart I) is water soluble at pH 7, where it presumably exists as the N-protonated cation.

In order to observe measurable base pairing derived binding interactions by proton NMR spectroscopy, however, we required compounds with good solubility in organic solvents. To this end we prepared and tested a variety of compounds formally derived from the secondary amines **1** and **2**. Unfortunately, in our first efforts, we found that neither benzyl nor tosyl groups were able to increase substantially the solubility of the deprotected, mixed dimer **2** in DMSO. Indeed, these N-substituted systems were barely sufficiently soluble to allow a proton NMR spectrum to be obtained. After a number of related functionalization studies, we eventually determined to use a poly(ethylene glycol) (PEG) moiety as a solubilizing group. Here, the idea was to produce DMSO-soluble compounds possessing amphoteric properties. This group was joined to the nucleobases using a simple amide linkage, which is resistant to the deprotecting conditions outlined above. The homodimeric amines **14** and **22**, the heterodimeric amine **23**, as well as the monomeric primary amines **13** and **21** were all derivatized in this fashion (c.f. Scheme IV). Upon deprotection this provided a full set of the solubilized nucleobase monomers and dimers (Chart II). The PEG monomethyl ether **25** which was selected is commercially available as a mixture of polymers having an average molecular weight of 750. Interestingly, the assumed mixture of chain lengths was not reflected in the observed chromatographic behavior or in the ^{1}H NMR spectra of the nucleobase derivatives. The mass spectra, however, showed a distribution of molecular ion peaks each of which differed by the expected 44 amu.

All but one of the deprotected bases of Chart II were sufficiently soluble (at a level >100 mM) in deuterated dimethyl sulfoxide (DMSO-d_6) to allow study by ^{1}H NMR. The exception was the guanine dimer **31** which formed a gel at those concentrations required for ^{1}H NMR analysis. In order to circumvent this problem, we attempted to study its affinity for the cytosine dimer **33** at 50 °C, where a solution existed. Unfortunately, the low concentration

Scheme IV

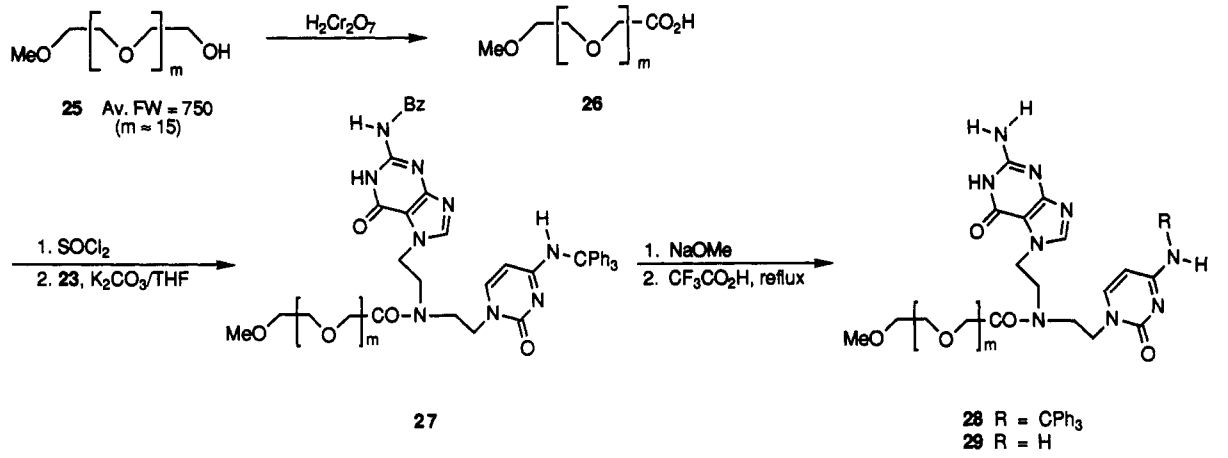
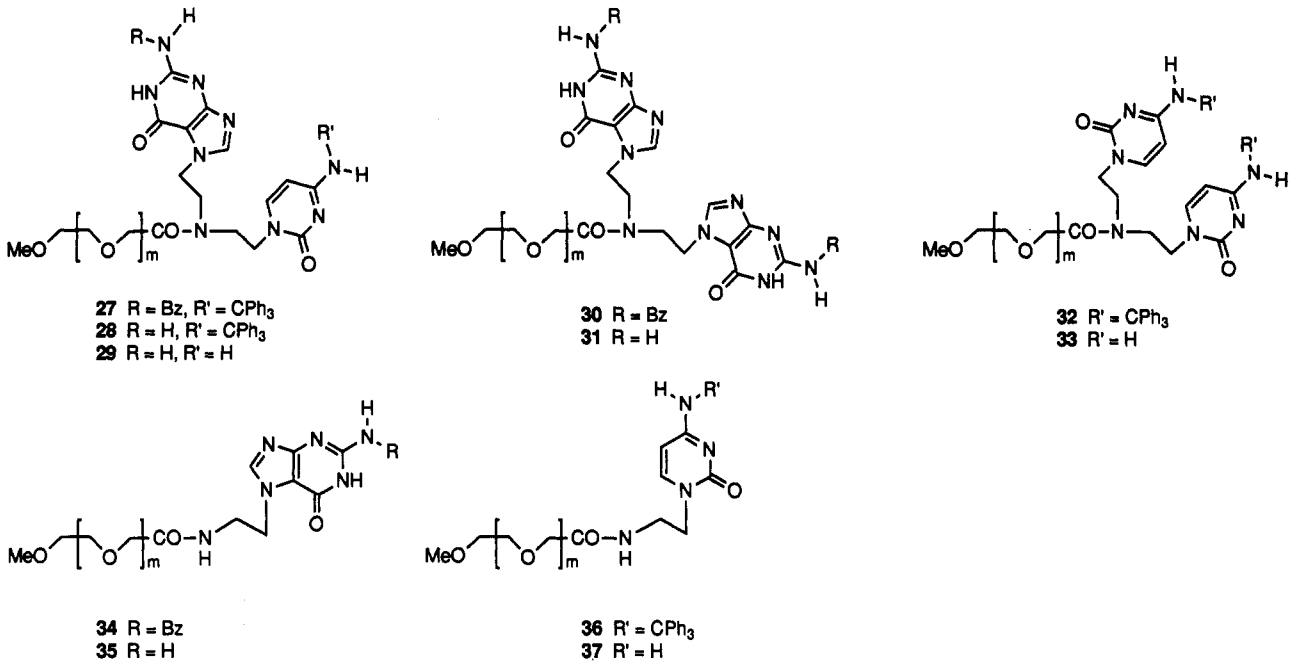


Chart II



of complex at this higher temperature has thus far prevented accurate formation constant evaluation in this system.

Binding constants were determined from standard Scatchard plots using ^{1}H NMR titration data.[21] A solution of the self-complementary heterodimer derivative **29** in DMSO-d_6 was diluted with the same, and chemical shift changes were observed. In the other cases, a DMSO-d_6 solution of guanine substrate was titrated with a concentrated DMSO-d_6 solution of the cytosine-containing ligand. Effects due to ligand and substrate self-association were considered to be negligible at the concentrations employed in the titration experiment; where substrate = **29**, ligand = **29**, K_b = 4.5–6.8 M^{-1}, where substrate = **35**, ligand = **37**, K_b = 3.9–4.7 M^{-1}.

The results of the NMR study were somewhat surprising. Little increase in the association constant is observed in the dimer relative to the monomers, suggesting that little additional binding affinity is produced by the use of dimers (cf. Table I). There are several reasons why this might be so. The low values for dimer association may reflect

Table I. Binding Interactions between Nucleobase Analogues in DMSO-d_6 at 23 °C

substrate	ligand	proton[a]	K_b[b] (M^{-1})	$\Delta\delta$[c] (ppm)
29	**29**	C^4–NH_2	6.8	0.20[d]
		C^2–NH_2	5.6	0.35[d]
		N^1–H	4.5	0.61[d]
31	**33**	C^2–NH_2	*f*	*f*
		N^1–H	*f*	*f*
35	**37**	C^2–NH_2	4.7	0.71[e]
		N^1–H	3.9	1.20[e]

[a] Refers to proton signal studied. [b] Calculated binding constants; error <±20%. [c] Induced chemical shift (δ_{obs}–$\delta_{initial}$); experimental values; error <±0.02 ppm. [d] [**29**] = 0.090 M. [e] [**35**] = 0.033 M, [**37**] = 0.327 M. [f] Not measurable.

the larger entropic requirement necessary to produce a ditopic complex. Another possible cause may be the formation of intramolecular hydrogen bonds in the dimer (full base pairing is not possible) which must be broken in order for intermolecular complexes to form. Nonetheless, it is clear from the data that the guanine imino proton is shifted downfield to a roughly 2-fold greater extent than the amino protons, implying that simultaneous, i.e., Watson–Crick-like, interactions are occurring.[11] The magnitude of the binding constants is in line with previous studies in

(21) Conners, K. A. *Binding Constants*; Wiley: New York, 1987; Chapter 5.

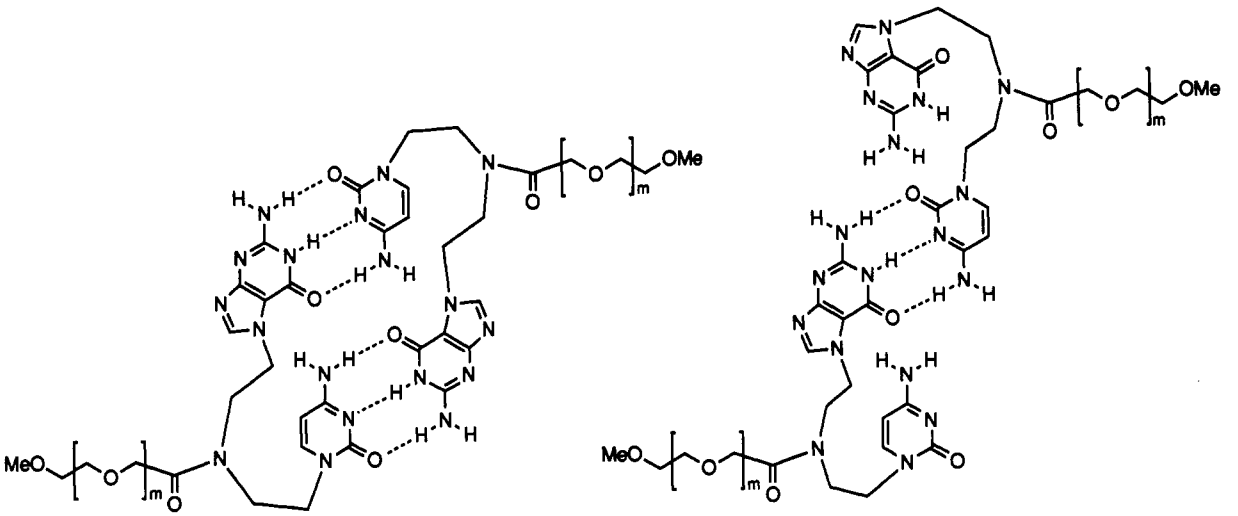


Figure 1. Possible monotopic and ditopic binding modes for self-association of heterodimer **29** in DMSO-d_6.

DMSO.[11] This finding again supports the conclusion that normal base pairing is occurring in an intermolecular fashion. In addition, a symmetric dimerization model was used in calculating the binding constants. The chemical shift change ($\Delta\delta$) obtained would appear to rule out simple one-point as opposed to two-point binding, as these values would be twice as large if only the former were occurring (the K_b values are not effected). Figure 1 illustrates what is meant by these two limiting intermolecular binding modes, at least for the specific case of the self-complementary "mixed" dimer **29**.

The question of whether stacking interactions occur in the dimeric derivatives was also of interest to us as these might help to preorganize these systems for base pairing. Although stacking between monomers is not believed to occur in nonpolar solvents such as DMSO, this might be energetically favorable in an intramolecular situation. One interesting observation along these lines was finding that a number of base proton signals are split in the case of the dimers which are unsplit in the spectra of the monomers. These split peaks coalesced as the temperature was increased, implicating a conformational equilibrium of some type. Initially it was thought that cis/trans stacking isomerism was giving rise to the differing signals. However, slow rotation of the amide group linking the poly(ethylene glycol) unit appears to be responsible for the observed effect. Similar splitting patterns were also observed in the ^{1}H NMR spectra of malonyl and succinyl diamide derivatives of **13** and **21**.[22] Stacking isomers, if they indeed occur, must exchange rapidly on the NMR time scale. Further, there was no evidence of the kind of *upfield* shifts that would be expected if stacking dimerization were occurring.

The solubility of dimeric nucleobases **29**, **31**, and **33** in $CDCl_3$ was too low to be detected by ^{1}H NMR. Monomers **35** and **37**, on the other hand, were found to be quite soluble in this solvent. These results suggest that these latter compounds possess solubility and binding characteristics which may be usable in a recognition context. Systems containing ordered structures based upon these interactions are presently being developed. Indeed, in preliminary work we have prepared a set of porphyrin-substituted analogues of **35** and **37** and found that they undergo complementary recognition (i.e., association) and facilitated photoinduced interporphyrin energy transfer and electron transfer between porphyrin and quinone in chloroform (or dichloromethane) solution.[15]

(22) Magda, D. Ph.D. Dissertation, University of Texas at Austin, 1990.

Experimental Section

General Methods. All solvents and reagents were of reagent-grade quality, purchased anhydrous, and used without further purification. Electronic spectra were recorded in water at pH 7. Proton and ^{13}C NMR spectra were obtained in $CDCl_3$, CD_3OD, or DMSO-d_6 using either Me_4Si or the residual DMSO signal (δ = 2.49 ppm) as internal standards. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Ethylene oxide was purchased from Eastman Kodak Co. (Caution: Ethylene oxide is a known carcinogen; observe manufacture's recommendations for handling and storage). Thin-layer chromatography (TLC) was carried out on silica plates (Whatman K6F) or alumina plates (Polygram Alox N/UV_{254}, Macherey-Nagel) using 12:7:1 $CHCl_3$/MeOH/H_2O (system A), 10% MeOH in $CHCl_3$ (system B), or 5% MeOH in $CHCl_3$ (system C). Column chromatography was performed using Merck silica gel 60. Melting points are uncorrected.

2-Amino-7-(2-hydroxyethyl)purin-6-one (7).[18] Guanosine hydrate (25.0 g, 88 mmol) was suspended in acetic acid (500 mL) and stirred under a nitrogen atmosphere for several minutes. Ethylene oxide (20 mL, 404 mmol) was transferred into the vessel using a cold syringe, and the reaction was allowed to proceed for 6 h or until judged complete by TLC (system A, guanosine R_f = 0.30, product nonmobile). Following evaporation of excess ethylene oxide and solvent in vacuo, water (250 mL) was added to form a clear solution. After the solution was heated at 80–100 °C for 2 h, the white precipitate which formed upon cooling was filtered, washed with cold water (100 mL), and recrystallized from hot water (4 L) to afford **7** as white needles (11.4 g, 66%): mp >300 °C dec; ^{1}H NMR (DMSO-d_6) δ 3.68 (2 H, t, CH_2CH_2OH), 4.19 (2 H, t, CH_2CH_2OH), 4.85 (1 H, t, CH_2OH), 6.07 (2 H, s, NH_2), 7.82 (1 H, s, C^8H); ^{13}C NMR (DMSO-d_6) δ 160.1, 154.9, 152.5, 143.6, 108.1, 60.0, 48.3; UV λ_{max} (pH 7), 216.0 nm (log ϵ 4.56), 242.0 (4.01, sh), 283.5 (4.11) (lit.[18] 245 (3.74, sh), 284 (3.86)); MS *m/e* 195 (M^+).

2-Benzamido-7-[2-(benzoyloxy)ethyl]purin-6-one (8). Compound **7** (19.00 g, 97.4 mmol) was suspended in dry pyridine (400 mL) containing benzoyl cyanide (38.3 g, 292 mmol). After the addition of 4-(dimethylamino)pyridine (DMAP) (11.90 g, 97.4 mmol), the mixture was allowed to stir under nitrogen at 75 °C for 3 h and cool for 3 h. The reaction was then quenched by the addition of H_2O (200 mL). The resulting precipitate was collected by filtration and washed with $CHCl_3$ (3 × 60 mL) and dried in vacuo to produce 30.9 g of a tan solid. This crude material was recrystallized from CH_3CN (10.5 L) to produce **8** as very fine crystals (25.37 g, 64.6%): mp 259–260 °C; R_f = 0.57 (system B); ^{1}H NMR (DMSO-d_6) δ 4.68 (2 H, t, CH_2CH_2OBz), 4.70 (2 H, t, CH_2CH_2OBz), 7.51 (4 H, m, BzH), 7.63 (2 H, m, BzH), 7.87 (2 H, d, BzH), 8.04 (2 H, d, BzH), 8.31 (1 H, s, C^8H), 11.85 (1 H, s, NH), 12.38 (1 H, s, NH); CIMS (chemical ionization mass

spectrum) m/e 404 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{17}N_5O_4$: C, 62.53; H, 4.25; N, 17.36. Found: C, 62.70; H, 4.29; N, 17.53.

2-Benzamido-7-(2-hydroxyethyl)purin-6-one (9). Sodium methoxide (10.0 g, 186 mmol) was dissolved in anhydrous methanol (1 L) at room temperature and the solution cooled to 0 °C. Compound 8 (25.0 g, 62.0 mmol) was added and the resulting solution stirred for 1 h at which time concd HCl was added until neutral to pH paper. The neutralized solution was stored at 4 °C overnight and then filtered. The precipitate was washed with MeOH (100 mL) and dried in vacuo to give analytically pure 9 (2.90 g, 79%): mp 234–235 °C (5% MeOH/$CHCl_3$)); R_f = 0.45 (system B); ^{1}H NMR (DMSO-d_6) δ 3.74 (2 H, t, J = 5.3 Hz, CH_2CH_2OH), 4.33 (2 H, t, J = 5.3 Hz, CH_2CH_2OH), 4.95 (1 H, t, J = 5.4 Hz, O*H*), 7.54 (2 H, t, J = 7.6 Hz, Bz*H*), 7.66 (1 H, t, J = 7.2 Hz, Bz*H*), 8.04 (2 H, d, J = 7.4 Hz, Bz*H*), 8.12 (1 H, s, C^8*H*), 11.83 (1 H, s, N*H*), 12.33 (1 H, s, N*H*); ^{13}C NMR (DMSO-d_6) δ 168.8, 157.2, 152.9, 146.9, 145.0, 133.0, 132.2, 128.5, 128.4, 111.6, 60.1, 49.1; MS m/e 299 (M^+); HRMS calcd for $C_{14}H_{13}N_5O_3$ 299.1018, found 299.1012.

2-Benzamido-7-[2-[(methanesulfonyl)oxy]ethyl]purin-6-one (10). Compound 9 (4.00 g, 13.4 mmol) was dissolved in dry pyridine (200 mL). Methanesulfonyl chloride (3.2 mL, 41.3 mmol) was added, and the mixture was allowed to stir under nitrogen for 2 h. The resulting solution was poured into water (500 mL) and extracted with two portions of 10% MeOH in $CHCl_3$ (2 × 200 mL). Solvents were removed from the $CHCl_3$ extract in vacuo at 40–50 °C, and the residue was recrystallized from hot ethanol (1500 mL). A second crop of the white crystals, which formed upon cooling at 4 °C, was obtained from 100 mL of the concentrated filtrate, affording 10 (3.86 g) in 76.5% combined yield: mp >310 °C dec (DMSO); R_f = 0.55 (system B); ^{1}H NMR (DMSO-d_6) δ 3.13 (3 H, s, OMs), 4.64 (4 H, s, CH_2CH_2OMs), 7.54 (2 H, t, J = 7.6 Hz, Bz*H*), 7.65 (1 H, t, J = 7.2 Hz, Bz*H*), 8.05 (2 H, d, J = 7.8 Hz, Bz*H*), 8.22 (1 H, s, C^8*H*), 11.88 (1 H, s, N*H*), 12.41 (1 H, s, N*H*); ^{13}C NMR (DMSO-d_6) δ 168.8, 157.3, 152.9, 147.2, 145.0, 133.0, 132.2, 128.5, 128.4, 111.6, 68.6, 45.7, 36.7; CIMS m/e 378 ($M^+ + 1$); HRMS calcd for $C_{15}H_{15}N_5O_5S$ 377.0794, found 377.0788.

2-Benzamido-7-(2-iodoethyl)purin-6-one (11). Compound 10 (2.00 g, 5.31 mmol) was added to 15% NaI in acetone (75 mL) and heated at reflux for 4 h under N_2. After the solvent was removed on a rotory evaporator, the residue was partitioned between 10% MeOH in $CHCl_3$ (250 mL) and water (200 mL) to form a solution. This was separated, and the $CHCl_3$ extract was washed with additional water (100 mL). Following removal of solvent and drying in vacuo, compound 11 was obtained as an off-white powder (2.10 g, 97.0%): mp 192–193 °C dec (DMSO); R_f = 0.64 (system B); ^{1}H NMR (DMSO-d_6) δ 3.68 (2 H, t, J = 6.3 Hz, CH_2CH_2I), 4.60 (2 H, t, J = 6.3 Hz, CH_2CH_2I), 7.54 (2 H, t, J = 7.6 Hz, Bz*H*), 7.65 (1 H, t, J = 7.0 Hz, Bz*H*), 8.04 (2 H, d, J = 7.9 Hz, Bz*H*), 8.25 (1 H, s, C^8*H*), 11.87 (1 H, s, N*H*), 12.40 (1 H, s, N*H*); ^{13}C NMR (DMSO-d_6) δ 168.8, 157.4, 152.8, 147.1, 144.6, 133.0, 132.2, 128.5, 128.3, 111.4, 48.1, 5.6; MS m/e 409 (M^+); HRMS calcd for $C_{14}H_{12}N_5O_2I$ 409.0041, found 409.0036.

7-(2-Azidoethyl)-2-benzamidopurin-6-one (12). Compound 10 (15.00 g, 39.8 mmol) and NaN_3 (7.50 g, 115 mmol) were suspended in DMF (125 mL) and heated to 100 °C for 19 h. The solvent was then removed in vacuo and the residue dissolved in MeOH/$CHCl_3$ (500 mL) and washed with water (2 × 500 mL). The solvent was then removed on a rotary evaporator and the residue recrystallized from EtOH (800 mL) to afford 12 (8.25 g, 64.0%): mp 200–201 °C dec (DMSO); R_f = 0.63 (system B); ^{1}H NMR (DMSO-d_6) δ 3.82 (2 H, t, J = 5.5 Hz, $CH_2CH_2N_3$), 4.49 (2 H, t, J = 5.5 Hz, $CH_2CH_2N_3$), 7.54 (2 H, t, J = 7.5 Hz, Bz*H*), 7.66 (1 H, t, J = 7.3 Hz, Bz*H*), 8.05 (2 H, d, J = 7.4 Hz, Bz*H*), 8.24 (1 H, s, C^8*H*), 11.85 (1 H, s, N*H*), 12.39 (1 H, s, N*H*); ^{13}C NMR (DMSO-d_6) δ 168.8, 157.4, 152.8, 147.2, 144.8, 133.0, 132.2, 128.5, 128.3, 111.6, 50.9, 45.8; CIMS m/e 325 ($M^+ + 1$); HRMS calcd for $C_{14}H_{12}N_8O_2$ 324.1083, found 324.1071.

7-(2-Aminoethyl)-2-benzamidopurin-6-one (13). Compound 12 (5.00 g, 15.4 mmol), Pd(C) (2.50 g), and HCO_2NH_4 (4.86 g, 77.1 mmol) were suspended in 95% EtOH (250 mL) and stirred under N_2 for 4 h. Additional EtOH (250 mL) was added, and the solution heated to reflux and filtered. The catalyst was resuspended in boiling EtOH (500 mL) and filtered again. The combined filtrates were allowed to cool during which time white crystals of 13 were deposited. After filtering, a second crop was obtained by reducing the volume of the filtrate to 500 mL and recrystallizing again to afford 13 (3.80 g, 82.7%): mp 210–211 °C (DMSO); R_f = 0.39 (system A); ^{1}H NMR (DMSO-d_6) δ 2.99 (2 H, t, J = 5.8 Hz, $CH_2CH_2NH_2$), 4.27 (2 H, t, J = 5.8 Hz, $CH_2CH_2NH_2$), 7.18 (2 H, br s, NH_2), 7.51 (2 H, t, J = 7.4 Hz, Bz*H*), 7.61 (1 H, t, J = 7.1 Hz, Bz*H*), 8.05 (2 H, d, J = 7.7 Hz, Bz*H*), 8.10 (1 H, s, C^8*H*); ^{13}C NMR (DMSO-d_6) δ 169.4, 157.8, 153.5, 148.9, 144.5, 133.7, 132.4, 128.3 (2 C), 111.4, 48.4, 41.7; CIMS m/e 299 ($M^+ + 1$); HRMS calcd for $C_{14}H_{15}N_6O_2$ 299.1256, found 299.1264.

Bis[2-[7-(2-benzamido-6-oxopurinyl)]ethyl]amine (14). Compound 13 (2.50 g, 8.39 mmol), compound 11 (3.43 g, 8.39 mmol), and K_2CO_3 (1.16 g, 8.40 mmol) were suspended in acetonitrile (125 mL) and heated at reflux for 66 h. The solvent was removed on a rotary evaporator after cooling. The residue was dissolved in 0.1 N NaOH (125 mL) and filtered. The filtrate was made acidic (pH = ca. 1) using concd HCl. The white precipitate which formed was then filtered, washed with water (75 mL), 50% THF/water (75 mL), and THF (75 mL) and then suspended in 50% H_2O/THF (450 mL). Aqueous sodium hydroxide (50%, ca. 0.5 mL) was then added to form a solution (pH 7) which was again filtered. The THF was then removed on a rotary evaporator and the resulting white precipitate was filtered, washed with water (50 mL), and dried to afford 14 (1.81 g, 37.2%): mp 263–264 °C (DMSO); R_f = 0.29 (system B); ^{1}H NMR (DMSO-d_6) δ 2.94 (4 H, t, J = 5.4 Hz, CH_2CH_2NH), 4.29 (4 H, t, J = 5.4 Hz, CH_2CH_2NH), 7.51 (4 H, t, J = 7.6 Hz, Bz*H*), 7.63 (2 H, t, J = 7.1 Hz, Bz*H*), 8.04 (4 H, d, J = 7.9 Hz, Bz*H*), 8.05 (2 H, s, C^8*H*); ^{13}C NMR (DMSO-d_6) δ 168.8, 157.1, 152.8, 146.9, 144.7, 133.0, 132.2, 128.5, 128.3, 111.7, 48.6, 46.3; FABMS (fast atom bombardment mass spectrum) m/e 580 ($M^+ + 1$); HRMS calcd for $C_{28}H_{26}N_{11}O_4$ 580.2169, found 580.2164.

Sodium Salt of Cytosine (15).[23] Cytosine (50.0 g, 0.45 mol) was added to a solution of NaOH (26.0 g, 0.65 mol) in 95% EtOH (2 L) and stirred until a solution was formed. Trace amounts of solid were then removed by filtration, and the filtrate was taken to dryness on a rotary evaporator. EtOH (abs, 500 mL) was added to form a suspension which was allowed to stir overnight and then filtered and washed with EtOH (abs, 100 mL). This was dried under reduced pressure to produce compound 15 as a powder (54.6 g, 91.1%): R_f = 0.19 (system A, alumina plates); ^{1}H NMR (DMSO-d_6) δ 5.59 (1 H, d, C^5*H*), 7.15 (2 H, s, NH_2), 7.35 (1 H, d, C^6*H*).

4-Amino-1-(2-hydroxyethyl)pyrimidin-2-one (16).[20] To a suspension of compound 15 (45.00 g, 0.338 mol) in DMF (700 mL) was added ethylene carbonate (89.38 g, 1.02 mol) with stirring. This mixture was allowed to stir at 100–110 °C for 8.5 h or until TLC indicated the absence of starting material. The solution was then allowed to cool to 70 °C, and solvent was removed in vacuo. The resulting residue was then triturated with hot 95% EtOH (2 L), filtered, and allowed to crystallize at 4 °C, producing 16 as yellow needles. Additional product was obtained by trituration of the filtered precipitate with boiling 95% EtOH (1 L). The combined first and second crop yielded 34.77 g of 16 (66.2%): mp 227–228 °C (EtOH) (lit.[20] mp 228–229 °C); R_f = 0.39 (system A, alumina plates); ^{1}H NMR (DMSO-d_6) δ 3.52 (2 H, t, CH_2CH_2OH), 3.66 (2 H, t, CH_2CH_2OH), 4.85 (1 H, s, O*H*), 5.61 (1 H, d, C^5*H*), 7.00 (2 H, s, NH_2), 7.46 (1 H, d, C^6*H*).

4-Amino-1-[2-(benzoyloxy)ethyl]pyrimidin-2-one (17). To a suspension of compound 16 (40.0 g, 0.258 mol) in DMF (600 mL) was added benzoyl cyanide (100 g, 0.763 mol) with stirring. The reaction was initiated by the addition of triethylamine (6 mL) and was then allowed to stir for exactly 30 min before quenching by adding MeOH (100 mL). The solvents were then removed in vacuo. MeOH (500 mL) was then added, and the sides of the flask were scraped to form a suspension which was stirred for several hours and allowed to stand at 4 °C overnight. The precipitate was filtered and washed with cold MeOH until the filtrate clarified to produce 17 as a dry powder (39.26 g, 58.7%): mp 237–238 °C (MeOH); R_f = 0.30 (system B); ^{1}H NMR (DMSO-d_6) δ 4.02 (2 H, t, CH_2CH_2OBz), 4.44 (2 H, t, CH_2CH_2OBz), 5.61 (1 H, d, C^5*H*), 7.05 (2 H, s, NH_2), 7.51 (2 H, t, Bz*H*), 7.64 (3 H, m, C^6*H*, Bz*H*), 7.93 (2 H, d, Bz*H*); ^{13}C NMR (DMSO-d_6) δ 166.0, 165.4, 155.7, 146.4, 133.4, 129.4, 129.2, 128.7, 93.1, 62.5, 47.9; MS m/e 259 (M^+); HRMS calcd for $C_{13}H_{13}N_3O_3$ 259.0957, found 259.0951.

(23) Holy, A.; Sorm, F. *Collect. Czech. Chem. Commun.* **1969**, *34*, 3383.

1-(2-Hydroxyethyl)-4-[(triphenylmethyl)amino]pyrimidin-2-one (18). To a suspension of compound **17** (30.0 g, 0.116 mol) in pyridine (500 mL) was added triphenylmethyl bromide (67.5 g, 0.209 mol), and the mixture was brought to 110 °C for 18 h. Water (100 mL) was added to the resulting solution which was then allowed to cool. After $CHCl_3$ (500 mL) was added, the solution was washed with water (2 × 500 mL), and the solvents were removed on a rotary evaporator. Sodium methoxide (7.50 g, 0.139 mol) was added to the residue along with a quantity of MeOH (500 mL). The suspension was allowed to stir overnight. It was then filtered and washed with MeOH (100 mL). The filtrate was evaporated to dryness using a rotary evaporator. MeOH (250 mL) was then added, and the suspension was allowed to stir for several hours before filtrating and washing with MeOH (50 mL). The solvent was removed from the filtrate on a rotary evaporator and the residue purified by column chromatography using 2.5% MeOH/$CHCl_3$ as eluent to afford compound **18** (43.39 g, 94.2%): mp 262–264 °C dec ($CHCl_3$); R_f = 0.50 (system B); ^{1}H NMR (DMSO-d_6) δ 3.46 (2 H, t, CH_2CH_2OH), 3.54 (2 H, t, CH_2CH_2OH), 4.81 (1 H, t, O*H*), 6.14 (1 H, d, C^5*H*), 7.03–7.32 (15 H, m, Tr*H*), 7.38 (1 H, d, C^6*H*), 8.32 (1 H, s, N*H*); ^{13}C NMR ($CDCl_3$) δ 165.5, 156.6, 146.5, 143.7, 128.7, 128.3, 127.5, 94.4, 71.0, 60.8, 52.9; MS *m/e* 397 (M^+); HRMS calcd for $C_{25}H_{23}N_3O_2$ 397.1790, found 397.1797.

1-(2-Chloroethyl)-4-[(triphenylmethyl)amino]pyrimidin-2-one (19). Thionyl chloride ($SOCl_2$, 400 mL) was added to compound **18** (50.0 g, 0.126 mol), and the resulting suspension was brought to reflux for 30 min to form a solution. After being cooled, the solvent was removed in vacuo, and 10% MeOH/$CHCl_3$ (400 mL) was added to dissolve the residue. Aqueous sodium hydroxide (50%) was then added until the solution was alkaline, and the solution was washed with water (400 mL) and 2 M $KHCO_3$ (400 mL). The organic layer was filtered and the solvent removed on a rotary evaporator to produce **19** (47.74 g, 91.3%). This compound was stored at −10 °C and used without further purification: mp 168–170 °C dec ($CHCl_3$); R_f = 0.43 (system C); ^{1}H NMR ($CDCl_3$) δ 3.73 (2 H, t, *J* = 5.3 Hz, CH_2CH_2Cl), 3.89 (2 H, t, *J* = 5.3 Hz, CH_2CH_2Cl), 4.93 (1 H, d, *J* = 7.4 Hz, C^5*H*), 6.94 (1 H, d, *J* = 7.4 Hz, C^6*H*), 6.88 (1 H, s, N*H*), 7.16–7.26 (15 H, m, Tr*H*); ^{13}C NMR ($CDCl_3$) δ 165.7, 155.3, 146.0, 143.6, 128.5, 128.2, 127.4, 93.9, 70.8, 52.0, 42.0; MS *m/e* 415 (M^+); HRMS calcd for $C_{25}H_{22}N_3OCl$ 415.1451, found 415.1456.

1-(2-Phthalimidoethyl)-4-[(triphenylmethyl)amino]pyrimidin-2-one (20). To a solution of compound **19** (27.01 g, 0.065 mol) in DMF (200 mL) was added potassium phthalimide (13.26 g, 0.072 mol). The resulting suspension was heated at 100 °C for 12 h, then allowed to cool and the solvent removed in vacuo. The residue was dissolved in 10% MeOH/$CHCl_3$, washed with water (2 × 100 mL), and taken to dryness on a rotary evaporator. The resulting crude material was recrystallized from hot 95% EtOH (2 L) to afford **20** (27.15 g, 79.3%): mp 254–255 °C dec ($CHCl_3$); R_f = 0.88 (system B, then system C); ^{1}H NMR ($CDCl_3$) δ 4.00 (4 H, s, CH_2CH_2Phth), 4.87 (1 H, d, *J* = 7.3 Hz, C^5*H*), 6.77 (1 H, d, *J* = 7.3 Hz, C^6*H*), 7.20–7.33 (16 H, m, N*H*, Tr*H*), 7.72–7.86 (4 H, m, Phth*H*); ^{13}C NMR ($CDCl_3$) δ 167.8, 165.5, 155.3, 144.7, 143.8, 134.0, 131.8, 128.7, 128.3, 127.5, 123.4, 94.6, 71.0, 48.3, 36.7; MS *m/e* 526 (M^+); HRMS calcd for $C_{33}H_{26}N_4O_3$ 526.2005, found 526.1990.

1-(2-Aminoethyl)-4-[(triphenylmethyl)amino]pyrimidin-2-one (21). To a suspension of compound **20** (25.00 g, 47.5 mmol) in 95% EtOH (500 mL) at reflux was added hydrazine hydrate (5.00 g, 156 mmol). The resulting solution was stirred for 1 h then allowed to cool and the solvent removed on a rotary evaporator. The residue was suspended in 10% MeOH/$CHCl_3$ and washed with 2% NaOH (200 mL) and water (200 mL). The solvent was removed on a rotary evaporator and the crude material purified by column chromatography using 10% MeOH/$CHCl_3$ as eluent. Upon drying in vacuo, this afforded **21** as a white foam (18.59 g, 98.8%): mp 172–174 °C dec ($CHCl_3$); R_f = 0.57 (system A); ^{1}H NMR ($CDCl_3$) δ 3.01 (2 H, t, *J* = 6.0 Hz, $CH_2CH_2NH_2$), 3.75 (2 H, t, *J* = 6.0 Hz, $CH_2CH_2NH_2$), 4.97 (1 H, d, *J* = 7.3 Hz, C^5*H*), 6.81 (1 H, s, N*H*), 7.00 (1 H, d, *J* = 7.3 Hz, C^6*H*), 7.23–7.35 (15 H, m, Tr*H*); ^{13}C NMR ($CDCl_3$) δ 165.7, 156.2, 145.7, 143.9, 128.6, 128.2, 127.4, 94.1, 70.8, 52.6, 40.4; MS *m/e* 396 (M^+); HRMS calcd for $C_{25}H_{24}N_4O$ 396.1950, found 396.1955.

***N,N*-Bis[2-[1-[2-oxo-4-[(triphenylmethyl)amino]pyrimidinyl]]ethyl]amine (22).** Compound **21** (1.91 g, 4.82 mmol) and compound **19** (1.00 g, 2.41 mmol) were dissolved in 15% NaI/EtOH (abs, 50 mL), and the resulting solution was brought to reflux for 16 h. The solvent was removed on a rotary evaporator upon cooling and the residue dissolved in $CHCl_3$ (250 mL) and water (250 mL). The $CHCl_3$ layer was separated and washed with water (250 mL), and solvent was removed once more. The crude material obtained was purified by column chromatography using 5% MeOH/$CHCl_3$ as eluent to afford compound **22** (1.16 g, 62.2%): mp 297–298 °C dec ($CHCl_3$); R_f = 0.46 (system B); ^{1}H NMR ($CDCl_3$) δ 2.83 (4 H, t, CH_2CH_2NH), 3.65 (4 H, t, CH_2CH_2NH), 4.83 (2 H, d, C^5*H*), 6.75 (2 H, d, C^6*H*), 6.77 (2 H, s, N*H*), 7.25 (30 H, m, Tr*H*); ^{13}C NMR ($CDCl_3$) δ 165.2, 155.7, 145.7, 143.6, 128.3, 127.9, 127.2, 93.5, 70.4, 49.8, 47.0; CIMS *m/e* 776 (M^+ + 1); HRMS calcd for $C_{50}H_{46}N_7O_2$ 776.3713, found 776.3699.

***N*-[2-[7-(2-Benzamido-6-oxopurinyl)]ethyl]-*N*-[2-[2-oxo-1-[4-[(triphenylmethyl)amino]pyrimidinyl]]ethyl]amine (23).** Compound **21** (5.00 g, 12.6 mmol), compound **11** (5.16 g, 12.6 mmol), and K_2CO_3 (1.74 g, 12.6 mmol) were suspended in acetonitrile (125 mL) and heated at reflux for 23 h. After the solution was cooled, 10% MeOH/$CHCl_3$ (300 mL) was added to the resulting suspension, and the solution was washed with water (250 mL). The solvents were then removed on a rotary evaporator, and the residue was dissolved in 20% MeOH/$CHCl_3$ (10 mL) and purified by column chromatography using 10% MeOH/$CHCl_3$ as eluent to afford compound **23** (2.87 g, 33.6%): mp 227–228 °C (DMSO); R_f = 0.39 (system B); ^{1}H NMR (DMSO-d_6) δ 2.65 (2 H, t, *J* = 5.8 Hz, CH_2CH_2NH), 2.89 (2 H, t, *J* = 5.4 Hz, CH_2CH_2NH), 3.17 (1 H, s, N*H*), 3.51 (2 H, t, *J* = 5.8 Hz, CH_2CH_2NH), 4.28 (2 H, t, *J* = 5.4 Hz, CH_2CH_2NH), 6.12 (1 H, d, C^5*H*), 7.09–7.25 (15 H, m, Tr*H*), 7.34 (1 H, d, *J* = 7.2 Hz, C^6*H*), 7.53 (2 H, t, *J* = 7.6 Hz, Bz*H*), 7.64 (1 H, t, *J* = 7.3 Hz, Bz*H*), 8.04 (2 H, d, *J* = 8.8 Hz, Bz*H*), 8.07 (1 H, s, C^8*H*), 8.27 (1 H, s, N*H*); ^{13}C NMR ($CDCl_3$) δ 168.8, 163.7, 157.1, 154.8, 152.9, 147.0, 145.2, 144.7, 133.0, 132.3, 128.7, 128.5, 128.4, 127.4, 126.2, 111.7, 94.9, 70.1, 48.9, 48.6, 46.9, 46.2; FABMS *m/e* 678 (M^+ + 1); HRMS calcd for $C_{39}H_{36}N_9O_3$ 678.2941, found 678.2968.

α-Carboxy-ω-(methoxymethyl)poly(ethylene glycol) (26). Potassium dichromate (48.0 g, 163 mmol) was slowly dissolved in concd H_2SO_4 (45 mL), and the resulting acid solution was diluted with water (240 mL). Compound **25** (30.0 g, 40.0 mmol) was dissolved in water (100 mL), and this solution was added slowly to the above acid solution and allowed to stir for 18 h. The resulting dark colored solution was extracted with $CHCl_3$ (4 × 200 mL) and washed with water (100 mL). The water wash was then extracted with $CHCl_3$ (2 × 50 mL). The combined $CHCl_3$ extracts were then taken to dryness on a rotary evaporator, providing the polymer acid **26** as a clear oil (25.66 g, 84.0%). Some of this material (ca. 10 g) was further purified by extracting a $CHCl_3$ solution (100 mL) with 0.5 N NaOH (100 mL), followed by water (100 mL). Careful neutralization of the aqueous fractions with concd HCl and back extraction with $CHCl_3$ (5 × 50 mL) then yielded the purified material: R_f = 0.32 (system B); ^{1}H NMR ($CDCl_3$) δ 3.38 (3 H, s, CH_3O), 3.54–3.76 (60 H, m, CH_2O), 4.16 (2 H, s, CH_2CO_2H); ^{13}C NMR ($CDCl_3$) δ 171.8, 71.7, 70.9, 70.8, 70.3, 70.2, 68.5, 58.8; CIMS *m/e* 796 ($\pm n \times 44$ amu) (M^+ + 1); HRMS calcd for $C_{35}H_{71}O_{19}$ 795.4590, found 795.4581.

α-[*N*-[2-[7-(2-Benzamido-6-oxopurinyl)]ethyl]-*N*-[2-[1-[2-oxo-4-[(triphenylmethyl)amino]pyrimidinyl]]ethyl]-amino]-ω-(methoxymethyl)poly(ethylene glycol) (27). The "polymer" acid **26** (1.85 g, 2.33 mmol) was placed in a flask and $SOCl_2$ (50 mL) was added, followed by DMF (ca. 50 μL). The solution was stirred at room temperature for 12 h, after which time the $SOCl_2$ was removed in vacuo. Benzene (2 × 50 mL) was then added and removed (to remove remaining $SOCl_2$). THF (50 mL) and compound **23** (1.05 g, 1.55 mmol) were added, followed by K_2CO_3 (0.31 g, 2.27 mmol), and the mixture stirred for 24 h. MeOH (5 mL) was then added, and the solvents were removed on a rotary evaporator. The residue was dissolved in 10% MeOH/$CHCl_3$ (50 mL), filtered, and the filtrate taken to dryness under reduced pressure. The crude material was then purified by column chromatography using 7.5–10% MeOH/$CHCl_3$ as the eluent to provide compound **27** (2.09 g, 92.6%): R_f = 0.48 (system B); ^{1}H NMR (DMSO-d_6) δ 3.22 (3 H, s, CH_3O), 3.33–3.58 (66 H, m, CH_2O, CH_2CH_2NCO), 3.63 (2 H, t, CH_2CH_2NCO), 4.39 (2 H,

t, CH_2CH_2NCO), 6.16 (1 H, d, C^5H), 7.17–7.23 (15 H, m, Tr*H*), 7.40 (1 H, d, J = 7.1 Hz, C^6H), 7.54 (2 H, t, J = 7.5 Hz, Bz*H*), 7.65 (1 H, t, J = 7.2 Hz, Bz*H*), 8.06 (2 H, d, J = 8.2 Hz, Bz*H*), 8.18 (1 H, s, C^8H), 8.41 (1 H, s, N*H*), 11.89 (1 H, br s, N*H*), 12.37 (1 H, br s, N*H*); ^{13}C NMR (DMSO-d_6) δ 169.1, 168.8, 163.9, 157.1, 154.6, 152.9, 146.9, 144.8, 144.6, 133.0, 132.2, 128.7, 128.5, 128.3, 127.4, 126.2, 112.0, 111.6, 95.6, 71.3, 70.4, 70.2, 69.8, 69.6, 68.2, 58.0, 47.1, 45.1, 44.2, 43.8; FABMS m/e 1455 ($\pm n \times 44$ amu) ($M^+ + 1$); HRMS calcd for $C_{74}H_{104}N_9O_{21}$ 1454.7347, found 1454.7324.

α-[*N*-[2-[7-(2-Amino-6-oxopurinyl)]ethyl]-*N*-[2-[1-[[4-(triphenylmethyl)amino]-2-oxopyrimidinyl]]ethyl]-amino]-ω-(methoxymethyl)poly(ethylene glycol) (28). Compound **27** (1.00 g, 0.688 mmol) was dissolved in 0.1 N NaOMe/MeOH (50 mL), and the resulting solution was heated at reflux for 3.5 h. The cooled solution was neutralized with 2 N HCl and the solvents removed on a rotary evaporator. The resulting residue was suspended in 10% MeOH/$CHCl_3$ (20 mL), extracted with water (10 mL), and then taken to dryness under reduced pressure. The crude material obtained was purified by column chromatography using 20% MeOH/$CHCl_3$ as the eluent to provide **28** (0.85 g, 91.3%): R_f = 0.51 (system B); ^1H NMR (DMSO-d_6) δ 3.14 (3 H, s, CH_3O), 3.33–3.68 (64 H, m, CH_2O, CH_2CH_2NCO), 3.73 (2 H, br, CH_2CH_2NCO), 4.18 (4 H, t, CH_2CH_2NCO), 6.13 (1 H, br, C^5H), 6.58 and 6.65 (2 H, br, NH_2), 7.14–7.24 (15 H, m, Tr*H*), 7.39 (1 H, d, C^6H), 7.72 and 7.83 (1 H, s, C^8H), 8.29 and 8.39 (1 H, s, N*H*); ^{13}C NMR (DMSO-d_6) δ 169.3, 169.2, 164.053, 160.1, 160.0, 154.8, 154.7, 154.6, 153.5, 153.2, 144.9, 144.7, 143.5, 143.2, 128.8, 127.5, 126.3, 108.2, 107.9, 95.8, 95.7, 71.3, 70.5, 70.3, 69.8, 69.7, 69.6, 68.3, 68.1, 58.1, 47.1–43.5; FABMS m/e 1351 ($\pm n \times 44$ amu) ($M^+ + 1$); HRMS calcd for $C_{67}H_{100}N_9O_{20}$ 1350.7084, found 1350.7136.

α-[*N*-[2-[7-(2-Amino-6-oxopurinyl)]ethyl]-*N*-[2-[1-(4-amino-2-oxopyrimidinyl)]ethyl]amino]-ω-(methoxymethyl)poly(ethylene glycol) (29). Compound **28** (0.50 g, 0.37 mmol) was dissolved in trifluoroacetic acid (25 mL), and the resulting solution was heated at reflux for exactly 30 min. The solution was allowed to cool to room temperature and the solvent removed in vacuo. MeOH (25 mL) was then added and the resulting solution carefully neutralized using 0.1% NaOMe/MeOH. The solvent was then removed on a rotary evaporator and the crude material purified by column chromatography using 12:7:1 $CHCl_3$/MeOH/H_2O as eluent to provide **29** (0.38 g, 91.7%): R_f = 0.74 (system A); ^1H NMR (DMSO-d_6) δ 3.27 (3 H, s, CH_3O), 3.38–3.76 (64 H, m, CH_2O, CH_2CH_2NCO), 4.08 (2 H, t, CH_2CH_2NCO), 4.30 (4 H, t, CH_2CH_2NCO), 5.63 (1 H, d of d, C^5H), 6.36 (2 H, d, guanine-NH_2), 7.14 (2 H, d, cytosine-NH_2), 7.45 (1 H, d of d, C^6H), 7.81 and 7.89 (1 H, s, C^8H), 11.22 (1 H, br s, N*H*); ^{13}C NMR (DMSO-d_6) δ 169.2, 166.1, 166.0, 160.4, 160.2, 156.2, 156.0, 155.9, 153.8, 146.1, 143.1, 143.0, 108.1, 180.0, 93.5, 93.4, 71.2, 70.3, 70.0, 69.7, 69.6, 69.4, 68.1, 68.0, 58.0, 47.0–43.6; FABMS m/e 1108 ($\pm n \times 44$ amu) ($M^+ + 1$); HRMS calcd for $C_{48}H_{86}N_9O_{20}$ 1108.5989, found 1108.5950.

α-[*N*,*N*-Bis[2-[7-(2-benzamido-6-oxopurinyl)]ethyl]-amino]-ω-(methoxymethyl)poly(ethylene glycol) (30). Compound **26** (1.98 g, 2.59 mmol) was dissolved in $SOCl_2$ (20 mL) and DMF (20 μL), and the solution was allowed to stir for 29 h. The excess $SOCl_2$ was removed in vacuo. Benzene (2 × 30 mL) was then added and removed in vacuo (to remove the traces of $SOCl_2$ remaining). DMF (25 mL) and K_2CO_3 (536 mg, 2.88 mmol) were then added, followed by compound **14** (500 mg, 864 μmol). After stirring for 21 h at room temperature, the reaction was quenched with water. The solvents were removed in vacuo and the residue dissolved in 10% $CHCl_3$/MeOH (100 mL). After the solution was washed with water (50 mL), the solvents were removed on a rotary evaporator. The residue was purified by column chromatography using 20% MeOH/$CHCl_3$ as eluent to provide **30** (437 mg, 37.3%): R_f = 0.46 (system B); ^1H NMR (DMSO-d_6) δ 3.22 (3 H, s, CH_3O), 3.32–3.59 (66 H, m, CH_2O, CH_2CH_2NCO), 4.32 (2 H, t, J = 5.4 Hz, CH_2CH_2NCO), 4.40 (2 H, t, CH_2CH_2NCO), 7.50 and 7.53 (4 H, t, Bz*H*), 7.64 and 7.65 (2 H, t, Bz*H*), 7.98 and 8.04 (4 H, d, J = 7.7, 7.5 Hz, Bz*H*), 8.11 and 8.19 (2 H, s, C^8H), 11.83 (4 H, br, N*H*); ^{13}C NMR (DMSO-d_6) δ 169.2, 168.8, 168.7, 157.0, 152.8, 147.2, 146.8, 144.7, 144.6, 133.0, 132.2, 128.5, 128.5, 128.3, 111.7, 111.5, 70.2, 70.4, 69.7, 69.5, 68.3, 58.0, 44.8–47.0; CIMS m/e 1356 ($\pm n \times 44$ amu) ($M^+ + 1$); HRMS calcd for $C_{63}H_{94}N_{11}O_{22}$ 1356.6575, found 1356.6580.

α-[*N*,*N*-Bis[2-[7-(2-amino-6-oxopurinyl)]ethyl]amino]-ω-(methoxymethyl)poly(ethylene glycol) (31). Compound **30** (145 mg, 107 μmol) was dissolved in 0.1 N NaOMe/MeOH (5 mL, 500 μmol), and the resulting solution was brought to reflux for 4 h. After the solution cooled, 2 N HCl was added until the solution became slightly acidic. The solvents were then removed on a rotary evaporator, and the resulting residue was purified by column chromatography using 12:7:1 $CHCl_3$/MeOH/H_2O as eluent to provide **31** (92 mg, 75%): R_f = 0.40 (system B: streaks); ^1H NMR (DMSO-d_6, 50 °C) δ 3.25 (3 H, s, CH_3O), 3.28–3.91 (66 H, m, CH_2O, CH_2CH_2NCO), 4.21 and 4.23 (4 H, t, CH_2CH_2NCO), 6.44 and 6.48 (4 H, br, NH_2), 7.73 and 7.80 (2 H, s, C^8H), 11.27 (2 H, br s, N*H*); ^{13}C NMR is not observable due to gel formation; FABMS m/e 1148 ($\pm n \times 44$ amu) ($M^+ + 1$); HRMS calcd for $C_{49}H_{86}N_{11}O_{20}$ 1148.6050, found 1148.5428.

α-[*N*,*N*-Bis[2-[1-[2-oxo-4-[(triphenylmethyl)amino]pyrimidinyl]]ethyl]amino]-ω-(methoxymethyl)poly(ethylene glycol) (32). Compound **22** (1.00 g, 1.29 mmol) was reacted with compound **26** as described for compound **27** above, except that benzene was used as solvent. The crude material was purified by column chromatography using 30% MeOH/$CHCl_3$ as eluent to provide **32** (1.00 g, 50.0%): R_f = 0.52 (system B); ^1H NMR ($CDCl_3$) δ 3.38 (3 H, s, CH_3O), 3.51–3.75 (68 H, m, CH_2O, CH_2CH_2NCO, CH_2CH_2NCO), 3.86 (2 H, m, CH_2CH_2NCO), 4.97 and 4.99 (2 H, d, C^5H), 6.78–7.17 (4 H, d, C^6H), 7.21–7.36 (30 H, m, Tr*H*); ^{13}C NMR ($CDCl_3$) δ 170.1, 165.8, 155.8, 155.7, 145.4, 145.6, 143.7, 128.5, 128.2, 127.5, 94.6, 94.5, 71.8, 70.9, 70.8, 70.6, 70.4, 70.1, 58.8, 48.3, 48.0, 46.5, 45.32; FABMS m/e 1551 ($\pm n \times 44$ amu) ($M^+ + 1$); HRMS calcd for $C_{83}H_{109}N_7O_{19}$ 1507.7778, found 1507.7671.

α-[*N*,*N*-Bis[2-[1-(4-amino-2-oxopyrimidinyl)]ethyl]-amino]-ω-(methoxymethyl)poly(ethylene glycol) (33). Compound **32** (1.00 g, 645 μmol) was dissolved in trifluoroacetic acid (20 mL), and the solution was heated at reflux for 1 h. After the solution was cooled, the solvent was removed in vacuo and the residue was dissolved in MeOH (50 mL). HCl (2 N) was then added until neutral, and solvents were removed on a rotory evaporator. The crude product was purified by column chromatography using 12:7:1 $CHCl_3$/MeOH/H_2O as eluent to afford **33** (258 mg, 37.5%): R_f = 0.54 (20% MeOH/$CHCl_3$); ^1H NMR (CD_3OD) δ 3.27 (3 H, s, CH_3O), 3.44–3.63 (66 H, m, CH_2O, CH_2CH_2NCO), 3.86 and 3.89 (4 H, t, J = 6.3, 6.3 Hz, CH_2CH_2NCO), 4.07 (4 H, s, NH_2), 5.77 and 5.75 (2 H, d, J = 6.8, 6.8 Hz, C^5H), 7.41 and 7.48 (2 H, d, J = 7.2, 7.2 Hz, C^6H); ^{13}C NMR (CD_3OD) δ 172.5, 168.1, 168.0, 159.1, 159.0, 147.6, 96.0, 72.9, 71.5, 71.4, 71.3, 71.2, 71.0, 70.8, 69.8, 59.1, 46.4, 45.6; FABMS m/e 1066 ($\pm n \times 44$ amu) ($M^+ - 1$); HRMS calcd for $C_{47}H_{85}N_7O_{20}Na$ 1090.5747, found 1090.5726.

α-[*N*-[2-[7-(2-Benzamido-6-oxopurinyl)]ethyl]amino]-ω-(methoxymethyl)poly(ethylene glycol) (34). Compound **13** (500 mg, 1.68 mmol) was reacted with compound **26** (1.92 g, 2.51 mmol) as described above for compound **27**. The crude product was purified by column chromatography using 7.5% MeOH/$CHCl_3$ as eluent to provide **34** (572 mg, 31.7%): R_f = 0.48 (system B); ^1H NMR ($CDCl_3$) δ 3.38 (3 H, s, CH_3O), 3.48–3.83 (64 H, m, CH_2O, CH_2CH_2NHCO), 4.54 (2 H, t, J = 5.5 Hz, CH_2CH_2NHCO), 7.55 (3 H, t, J = 7.6 Hz, Bz*H*, CONH), 7.65 (1 H, t, J = 6.9 Hz, Bz*H*), 7.78 (1 H, s, C^8H), 8.01 (2 H, d, J = 7.8 Hz, Bz*H*), 9.51 (1 H, br s, N*H*), 12.36 (1 H, br s, N*H*); ^{13}C NMR ($CDCl_3$) δ 170.0, 167.7, 156.1, 152.1, 146.3, 143.3, 132.1, 131.2, 127.5, 127.3, 110.9, 70.8, 70.0, 69.9, 69.7, 69.4, 69.3, 69.2, 69.0, 67.4, 57.7, 45.4, 38.7; CIMS m/e 1075 ($\pm n \times 44$ amu) ($M^+ + 1$); HRMS calcd for $C_{49}H_{83}N_6O_{20}$ 1075.5662, found 1075.5678.

α-[*N*-[2-[7-(2-Amino-6-oxopurinyl)]ethyl]amino]-ω-(methoxymethyl)poly(ethylene glycol) (35). Compound **34** (456 mg, 425 μmol) was dissolved in 0.1 N sodium methoxide/MeOH (25 mL), and the solution was heated at reflux for 3 h. After being cooled, the solution was neutralized with 2 N HCl, and the solvents were removed with a rotary evaporator. The residue was dissolved in 10% MeOH/$CHCl_3$ (10 mL) and filtered and the filtrate taken to dryness. The crude product was purified by column chromatography using 20% MeOH/$CHCl_3$ as eluent to provide **35** (170 mg, 41.3%): R_f = 0.62 (20% MeOH/$CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.30 (3 H, s, CH_3O), 3.47–3.63 (62 H, m, CH_2O), 3.72 (2 H, t, CH_2CH_2NHCO), 3.94 (2 H, s, NH_2), 4.38 (2 H, t, CH_2CH_2NHCO), 7.62 (1 H, s, C^8H), 7.69 (1 H, t, CONH); ^{13}C NMR

($CDCl_3$) δ 170.9, 158.5, 155.8, 154.1, 142.6, 107.8, 71.7, 70.8, 70.3, 70.2, 69.9, 58.8, 46.0, 39.5; FABMS *m/e* 971 ($M^+ + 1$); HRMS calcd for $C_{42}H_{79}N_6O_{19}$ 971.5400, found 971.5367.

α-[*N*-[2-[1-[2-Oxo-4-[(triphenylmethyl)amino]pyrimidinyl]]ethyl]amino]-ω-(methoxymethyl)poly(ethylene glycol) (36). Compound **21** (1.19 g, 3.01 mmol) was reacted with compound **26** as described for compound **27** above, except that benzene was used as the solvent. The crude material was purified by column chromatography using 5% MeOH/$CHCl_3$ as the eluent to provide **36** (2.65 g, 75.2%): R_f = 0.48 (system B); ^1H NMR ($CDCl_3$) δ 3.38 (3 H, s, CH_3O), 3.53–3.72 (64 H, m, CH_2O, CH_2CH_2NHCO), 3.86 (2 H, t, *J* = 6.1 Hz, CH_2CH_2NHCO), 4.99 (1 H, d, *J* = 7.3 Hz, C^5H), 7.03 (1 H, d, *J* = 7.3 Hz, C^6H), 7.23–7.37 (15 H, m, Tr*H*), 7.51 (1 H, t, CON*H*); ^{13}C NMR ($CDCl_3$) δ 170.6, 165.3, 155.7, 145.7, 143.6, 128.5, 128.1, 127.4, 94.1, 71.7, 71.0, 70.8, 70.7, 70.6, 70.3, 70.0, 58.8, 48.8, 37.8; CIMS *m/e* 1174 (±*n* × 44 amu) ($M^+ + 1$); HRMS calcd for $C_{60}H_{93}N_4O_9$ 1173.6434, found 1173.6430.

α-[*N*-[2-[1-(4-Amino-2-oxopyrimidinyl)]ethyl]amino]-ω-(methoxymethyl)poly(ethylene glycol) (37). Compound **36** (2.29 g, 1.95 mmol) was dissolved in trifluoroacetic acid (25 mL) and the solution brought to reflux for exactly 30 min. The solvent was then removed in vacuo. Sodium hydroxide (0.5 N in MeOH) was then added to a solution of the residue in MeOH until neutral and the solvent again removed on a rotary evaporator. The crude material was purified by column chromatography using 20% MeOH/$CHCl_3$ as eluent to provide **37** (1.79 g, 98.6%): R_f = 0.59 (20% MeOH/$CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.16 (3 H, s, CH_3O), 3.33–3.42 (64 H, m, CH_2O, CH_2CH_2NHCO), 3.70 (2 H, t, CH_2CH_2NHCO), 5.67 (1 H, d, *J* = 7.1 Hz, C^5H), 6.62 (2 H, br s, NH_2), 7.04 (1 H, d, *J* = 7.1 Hz, C^6H), 7.61 (1 H, t, CON*H*); ^{13}C NMR ($CDCl_3$) δ 170.3, 165.9, 156.4, 145.3, 94.1, 71.4, 70.6, 70.0, 69.7, 58.5, 48.5, 37.8; FABMS *m/e* 929 ($M^+ + 1$); HRMS calcd for $C_{41}H_{78}N_4O_{19}K$ 969.4897, found 969.4877.

Determination of Binding Constants. For the dimerization study of **29**, 15 samples of DMSO-d_6 solutions of various concentrations (0.017–0.090 M) were prepared and the chemical shifts of the N^1–H, C^2–NH_2, and C^4–NH_2 protons of **29** recorded using a Nicolet NT-360 NMR (360 MHz) at 23 °C. For the titration of **35** with **37**, six separate aliquots (100–200 μL) of a 0.53 M DMSO-d_6 solution of **37** were added to a 0.086 M solution (500 μL) of **35** and the chemical shifts of the guanine N^1–H and C_2–NH_2 protons recorded as a function of relative nucleobase concentration. Data reduction was then effected using standard Scatchard plots.[21] Because of the low chemical shift (Δδ) values involved, the errors are considered to be significantly larger (<±20%) than might otherwise be expected for this sort of measurement and analysis.

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Supplementary Material Available: ^1H NMR spectra for **9–14, 17–23,** and **26–37**; ^{13}C NMR spectra for **9–14, 17–23, 26–30,** and **32–37**; binding data and equilibrium calculation information for complexes presented in Table I (53 pages). Ordering information is given on any current masthead page.

New Crown Ether-like Macrocycles Containing a Nitrophenol Unit. Synthesis and Metal Ion Effects on the Reactivity of Their Acetates in Transacylation Reactions

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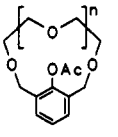
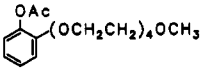
A series of crown ether-like macrocyclic compounds **3** containing the 2,6-dibenzyl-4-nitrophenol substructure have been prepared by cyclization reactions of disalicylideneacetone **4** with ditosylates **7** of oligoethylene glycols, followed by hydrogenation and double aldol condensation with nitromalondialdehyde. These compounds may be regarded as possessing a section of a 1,3-crowned calix[4]arene. X-ray analysis of two examples shows, however, that the three phenolic units linked via *o*-methylene groups adopt a conformation different to the all-cis conformation found in calix[4]arenes. The reaction of the nitrophenyl acetates derived from **3** and from suitable model compounds with ethoxide in ethanol was studied kinetically. This reaction is accelerated by the addition of $SrBr_2$ and $BaBr_2$ in all cases, indicating that the metal ion is bound more strongly to the transition state than to the initial state. Especially high acceleration factors (up to 700 in the case of **10e**) were observed for cyclic and open-chain compounds with longer flexible oligoethylene oxide chains, which means that only in these cases do the ether oxygens contribute effectively to the binding of the metal ion in the transition state.

In recent studies[1-3] of the effect of metal ions on acyl transfer reactions from aryl acetates to methoxide ion it was reported that alkali and alkaline-earth metal ions more or less firmly held in the proximity of the acetoxy group by strategically placed polyether chains, such as those in **1** and **2** (Chart I), greatly enhance reaction rates. The results, which were discussed in terms of differential binding of metal ions to transition state and reactant state, pointed to a selective transition-state stabilization resulting

Chart I



1 (n=2–6)



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