Acknowledgment. Support of this research by the National Science Foundation is gratefully acknowledged as is support of early stages by NIH Grant GM07487.

Registry No. **5**, 137570-31-1; **6**, 79919-09-8; **7**, 3263-79-4; **8**, 137570-32-2; **9**, 137570-33-3; **10**, 4400-53-7; **11**, 2892-41-3; **15**, 137570-34-4; **16**, 137570-35-5; **17**, 137570-36-6.

Supplementary Material Available: Details of the general photolysis conditions and preparative information as well as quantum yield determinations and runs and a table of thioxanthone sensitized quantum yields (3 pages). Ordering information is given on any current masthead page.

Molecular Recognition: Bis-Acylguanidiniums Provide a Simple Family of Receptors for Phosphodiesters

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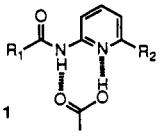
Recent reports from this[1] and other laboratories[2] have shown that molecules containing several hydrogen-bonding groups directed into a cleft or cavity can effectively recognize neutral substrates. For example, 2-(acylamino)pyridine derivatives form strong complexes with carboxylic acids[1a] via a neutral bidentate hydrogen-bonding interaction (**1**). We were interested in extending this directed hydrogen-bonding approach to anionic substrates such as phosphate and carboxylate. A straightforward strategy would involve protonating the pyridine to form the bidentate ion pair **2**. However, crystals grown from a 1:1 mixture of 2,6-dibutyr-



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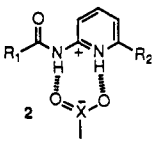
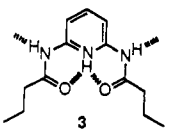


2

amidopyridine (**3**) and diphenylphosphoric acid[3] show, in the solid state (Figure 1), that while proton transfer occurs the cyclic bidentate complex does not. Instead, the N–pyridine bonds rotate 180° to form two intramolecular hydrogen bonds between the pyridinium H and amide CO and two intermolecular hydrogen bonds between the amide NHs and two phosphate units.[4]

An intramolecular hydrogen bond of this type might be exploited as a rigidifying element in receptor design if an additional binding group were positioned at a site corresponding to the pyridine 3-carbon in **3**. This arrangement exists in 2-(acylamino)imidazolines, **4**, and a crystal structure of 2-(benzoyl-



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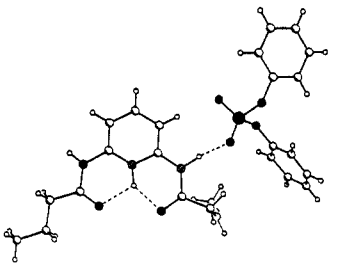
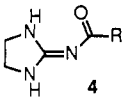


Figure 1.



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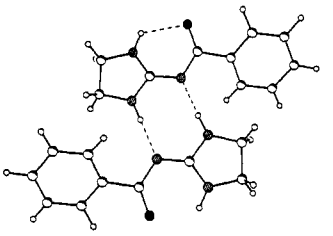
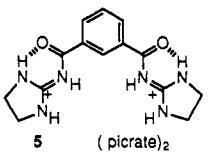


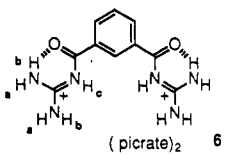
Figure 2.

amino)imidazoline (Figure 2) showed that an intramolecular hydrogen bond between one ring NH and the benzoyl CO was present. In addition, the other NH and the acyl N were positioned to form a cyclic bidentate interaction with a second molecule. On the basis of our earlier studies of phosphorodiamidate recognition,[5] we reasoned that linking two protonated aminoimidazolines through an isophthalic acid spacer should lead to a simple receptor for phosphate ester anions.

Reaction of dimethyl isophthalate with 2-aminoimidazolinium *p*-toluenesulfonate in MeOH and NaOMe[6] followed by alumina chromatography (CH_2Cl_2–MeOH, 50:1 eluent) gave the corresponding bis-2-(acylamino)imidazoline in 16% yield. The basicity of (acylamino)imidazolines (pK_a = 7.09) is reduced relative to aminoimidazolines (pK_a = 13.58);[7] however, they can be readily protonated, and treatment with picric acid gave the dicationic receptor **5**. An even simpler receptor, **6**,[8] containing two acyl-



5 (picrate)$_2$



(picrate)$_2$ **6**

guanidinium groups can be formed from the reaction of guanidinium hydrochloride and dimethyl isophthalate.[9] Both **5** and **6** could be converted into their tetraphenylborate (TBP) salts by treating the corresponding bis-hydrochloride with sodium tetraphenylborate. The ^1H NMR spectrum of **6** in CD_3CN shows three broad signals due to guanidinium hydrogens a, b, and c at 7.4, 8.2, and 11.2 ppm, respectively.[10] The large downfield shift of the b protons is consistent with the formation of an intramolecular hydrogen bond to each of the isophthaloyl carbonyl groups, as depicted in **6**.[10] These provide additional rigidity to the molecule,

(1) (a) Garcia-Tellado, F.; Goswami, S.; Chang, S. K.; Geib, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1990**, *112*, 7393. (b) Goswami, S.; Van Engen, D.; Hamilton, A. D. *J. Am. Chem. Soc.* **1989**, *111*, 3425. (c) Chang, S. K.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 1318. (b) Muehldorf, A. V.; Van Engen, D.; Warner, J. C.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 6561.

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(3) Dissolved in CH_2Cl_2–hexane.

(4) This solid-state hydrogen-bonding motif appears to be general for 2,6-di(acylamino)pyridinium diphenylphosphate salts: Geib, S. J.; Hirst, S. C.; Vicent, C.; Hamilton, A. D. *J. Chem. Soc., Chem. Commun.* **1991**, 1283.

(5) Tecilla, P.; Chang, S. K.; Hamilton, A. D. *J. Am. Chem. Soc.* **1990**, *112*, 9586.

(6) Bicking, J. B.; Robb, C. M.; Kwong, S. F.; Cragoe, E. J. *J. Med. Chem.* **1967**, *10*, 598.

(7) Storey, B. T.; Sullivan, W. W.; Moyer, C. L. *J. Org. Chem.* **1964**, *29*, 3118.

(8) ^1H NMR of **6** (CD_3CN): δ 11.16 (br s, 2 H, CONH), 8.73 (s, 4 H, picrate), 8.49 (s, 1 H, 2-isophth), 8.26 (br s, 4 H, endo NH), 8.17 (dd, *J* = 8, 2 Hz, 2 H, 4,6-isophth), 7.69 (t, *J* = 8 Hz, 5-isophth), 7.40 (br s, 4 H, exo NH).

(9) For other examples of guanidinium-containing synthetic receptors, see: Dietrich, B.; Fyles, D. L.; Fyles, T. M.; Lehn, J. M. *Helv. Chim. Acta* **1979**, *62*, 2763. Müller, M.; Riede, J.; Schmidtchen, F. P. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1516. Echaverren, A.; Galan, A.; Lehn, J. M.; de Mendoza, J. *J. Am. Chem. Soc.* **1989**, *111*, 4994. Schmidtchen, F. P. *Tetrahedron Lett.* **1989**, 4493.

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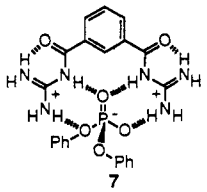
ensuring that the only flexibility is in the phenyl–carbonyl bonds.

Addition of 1 equiv of tetrabutylammonium diphenylphosphate (TDPP) to a CD_3CN solution of **6**-TPB_2 leads to both a sharpening and a downfield shifting of the b protons (0.22 ppm) and c protons (1.27 ppm) on the guanidinium. There is little shift, however, in the position of the outwardly-directed a protons. These results are consistent with the formation of a complex of type **7**,[11] in which both guanidiniums converge on the central cavity to form four hydrogen bonds to a single phosphate substrate.[12] The a protons do not participate in this hydrogen bonding and so hardly shift. Similar behavior, with up to 1 equiv of substrate, was seen with bis-imidazoline **5**.



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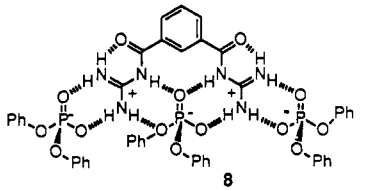

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With **6**, however, a second series of ^1H NMR changes occurs on further addition of TDPP (from 1 to approximately 3 equiv) to the CD_3CN solution. Now the guanidinium a protons shift dramatically downfield (2.48 ppm), the b protons move slightly upfield (0.22 ppm), and the c protons do not move. The outwardly-directed a protons represent two additional binding sites for the phosphodiester anions, and these NMR changes indicate the formation of a 3:1 complex, as in **8**.[14] These binding stoichiometries are supported by Job's plots,[15] generated by following the different H-bonding protons. The b and c protons give a maximum in the curve at a mole ratio of 0.5 (corresponding to a 1:1 complex), whereas the a proton reaches the maximum complex concentration at a mole ratio of receptor to substrate of 0.25 (corresponding to a 1:3 complex). Distinct spectroscopic changes of this type indicate strong 1:1 binding followed by weaker association of the second and third substrates. The absence of any significant higher order complexes until after 1 equiv of substrate has been added simplifies the analysis of the 1:1 complex. Dilution of a 1:1 mixture of **6**-TPB_2 and TDPP in CH_3CN gave a binding isotherm (following UV absorption at 266 nm) that was analyzed[16] by nonlinear regression methods to give an association constant for **7** of $(4.6 \pm 1.7) \times 10^4$ M^{-1}. In contrast, simple benzoylguanidinium tetraphenylborate has a K_a with TDPP of $(2.7 \pm 1.2) \times 10^3$ M^{-1}.

Receptors **5** and **6** are well-suited for the catalysis of phosphodiester cleavage. They possess a dicationic trigonal binding cavity that should be complementary both in terms of shape and electrostatics to the dianionic trigonal bipyramidal intermediate for nucleophilic attack on a phosphodiester.[5] Most importantly, the reduced basicity of the acylguanidines means that they can function not only as a binding site but also as an acid for protonating the alcohol leaving group. These studies will be the subject of a future publication.

Acknowledgment. We thank the National Institutes of Health (GM 35208) for financial support of this work and Ken Zweig for his assistance with the syntheses.

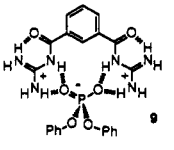
Registry No. **3**·DPP, 137695-76-2; **4**, 36145-66-1; **5**·$(chloride)_2$, 137718-31-1; **5**·$(picrate)_2$, 137718-30-0; **5**·$(TBP)_2$, 137718-32-2; **5**·DPP, 137718-33-3; **6**, 137695-71-7; **6**·$(chloride)_2$, 137695-72-8; **6**·$(picrate)_2$, 137695-70-6; **6**·$(TBP)_2$, 137695-73-9; **7**, 137695-74-0; **8**, 137695-75-1; TDPP, 429-42-5; DPP, 48168-03-2; dimethyl isophthalate, 1459-93-4; 2-aminoimidazolinium *p*-toluenesulfonate, 64103-00-0; *N*,*N*′-bis(3,4-dihydro-1*H*-imidazol-2-yl)-1,3-benzenedicarboxamide, 137718-29-7; guanidinium hydrochloride, 50-01-1.

Supplementary Material Available: Crystallographic details for 2,6-dibutyramidopyridinium diphenylphosphate and 2-(benzoylamino)imidazoline, including tables of atomic coordinates, thermal parameters, bond angles, and bond lengths (18 pages). Ordering information is given on any current masthead page.

(10) The two NH_2 groups of each guanidinium interconvert rapidly at room temperature; hence, only three signals are seen. Assignments were based on comparison to **5** and related derivatives.

(11) ^1H NMR of 1:1 complex **7** (CD_3CN): δ 12.30 (br s, 2 H, CONH), 8.67 (s, 4 H, picrate), 8.50 (br s, 4 H, endo NH), 8.41 (s, 1 H, 2-isophth), 8.22 (dd, J = 8, 2 Hz, 2 H, 4,6-isophth), 7.76 (t, J = 8 Hz, 1 H, 5-isophth), 7.51 (br s, 4 H, exo NH), 7.26 (t, J = 8.5 Hz, 2 H, 4-phenyl), 7.09 (m, 8 H, 2,3,5,6-phenyl), 3.06 (m, 8 H, NCH_2), 1.58 (m, 8 H, NCH_2CH_2), 1.35 (m, 8 H, CH_2CH_3), 0.95 (t, J = 7 Hz, 12 H, CH_3).

(12) At this point we cannot discount a complex structure as in **9**. Similar six-membered-ring H-bonding arrangements have been seen in urea–triphenylphosphine oxide cocrystals.[13]



9

(13) Etter, M. C.; Urbañczyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415.

(14) The upfield shift of the b protons is presumably due to a decrease in their acidity on phosphate binding to the geminal proton.

(15) Connors, K. A. *Binding Constants*; John Wiley & Sons: New York, 1987; p 24.

(16) Wilcox, C. S. *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H. J., Durr, H., Eds.; VCH: Weinheim, Germany, 1990.

Rate Constants for the Decomposition of a Simple Alkanediazoate at Physiological pH†

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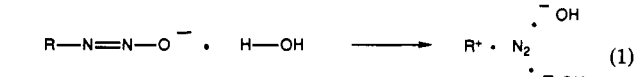
Received September 4, 1991

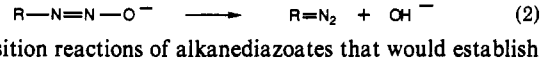
Alkanediazoates (**1**) are postulated to be reactive intermediates in the DNA-alkylating activity of a large number of compounds that contain an *N*-nitroso-*N*-alkyl functionality and are mutagenic, carcinogenic, or cancer-chemotherapeutic agents.[1] Simple *syn*- and *anti*-alkanediazoates were synthesized separately nearly 100 years ago.[2] Alkanediazoates are generally unstable in aqueous solutions, decomposing with the evolution of nitrogen gas, though some of the *anti* forms are reportedly stable in cold water.[3] The elegant isotope labeling studies of Moss and co-workers on the decomposition of secondary *syn*-alkanediazoates in heterogeneous aqueous media have been interpreted as supporting a mechanism involving rate-limiting fragmentation to yield an ion triplet (eq 1, R = secondary alkyl).[4a] In the case of some other *syn*-al-



(1)

1

kanediazoates, the products of decomposition in heterogeneous partly aqueous and homogeneous nonaqueous protic media include diazoalkanes to varying extents (eq 2, R = benzyl,[2b] allyl,[4a,b] cinnamyl,[4b] primary alkyl,[4a,c,d] and methyl[2b]), but the mechanism for the reaction of eq 2 is uncertain. Kinetic studies on the



(2)

decomposition reactions of alkanediazoates that would establish experimental criteria for possible mechanisms have not been carried out. We report in the present work the first rate constants for the decomposition of an *anti*-alkanediazoate (**2**) in aqueous

† Alkanediazoates have appeared in the literature as alkanediazotates.

(1) Lawley, P. D. In *Chemical Carcinogens*; Searle, C. D., Ed.; ACS Monograph 182; American Chemical Society: Washington, DC, 1984.

(2) (a) Thiele, J. *Justus Liebigs Ann. Chem.* **1910**, *376*, 239. (b) Hantzsch, A.; Lehmann, M. *Chem. Ber.* **1902**, *35*, 897.

(3) Thiele, J. *Chem. Ber.* **1908**, *41*, 2806.

(4) (a) Moss, R. A. *Acc. Chem. Res.* **1974**, *7*, 421. (b) Hart, H.; Brewbaker, J. L. *J. Am. Chem. Soc.* **1969**, *91*, 716. (c) Feiring, A. E.; Ciabattoni, J. *J. Org. Chem.* **1972**, *37*, 3784. (d) Kirmse, W.; Wachterhauser, G. *Justus Liebigs Ann. Chem.* **1967**, *707*, 44.

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