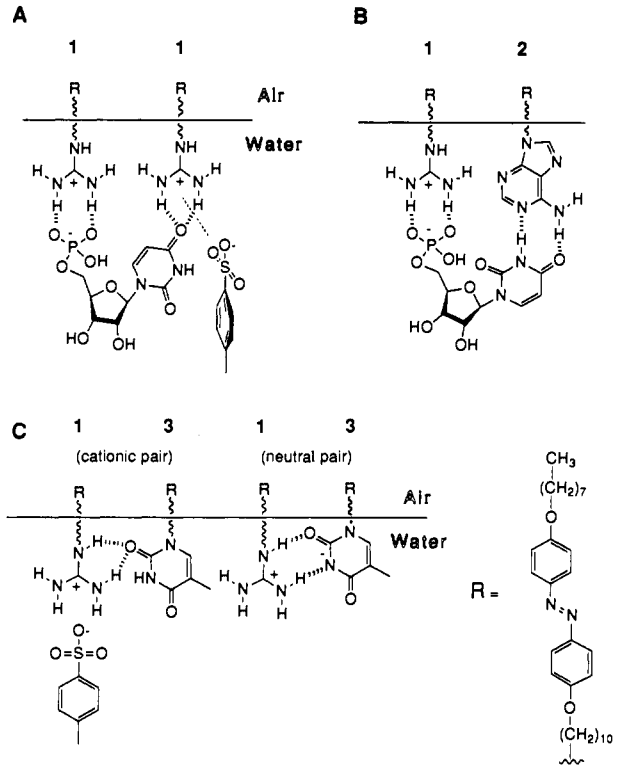

Figure 2. Monolayer receptors from amphiphiles **1**, **2**, and **3** and plausible schemes of nucleotide binding.

AMP is bound specifically to the guanidinium monolayer by the formation of the guanidinium/phosphate pair (Figure 1).[7a] A single set of parameters describes the binding behavior: $K = 3 \times 10^6$ M^{-1}, $\alpha = 1.0$ AMP/guan. The α value of 1.0 reveals that AMP binds to the guanidinium monolayer in a 1:1 correspondence. In contrast, UMP displays a binding saturation of 0.5–0.6 at 10^{-7}–10^{-5} M, and secondary binding occurs at higher UMP concentrations. The electrostatic interaction alone cannot explain this unique behavior, since UMP shows a simple equimolar saturation toward trimethylammonium monolayer **4**. The guanidinium unit is known to interact with the uracil carbonyl groups in protein–DNA/RNA complexes.[11] Thus, UMP can bind to monolayer **1** via both of the guanidinium–phosphate and guanidinium–uracil pairs (see Figure 2A).[12] An enhanced binding constant for UMP relative to that for AMP supports this interpretation.

The newly found role of the guanidinium monolayer is endorsed by bicomponent receptor **1–2** which combines guanidinium and adenine units. An equimolar saturation behavior ($\alpha = 0.9$ UMP/guan) is observed for UMP. This can be explained by assuming the formation of complementary adenine/uracil pairs as the secondary interaction (Figure 2B). As expected, AMP substrate does not display specific binding toward this bifunctional monolayer. Secondary interactions of the adenine component with AMP appear to interfere with the formation of specific complexes.

A third multifunctional receptor was prepared by a 1:1 mixed monolayer of **1** and **3**. Although this mixed monolayer exhibits saturation toward AMP and UMP, all of the guanidinium sites are not occupied at saturation ($\alpha < 1$). An IR spectrum of the transferred monolayer **1–3** exhibits shifts of the $\nu_{C=N}$ (**1**) and $\nu_{C2=O}$ (**3**)[13] peaks around 1700 cm^{-1} by >20 cm^{-1} relative to those of the single-component monolayer of **1** and **3** together with the appearance of a new peak at 1522 cm^{-1}, indicating hydrogen-bond formation between guanidinium and thymine head groups. XPS measurements showed a 25–30% reduction of bound anionic species (i.e., *p*-toluenesulfonate and nucleotides) at all nucleotide concentrations. The forced proximity of head groups may promote deprotonation of the thymine unit to form guanidinium/thymine ion pairs[14] and cause IR spectral changes and release of *p*-toluenesulfonate ion. The neutral ion pairs thus formed cannot bind nucleotides, thereby yielding [illegible]alues. The **1–3** pair in which the thymine unit is *not* d[illegible]ted acts as a specific receptor toward AMP and UMP.[15] [illegible]ding constant of AMP toward receptor **1–3** is enhanced (2.7 times) relative to that toward receptor **1**. In contrast, UMP shows virtually the same binding constants. The enhanced AMP binding appears to be induced by cooperative interaction of the guanidinium and thymine units.

The present findings amply demonstrate the versatility of guanidinium-based monolayer receptors. Spontaneous assembly of secondary recognition units gives rise to varied modes of nucleotide binding.

Acknowledgment. We thank Dr. Peter Berndt for his helpful discussions involving the adsorption data.

Supplementary Material Available: IR spectra of **1**, **3**, and **1–3** deposited from water and of **1–3** deposited from UMP and AMP and a plot of the binding curve of AMP and UMP to the guanidinium monolayer (5 pages). Ordering information is given on any current masthead page.

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(12) The average guanidinium–guanidinium distance in monolayer **1** can be calculated from the surface pressure–molecular area (π–A) isotherm to be 7.4 Å on 0.1 mM aqueous UMP. This distance is consistent with the binding mode described in Figure 2A, because the distance between the phosphate group and the carbonyl group of UMP in this binding mode is 7.5 ± 0.5 Å.

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(14) Guanidinium pK = 13.6: Hall, N. F.; Sprinkle, M. R. *J. Am. Chem. Soc.* **1932**, *54*, 3469.

(15) The IR peak at 1522 cm^{-1} is ascribable to the neutral ionic pair of the guanidinium and thymine groups. This peak disappears completely at 10^{-3} M aqueous AMP where all of the guanidinium groups are expected to interact with the phosphate group of AMP (AMP/guanidinium = 1.2) but not with the thymine group of **3**. This observation supports formation of complexes as illustrated in Figure 2C.

Larger and More Weakly Coordinating Anions: $Nb(OTeF_5)_6^-$ and $Ti(OTeF_5)_6^{2-}$

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The ability to generate coordinative unsaturation for a wide variety of cationic species (e.g., $[SiR_3]^+$,[1] $[Fe(Por)]^+$,[2,3] $[Re(Cp)(NO)(PPh_3)]^+$,[4] $[ZrCp'_2R]^+$[5]) in solution remains an elusive goal for synthetic and catalytic chemists because no solvent or anion is truly noncoordinating. Recent examples of larger and more weakly coordinating anions include fluorinated derivatives of BPh_4^- such as $B(C_6F_5)_4^-$ and $B(3,5\text{-}C_6H_3(CF_3)_2)_4^-$,[6] $CB_{11}H_{12}^-$

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(3) Abbreviations: Por = any porphyrinate dianion; TBA = tetra-*n*-butylammonium cation; teflate = pentafluorooxotellurate ($OTeF_5$ or $OTeF_5^-$).

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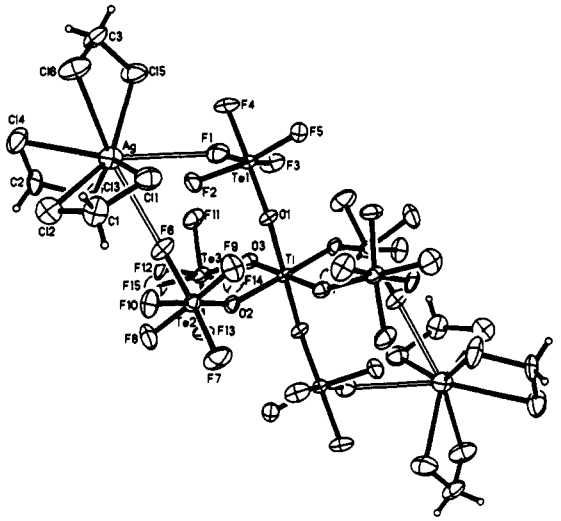

Figure 1. Structure of the centrosymmetric $[Ag(CH_2Cl_2)_3]_2[Ti(OTeF_5)_6]$ formula unit (50% probability ellipsoids except for hydrogen atoms). Selected distances (Å) and angles (deg): Ag–Cl, 2.656 (3)–3.049 (4); Ag···Fl, 3.029 (8); Ag···F6, 3.033 (6); Ti–O, 1.933 (6)–1.939 (9); Te–O, 1.812 (9)–1.822 (7); Te–F, 1.822 (7)–1.861 (8); C–Cl, 1.72 (1)–1.79 (2); O–Ti–O, 90.7 (3)–90.8 (3); Ti–O–Te, 142.3 (4)–145.2 (5); Cl–C–Cl, 110.2 (7)–113.2 (6).

and related carborane anions,[2a,b,7] and heteropolyanions (Keggin ions) such as $PW_{12}O_{40}^{3-}$.[8,9]

Our own efforts have focused on anions such as $Pd(OTeF_5)_4^{2-}$[10] and $B(OTeF_5)_4^-$.[11] These counterions have their negative charge delocalized over a large number of fluorine atoms, which diminishes the interaction of any given fluorine atom and a cationic center. The stability of teflate ($OTeF_5$) compounds with respect to fluoride abstraction[12] is another advantage they possess (BF_4^-, PF_6^-, and SbF_6^- are known to transfer a fluoride ion to strong cationic electrophiles[13]). However, it was found that cations such as Ag^+ could coordinate to the oxygen atoms of these teflate-based anions, forming relatively strong Ag–O(Te)–M bridges (M = Pd,[10] B[11b,d]). In addition, it was found that the putative cations $[SiR_3]^+$ and $[Fe(Por)]^+$ abstracted a teflate anion from $B(OTeF_5)_4^-$, presumably by formation of Si–O(Te)–B and Fe–O(Te)–B bridges.[11b] Simple dissociation of $OTeF_5^-$ from the borate anion was ruled out since no isotope exchange occured, even after many days, when $[TBA][^{17}OTeF_5]$ was mixed with $[TBA][B(^{16}OTeF_5)_4]$. The presence of an electrophile such as H^+ or Ag^+ was required to effect rapid (<1 h) isotope scrambling.

We are investigating a class of even larger complex anions, $M(OTeF_5)_6^{n-}$, and have found that they are (i) much less coordinating, (ii) much more stable in the presence of electrophiles, and (iii) much more solubilizing in weakly coordinating solvents than either $B(OTeF_5)_4^-$ or $Pd(OTeF_5)_4^{2-}$. The anions that are the subject of this paper are $Nb(OTeF_5)_6^-$ and $Ti(OTeF_5)_6^{2-}$, which had been prepared previously as their TBA^+[14] or Cs^+[15] salts, respectively. We have prepared their Ag^+ salts, which should prove useful as metathesis reagents, by mixing either $NbCl_5$ or $TiCl_4$ with 6 equiv of $AgOTeF_5$[10,16] in 1,1,2-trichlorotrifluoroethane (CFC-113):[17]

$$NbCl_5 + 6AgOTeF_5 \xrightarrow{\text{CFC-113}} AgNb(OTeF_5)_6 + 5AgCl$$

$$TiCl_4 + 6AgOTeF_5 \xrightarrow{\text{CFC-113}} Ag_2Ti(OTeF_5)_6 + 4AgCl$$

The compound $[Ag(CH_2Cl_2)_3]_2[Ti(OTeF_5)_6]$ was obtained by recrystallization of $Ag_2Ti(OTeF_5)_6$ from dichloromethane. Its structure consists of centrosymmetric $Ti(OTeF_5)_6^{2-}$ anions that bridge two symmetry-related $[Ag(CH_2Cl_2)_3]^+$ cations (Figure 1).[18] To within experimental error, the anion has an octahedral TiO_6 core, and the geometry of the $OTeF_5$ groups is normal.[19] Three bidentate dichloromethane ligands coordinate to silver in the $[Ag(CH_2Cl_2)_3]^+$ cation. The Ag–Cl bond distances range from 2.656 (3) to 3.049 (4) Å, which is a much greater range than in

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(17) Reaction conditions: 22 °C, 4 h. The mixture was filtered in a glovebox and the solvent was removed under vacuum to leave either $AgNb(OTeF_5)_6$ or $Ag_2Ti(OTeF_5)_6$ as extremely hygroscopic white powders. ^{19}F NMR (CH_2Cl_2, 22 °C, AB_4X pattern, X = ^{125}Te): $AgNb(OTeF_5)_6$, δ_A −41.4, δ_B −47.1 (J_{AB} = 195 Hz, J_{AX} = 3490 Hz, J_{BX} = 3650 Hz); $Ag_2Ti(OTeF_5)_6$, δ_A −34.7, δ_B −46.8 (J_{AB} = 186 Hz, J_{BX} = 3520 Hz). For both compounds, integration of ^{19}F resonances versus an internal intensity standard ($CFCl_3$) confirmed the presence of 30 fluorine atoms per formula unit.

(18) For $[Ag(CH_2Cl_2)_3]_2[Ti(OTeF_5)_6]$: triclinic, $P\bar{1}$, a = 10.944 (7) Å, b = 10.989 (7) Å, c = 11.142 (8) Å, α = 66.83 (5)°, β = 75.09 (6)°, γ = 83.44 (5)°, V = 1190 (1) Å^3, Z = 1, T = −135 (1) °C, ρ_{calcd} = 3.08 g cm^{-3}, $F(000)$ = 998. The compound's extremely hygroscopic nature and the ready loss of the dichloromethane ligands made these crystals extraordinarily difficult to work with. The data collection crystal was obtained with difficulty, and the precision of the unit cell parameters reported above reflects its quality. Nevertheless, given the difficulty of finding a better crystal, this crystal was accepted as satisfactory for data collection. Nicolet R3m diffractometer, $\theta/2\theta$ scans, $4° < 2\theta < 50°$; $\pm h, \pm k, +l$; 3786 unique reflections with $|F_o| > 2.5\sigma|F_o|$. Lorentz and polarization corrections; empirical absorption correction, μ(Mo Kα) = 54.0 cm^{-1}, T = 0.192–0.466. Weighted least-squares refinement on F with neutral atom scattering factors and anomalous dispersion, anisotropic thermal parameters, 287 parameters; R = 0.064, R_w = 0.095, GOF = 1.02.

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$[Ag(CH_2Cl_2)_2]_2[Pd(OTeF_5)_4]$ (2.775 (2)-2.882 (2) Å).[10]

The most significant feature of the structure is the absence of Ag-O bonds, which are present in $[Ag(CH_2Cl_2)_2]_2[Pd(OTeF_5)_4]$,[10] $AgB(OTeF_5)_4$,[11b] and $[Ag(CO)][B(OTeF_5)_4]$.[11d] Instead, each $[Ag(CH_2Cl_2)_3]^+$ cation is only *extremely weakly coordinated* to the $Ti(OTeF_5)_6^{2-}$ anion by two Ag···F contacts of 3.029 (8) and 3.033 (6) Å. For comparison, the Ag-F distances in $AgSbF_6$[20] and AgF[21] are 2.62 and 2.467 (3) Å, respectively, and the sum of the van der Waals radii for silver and fluorine is 3.15 ± 0.08 Å.[22] The relative strength of anion binding to Ag^+ is also evident in the number of dichloromethane molecules coordinated to Ag^+—three in $[Ag(CH_2Cl_2)_3]_2[Ti(OTeF_5)_6]$ but only two in $[Ag(CH_2Cl_2)_2]_2[Pd(OTeF_5)_4]$.

In contrast with the $B(OTeF_5)_4^-$ anion,[11b] $Nb(OTeF_5)_6^-$ does not undergo rapid exchange with labeled $OTeF_5^-$ in the presence of electrophilic cations such as H^+ and Ag^+. For example, when $[TBA][Nb(^{16}OTeF_5)_6]$ and $H^{18}OTeF_5$ were mixed in dichloromethane at 22 °C, IR spectra showed that isotope scrambling was only 22% complete after 47 h. The presence of a larger cation had an even more dramatic effect: when $AgNb(^{16}OTeF_5)_6$ and $Ag^{18}OTeF_5$ were mixed in dichloromethane at 22 °C, *no* exchange was observed after 72 h. On the basis of the structure of $[Ag(CH_2Cl_2)_3]_2[Ti(OTeF_5)_6]$, we propose that electrophiles larger than H^+ cannot form bridge bonds to the *oxygen* atoms of $Nb(OTeF_5)_6^-$. Without such bridge bonds, abstraction of $OTeF_5^-$ by even the strongest electrophiles will not occur rapidly. Thus, steric hindrance causes a *kinetic* stabilization of $Nb(OTeF_5)_6^-$ (and presumably of other structurally related anions as well) in the presence of electrophilic cations.

Our new silver salts are freely soluble in weakly coordinating, low dielectric solvents such as chlorinated hydrocarbons and chlorofluorocarbons. For example, the solubility of $Ag_2Pd(OTeF_5)_4$ in dichloromethane at 22 °C ($\epsilon \approx 9.1$) is only 0.35 M,[10] while the solubility of $Ag_2Ti(OTeF_5)_6$ is *many* times higher (in fact, its solubility is sufficiently high that measuring it quantitatively has been problematic). An even more striking example of solubilizing ability is evident when comparing solubilities in CFC-113 at 22 °C ($\epsilon \approx 2.4$): $AgOTeF_5$, insoluble; $AgB(OTeF_5)_4$, 0.004 M; $AgNb(OTeF_5)_6$, 0.4 M.

The anions $Nb(OTeF_5)_6^-$ and $Ti(OTeF_5)_6^{2-}$ have the potential of being less coordinating, more stable in the presence of electrophilic cations, and more solubilizing than any previously reported anions. Detailed comparisons with anions such as $B(3,5\text{-}C_6H_3(CF_3)_2)_4^-$ and $CB_{11}H_{12}^-$ will be reported in a full article. The use of $Nb(OTeF_5)_6^-$, $Ti(OTeF_5)_6^{2-}$, and other very large, highly fluorinated anions for the preparation, isolation, and complete characterization of "coordinatively unsaturated" metal and metalloid cations remains an active endeavor in this laboratory.

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Supplementary Material Available: Tables S-I-VI, listing crystallographic data, atomic coordinates and isotropic thermal parameters, bond distances, bond angles, anisotropic thermal parameters, and hydrogen atom coordinates and thermal parameters (8 pages); Table S-VII, listing observed and calculated structure factors (10 pages). Ordering information is given on any current masthead page.

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A General and Expedient Method for the Solid-Phase Synthesis of 1,4-Benzodiazepine Derivatives

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Very powerful methods have recently been developed for the combinatorial synthesis of large libraries of peptides which are then screened against a specific receptor or enzyme in order to determine the optimal peptide sequence for high affinity to that receptor or enzyme.[1] Unfortunately, peptides have limited utility as bioavailable therapeutic agents because they generally cannot be taken orally and have rapid physiological clearing times. The combinatorial synthesis and screening of bioavailable organic compounds would be a powerful extension of this approach. In this communication we report a general method for the expedient solid-phase synthesis of 1,4-benzodiazepine derivatives,[2] the critical first step in the combinatorial synthesis and screening of one of the most important classes of bioavailable therapeutic agents.[3] Because benzodiazepines are not polymers like the peptides and oligonucleotides that have previously been synthesized on solid support,[4] this report also demonstrates an important extension of solid-phase synthetic methods from the synthesis of biopolymers to the synthesis of nonpolymeric organic compounds.[5]

The 1,4-benzodiazepine derivatives are constructed on solid support from three separate components: 2-aminobenzophenones, amino acids, and alkylating agents (Scheme I). The 2-aminobenzophenone derivatives **1** are first attached to the polystyrene solid support through either a hydroxy or carboxylic acid functionality employing the acid-cleavable linker [4-(hydroxymethyl)phenoxy]acetic acid.[6] Synthesis of the benzodiazepine derivative on solid support then proceeds by removal of the FMOC protecting group from **2** by treatment with piperidine in DMF followed by coupling the resulting unprotected 2-aminobenzophenone to an α-*N*-FMOC-amino acid (Scheme I). Amide bond formation does not occur when the standard activation methods employed in solid-phase peptide synthesis are used (for example, carbodiimides and hydroxybenzotriazole or pentafluorophenyl active esters); however, treatment of the 2-aminobenzophenone with a methylene chloride solution of the α-*N*-FMOC-amino acid fluoride[7] in the presence of the acid scavenger 4-methyl-2,6-di-*tert*-butylpyridine results in complete coupling to provide amide **3**. The coupling conditions are suitable even for unreactive aminobenzophenone derivatives since complete coupling is observed for a derivative of **2** which contains both the *p*-chloro and the *m*-carboxy deactivating substituents (see **6i** and **6j** in Table I).

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