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Synthesis of 3,5-Bis(phosphonomethyl)benzoic Acid and Its Application as a Metal Oxide Surface Bivalent Anchor

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Abstract: A protected form of 3,5-bis(phosphonomethyl)benzoic acid (Bpb-OH), a metal oxide surface bivalent anchor, has been synthesized, coupled to an amine functionality, deprotected, and shown to bind to metal oxide surfaces. The protected anchor, 3,5-bis(dimethoxyphosphinylmethyl)benzoic acid (Me_4Bpb-OH) was synthesized in 23% yield over four steps, coupled to a proline-chromophore, deprotected with a solution of iodotrimethylsilane (TMSI) in acetonitrile and adsorbed to Tin(IV)-doped indium oxide and nanocrystalline TiO_2 electodes at surface coverages of 1.5×10^{-10} mol cm^{-2} and 4.9×10^{-11} mol cm^{-2}, respectively. Finally, Me_4Bpb-OH was converted to an amino derivative by attaching a diamino butane linker.

Keywords: Phosphonic acids and derivatives; Metals; Photochemistry; Electron transfer

Engineering of structurally defined arrays of photoactive molecules on the surface of semiconductor electrodes is an important element in the design of solid-state molecular devices, such as artificial photosynthetic centers, photovoltaic cells and photosensors.[1,2] Such artificial devices commonly contain an inorganic chromophore, such as a ruthenium(II)polypyridine complex, which is deposited at monolayer or sub-monolayer coverages on the surface of a metal oxide semiconductor.[3,4] Placement of the redox assembly onto a metal oxide surface such as nanocrystalline TiO_2 provides intimate electronic coupling between the metal center of the redox assembly and the conduction band of the semiconductor.[3,5] Upon photoexcitation, the adsorbed redox assembly acts as a charge-transfer sensitizer by injecting an electron into the conduction band of the metal oxide, which produces a charge-separated state. This light-induced redox reaction on a semiconductor electrode is of great interest in solid-state molecular devices.[1-3] An important factor in the design of such surface-bound molecular devices is optimization of the contact between the semiconductor and the redox assembly.

The goal of this paper is to report on the synthesis of a stable molecular anchor for attaching redox assemblies to metal oxide semiconductors based on the high binding affinity of organic phosphonates to metal oxide surfaces. Organic phosphonates and phosphates bind to metal oxide surfaces much more tightly than carboxylic acids.[6,7] The C-O-P linkage of an organic phosphate, such as $R\text{-}CH_2\text{-}O\text{-}PO_3^{2-}$, is easily hydrolyzed to form an alcohol ($R\text{-}CH_2\text{-}OH$) and an inorganic phosphate ($HO\text{-}PO_3^{2-}$). But the C-P bond of a phosphonate, such as $R\text{-}CH_2\text{-}PO_3^{2-}$, is stable to hydrolysis. In addition, two phosphonate groups on the same molecular anchor should bind much tighter to a metal oxide surface than one phosphonate group.

This paper describes the synthesis of a protected diphosphonate anchor, its coupling to a polypyridine

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Dedicated to the memory of Professor Bruce W. Erickson

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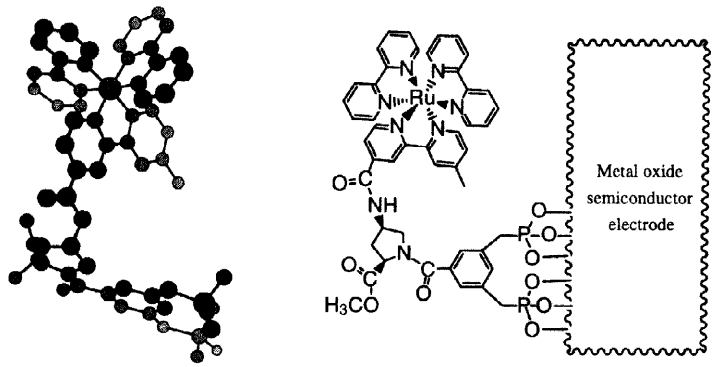

Figure 1. Two models of the anchor-proline-chromophore complex **12**, [Bpb-Pra($Ru^{II}b_2m$)-OCH_3]$^{2+}$: left, ball-and-stick model; right, metal-oxide bound model (protons not shown).

chromophore, its deprotection, and finally its demonstration as an anchor on nanocrystalline TiO_2 and Tin(IV)-doped indium oxide (ITO) electrode surfaces (Fig. 1). The protected diphosphonate anchor was also synthetically converted into an amino diphosphonate derivative which serves as a protected diphosphonate anchor and can be coupled to the C-terminus of peptide redox assemblies. This paper also reports on the deprotection of the methyl ester groups on the diphosphonic acid compound by using iodotrimethylsilane (TMSI) as a mild reagent that does not harm peptide bonds.

RESULTS AND DISCUSSION

Synthesis of the protected anchor Me_4Bpb-OH (5). 3,5-Bis(bromomethyl)benzoic acid (**4**) was prepared in three steps in 31% overall yield from commercially available trimethyl 1,3,5-benzenetricarboxylate (**1**, Lancaster, Inc.) (Fig. 2). The synthesis followed the reported procedure[8] with minor alterations. First, saponification of one methyl ester group of the triester (**1**) with one equivalent of sodium hydroxide led to 3,5-bis(methoxycarbonyl)benzoic acid (**2**). The crude product was not purified by a silica column as suggested but instead was recrystallized from 1/4 (v/v) ethyl acetate/carbon tetrachloride to afford NMR-pure diester **2** in 70% yield (Table 1). Second, diester **2** was reduced to the 3,5-bis(hydroxymethyl)benzoate (**3**) with 1 M lithium triethylborohydride in tetrahydrofuran (Super Hydride, Aldrich) as described. Anion-exchange chromatography (AG 50x5, formate form, BioRad Laboratories) of the crude product afforded NMR-pure 3,5-bis(hydroxymethyl)benzoic acid (**3**) in 49% yield. Third, acid **3** was brominated with phosphorous tribromide to yield NMR-pure 3,5-bis(bromomethyl)benzoic acid (**4**, 90% yield), which did not require recrystallization.

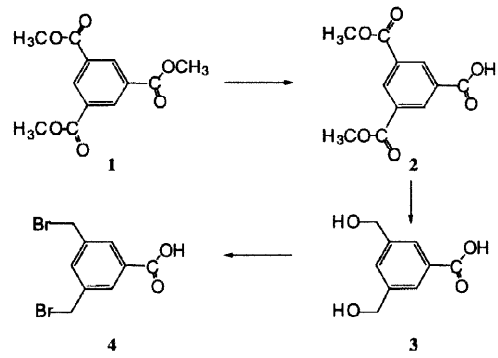

Figure 2. Synthesis of 3,5-bis(bromomethyl)benzoic acid (**4**).

A protected form of the desired molecular anchor, 3,5-bis(phosphonomethyl)benzoic acid (**7**, Bpb-OH) was needed to allow coupling of its carboxylic acid group to an amino group of a redox assembly without coupling of its free phosphonic acid groups. Thus, dibromide **4** was treated with excess trimethyl phosphite to form the desired protected anchor **5** (Fig. 3). This reaction generates methyl bromide as a byproduct. In our hands, it methylated the free carboxylic acid group of diphosphonate **5** to form a significant amount of the byproduct 3,5-bis(dimethoxyphosphinylmethyl)benzoic ester (**6**, Me_4Bpb-OCH_3). Saponification of methyl benzoate **6** with 1 to 2 equivalents of LiOH at 0°C, however, regenerated the desired benzoic acid **5**. When methyl benzoate **6** was treated with two or more equivalents of LiOH at room temperature, a substantial amount of the methyl phosponate bonds were inadvertently cleaved as indicated by TLC and percent yield calculations. The dibromide **4** was converted into the synthetically useful methyl-protected molecular anchor Me_4Bpb-OH (**5**) in 76% overall yield.

Table 1. ^{1}H NMR chemical shifts for Bpb-OH (**7**) and its precursors in various solvents.

		Chemical shift, ppm (multiplicity, Hz)				
Compound	Solvent	ϕCH_2	$POCH_3$	C^2H, C^6H	C^4H	$COCH_3$
1	$CDCl_3$	---	---	8.86 (s)	8.86 (s)	3.99 (s)
2	CD_3OD	---	---	8.77 (d 1.4)	8.75 (t 1.6)	3.97 (s)
3	CD_3OD	4.65 (s)	---	7.92 (s)	7.57 (s)	---
4	$CDCl_3$	4.52 (s)	---	8.06 (d 1.4)	7.68 (d 1.4)	---
5	D_2O	3.40 (d 22.2)	3.72 (d 10.6)	7.82 (d 1.8)	7.47 (br s)	---
6	D_2O	3.45 (d 21.7)	3.75 (d 11.0)	7.87 (d 1.8)	7.52 (br s)	3.94 (s)
7	D_2O	3.02 (d 20.3)	---	7.58 (br s)	7.34 (br s)	---

For multiplicity, br = broad; d = doublet; m = multiplet; s = singlet; t = triplet.

Synthesis of the proline-chromophore complex 10. The proline-based chromophore [Boc-Pra($Ru^{II}b_2$m)-OCH_3](PF_6) (**9**, Fig. 4), where Boc-Pra(m)-OCH_3 (**8**) is N^{α}-(1,1-dimethylethoxycarbonyl)-*cis*-4-(4'-methyl-2,2'-bipyridine-4-carboxamido)-L-proline methyl ester, Ru^{II} is ruthenium(II), and b is 2,2'-bipyridine, was prepared previously by coupling of the free carboxylic acid group of [$Ru^{II}b_2$m-OH]$^{2+}$ to the 4-amino group of Boc-Pra-OCH_3.[9,10] We report here a variation of this synthetic approach (Fig. 4). [Boc-Pra($Ru^{II}b_2$m)-OCH_3]$^{2+}$ (**9**) was synthesized by heating for 24 h at 65°C a solution of excess *cis*-bis(2,2'-bipyridine)dichlororuthenium(II) hydrate ($Ru^{II}b_2Cl_2$) and Boc-Pra(m)-OCH_3 (**8**) in methanol. Excess $Ru^{II}b_2Cl_2$, which is water insoluble, was removed by adding water and filtering. The Boc group of [Boc-Pra($Ru^{II}b_2$m)-OCH_3]$^{2+}$ (**9**) was removed by treatment with a solution of 1:1 (v/v) trifluoroacetic acid-dichloromethane to afford [H-Pra($Ru^{II}b_2$m)-OCH_3]$^{2+}$ (**10**). The decomposition products of the Boc group are volatile and were removed by rotary evaporation.

Synthesis of protected, anchor-proline-chromophore complex 11. We chose to demonstrate that the protected anchor **5**, Me_4Bpb-OH, can be attached to the amino group of proline-chromophore complex **10**, [H-Pra($Ru^{II}b_2$m)-OCH_3]$^{2+}$,(Fig. 4), for several reasons. First, the Ru^{II} core, $Ru^{II}b_2$m, is both a chromophore and a spectroscopic probe that can be monitored visually or by ultraviolet-visible absorption (UV/VIS) spectroscopy. Second, the secondary amino group of its 4-substituted proline ring is almost as

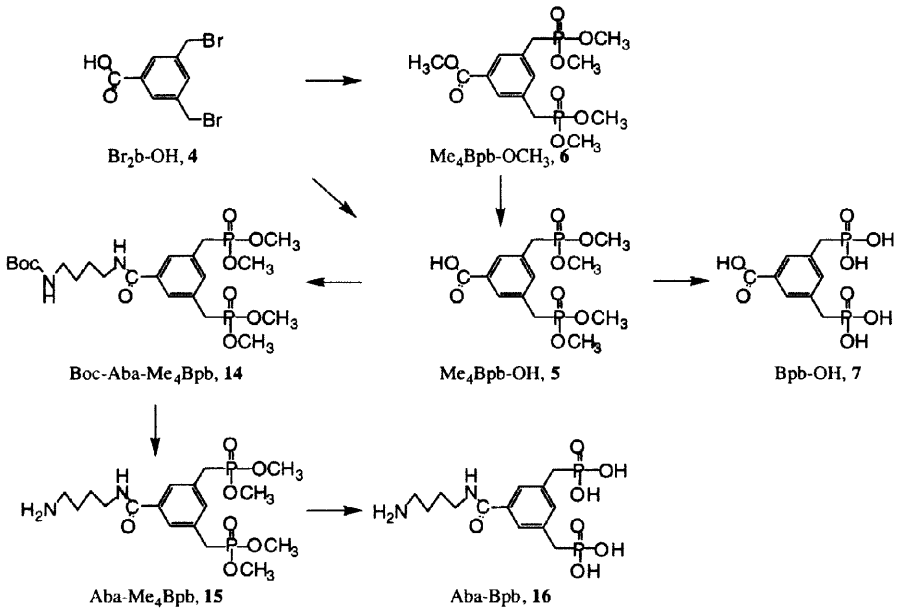

Figure 3. Synthesis of the protected anchors Me_4Bpb-OH (**5**) and Aba-Me_4Bpb (**15**), and the corresponding unprotected anchors Bpb-OH (**7**) and Aba-Bpb (**16**).

accessible to coupling with the protected anchor Me_4Bpb-OH as it is to the secondary amino group at the N-termini of oligoproline peptides, which have been used as the linear backbones of several redox arrays.[9,11] Third, the lifetimes of the metal-to-ligand charge transfer (MLCT) excited states of ruthenium(II)tris(bipyridine) complexes is sufficiently long to allow their exploitation in photochemical reactions.[12]

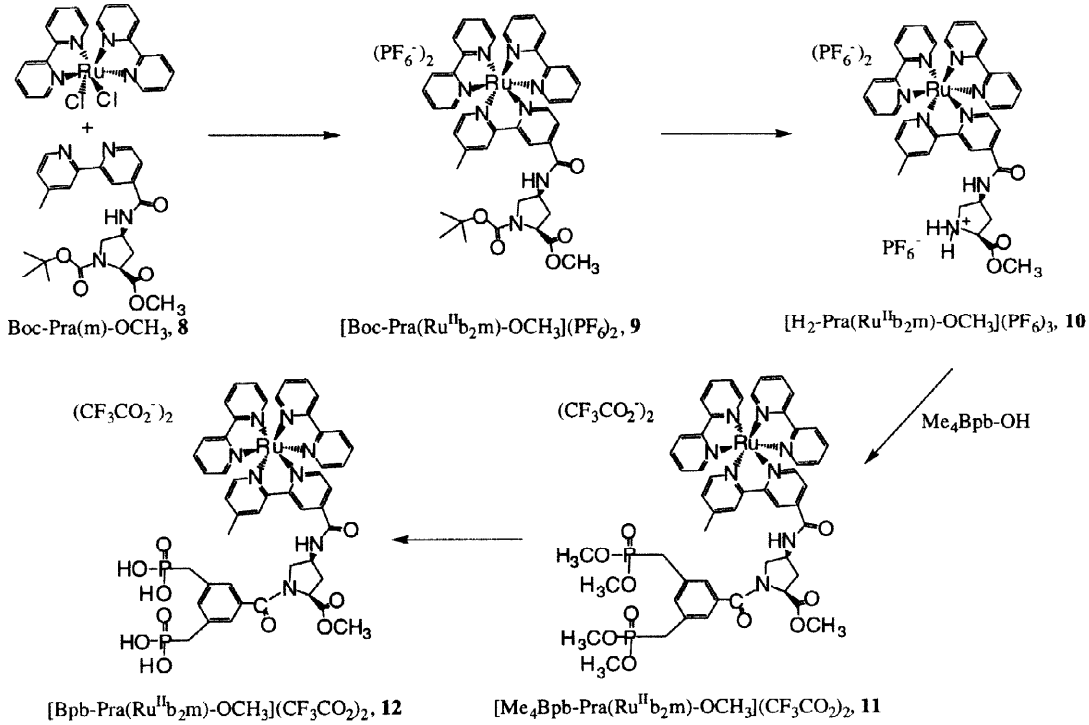

Figure 4. Synthesis and deprotection of the protected anchor-proline-chromophore (**11**).

Deprotection of methyl phosphonates. Acid-catalyzed hydrolytic dealkylation of protected phosphonates with 12 N HCl is a common procedure for deprotecting methyl phosphonates.[13] But this reagent is too harsh to use with acid-labile compounds such as peptides. Several milder reagents, such as iodotrimethylsilane (TMSI) and bromotrimethylsilane (TMSBr), also can be used to deprotect alkyl phosphonates.[13-15] These silyl reagents efficiently dealkylate phosphonate esters under neutral conditions to yield the corresponding silyl esters, which are hydrolyzed to the phosphonic acid upon aqueous workup. Both reagents contain silicon, a hard acid, which reacts readily with organic compounds containing oxygen, a hard base, forming a strong silicon-oxygen bond. The displaced iodide or bromide then acts as strong nucleophile in the subsequent displacement step, which results in cleavage of the carbon-oxygen bonds of the alkyl phosphonates and generation of alkyl iodide or alkyl bromide. Addition of water or methanol to the completed reaction results in cleavage of the silicon-oxygen bond and removal of the trimethylsilyl group from the phosphonic acid.[16] TMSBr in combination with trifluoroacetic acid generally takes 1-2 days to deprotect alkyl phosphonates.[17] We could not achieve full deprotection of protected anchor **5** in two days using a mixture of 1 M TMSI, 1 M thioanisole, and 10 equivalents *m*-cresol in trifluoroacetic acid (TFA) (Table 2). But a 1 M solution of TMSI in acetonitrile was found to deprotect both tetramethyl phosphonates **5** and **11** in less than 5 min at 0°C. We chose to use TMSI because it is generally more reactive than TMSBr.[14,18] Several other groups have reported that a solution of TMSI in acetonitrile, chloroform, or carbon tetrachloride cleaves alkyl phosphonate groups in minutes.[16,19]

Table 2. Reagents and conditions for the deprotection of the methoxy-protected diphosphonate compounds.

Compound	Reagents	Temperature (°C)	Time (h)	Deprotection (%)
5	12 N HCl	100	< 20	> 90
5	TMSI/ACN	0	< 0.1	> 90
5	TMSI/EDT/ACN	0	< 0.1	> 90
5	TMSI/thioanisole/ACN	0	< 0.1	> 90
5	TMSI/DTT/ACN	25	< 0.1	> 90
5	TMSI/TFA/thioanisole/ cresol	25	20	< 30
11	TMSI/ACN	0	< 2	> 90

As a precaution to guard against subsequent methylation by methyl iodide[14], we tested the deprotection of Me_4Bpb-OH by using TMSI with a combination of scavengers, such as thioanisole, ethanedithiol, dithiothreitol, and *m*-cresol. Addition of 10-50 equivalents of scavengers to the cleavage mixture still resulted in cleavage in less than 5 min, but the removal of the scavengers required additional purification steps.

TMSI cleaves other protective groups, including ethers, esters, carbamates, and ketals.[14] A 1 M solution of TMSI in acetonitrile at 0°C for two hours fully deprotected the dimethoxyphosphino groups of the protected anchor-proline-chromophore complex **11** but left the methoxycarbonyl group mostly intact. Electrospray ionization mass spectrometry showed that only ~10% of the methoxycarbonyl was hydrolyzed. Finally, reversed phase (RP) HPLC purification afforded NMR-pure [Bpb-Pra($Ru^{II}b_2m$)-OCH_3]$^{2+}$ (**12**) as the trifluoroacetate salt in 60% yield (Fig. 4).

Cyclic voltammetry and surface-binding studies. Cyclic voltammetry studies of solutions of both the protected and deprotected anchor-proline-chromophore complexes [Me_4Bbp-Pra($Ru^{II}b_2m$)-OCH_3]$^{2+}$ (**11**) and [Bpb-Pra($Ru^{II}b_2m$)-OCH_3]$^{2+}$ (**12**), respectively, in 0.1 M tetra(1-butyl)ammonium

hexafluorophosphate (TBAH) in CH_3CN revealed a reversible oxidation for the $Ru^{III/II}$ couple at 1.29 V vs. saturated calomel electrode (SCE) with a peak splitting of 70 mV at 100 mV/s. When the deprotected complex **12** ($[Bpb\text{-}Pra(Ru^{II}b_2m)\text{-}OCH_3]^{2+}$) was surface absorbed to a Sn(IV)-doped indium oxide (ITO) electrode from CH_3CN (Fig. 5) , it also displayed a reversible $Ru^{III/II}$ couple at 1.28 V with a peak splitting of 28 mV at 100 mV/s.

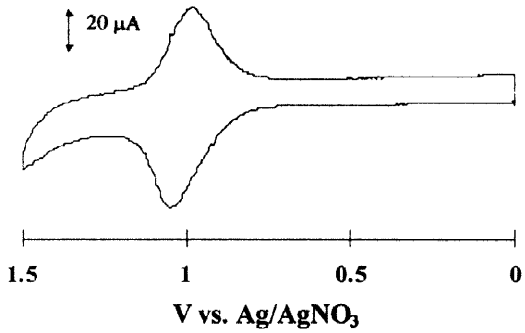

Figure 5. Cyclic voltammogram of $[Bpb\text{-}Pra(Ru^{II}b_2m)\text{-}OCH_3](CF_3CO_2)_2$ on ITO measured in 0.1M TBAH in CH_3CN at a scan rate of 100 mV/s.

The surface coverage of $[Bpb\text{-}Pra(Ru^{II}b_2m)\text{-}OCH_3]^{2+}$ (complex **12**) on ITO followed the Langmuir isotherm suggesting that the binding to the surface is reversible as peviously reported for other ruthenium polypyridine complexes[6], and reached saturation in a solution of 4×10^{-5} M complex **12** with a final coverage $\Gamma = 1.5 \times 10^{-10}$ mol/cm^2. From the Langmuir analysis, the equilibrium constant for surface adsorption was $K = 5 \times 10^5$ M^{-1}. For comparison, a limiting surface coverage of 1.1×10^{-10} mol/cm^2 with $K = 0.8 \times 10^5$ M^{-1} has been found for $[Ru^{II}(b)_2(4,4'\text{-}(CO_2H)_2b)](PF_6)_2$ adsorbed onto ITO from CH_3CN.[3] A monolayer coverage of 1.1×10^{-10} mol/cm^2 is calculated for $[Ru^{II}(b)_3]^{2+}$ complexes by assuming they are closely packed spheres with 7 Å radii (estimated from van der Waals radii) on a flat surface.[3] $[Bpb\text{-}Pra(Ru^{II}b_2m)\text{-}OCH_3]^{2+}$ (complex **12**) adsorbed onto the surface of nanocrystalline TiO_2 electrodes exhibited a MLCT absorbance at 458 nm. Based on the molar absorptivity of $[Ru^{II}(b)_3]^{2+}$ (13,000 M^{-1}cm^{-1}) and the surface roughness (η = 1330) for the nanocrystalline TiO_2 electrodes, the surface coverage of complex **12** on TiO_2 was estimated to be 4.9×10^{-11} mol/cm^2. Surface roughness of the nanocrystalline TiO_2 electrodes is defined as the ratio of the effective surface area on the nanocrystalline layer to its projected area and was calculated based on the absorption of $[Ru^{II}(b)_2(4,4(CO_2H)_2\text{-}b)]^{2+}$ at full coverage with $A(\lambda) = 1000\Gamma\varepsilon(\lambda)$ and $\eta = \Gamma/\Gamma_{monolayer}$.

$[Bpb\text{-}Pra(Ru^{II}b_2m)\text{-}OCH_3]^{2+}$ (complex **12**) adsorbed onto TiO_2 was stable for 24 h under standard peptide coupling conditions (millimolar concentrations of 1-benzotriazoleoxy)tris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP), 1-hydroxybenzotriazole hydrate (HOBT), *N*-methylmorpholine (NMM), and 0.1 mM 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2). Complex **12** adsorbed onto TiO_2 was also stable under Boc deprotection conditions (1:1 (v/v) trifluoroacetic acid/ methylene chloride). In water, the complex desorbed from a TiO_2 surface at pH above 3. Based on these results, it may be possible to adsorb a redox assembly containing the deprotected anchor Bpb onto a metal oxide surface such as ITO or TiO_2 and to covalently couple a variety of photoactive species to the redox assembly while it is anchored onto the electrode surface. This would allow rapid monitoring of the photophysical properties of new redox assemblies and may lead to a family of novel molecular devices.

Synthesis of diphosphonate anchors containing an amino group. 1-Amino-4-Boc-aminobutane (Boc-Aba-H) was coupled to the free carboxylic acid group of the protected anchor Me_4Bpb-OH (**5**) to furnish the fully protected, amine-containing anchor Boc-Aba-Me_4Bpb (**14**) in 38% yield (Fig. 3). The amino diphosphonate Aba-Bpb (**16**) contains two phosphonate groups for anchoring to a metal oxide electrode surface and an amino group for coupling to an N-protected amino acid. In this manner, the Bpb anchor could be present

at the C-terminus of a peptide and commercially available N-protected amino acids could be coupled through the formation of amide bonds. The Boc group of **15** was removed by treatment with 1:1 (v/v) trifluoroacetic acid/dichloromethane to afford Aba-Me_4Bpb (**15**). The free amino group of this protected diphosphonate anchor could be coupled to another residue and the dimethyl phosphonate groups could be deprotected with TMSI before adsorption of the new peptide-anchor to the surface of a metal oxide electrode. Deptrotection with TMSI afforded the fully unprotected Aba-Bpb (**16**), which may also be adsorbed to a metal oxide surface.

EXPERIMENTAL PROCEDURES

Materials and Methods. Uncorrected melting points were measured between glass cover slips. Whatman Diamondback F-254 silica-gel plates were used for TLC. ^{1}H NMR spectra were recorded at 500 MHz on a Bruker AMX500 spectrometer using 0.75% 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid sodium salt and tetramethylsilane as the internal standards. 4'-Methyl-2,2'-bipyridine-4-carboxylic acid (m-OH)[20], *cis*-N^{α}-Boc-4-amino- L-proline methyl ester (Boc-Pra-OCH_3)[10], and Boc-Pra(m)-OH[21] were synthesized as described. [Ru^{II}(b)$_2$(4,4'-$(CO_2H)_2$bpy)]$(PF_6)_2$ [3] was prepared as reported. N-Boc-1,4-diaminobutane (Boc-Aba) was purchased from Aldrich. Copper-stabilized TMSI was purchased from Aldrich and used immediately after opening. Analytical and preparative HPLC were performed with a Rainin Dynamax chromatograph monitored at 230 nm, 270 nm, or 460 nm. Octadecyl-silica (Vydac C18) was both used analytically (4.6 mm x 250 mm column eluted at 1.0 mL/min) and preparatively (12.5 mm x 250 mm column eluted at 5.0 mL/min). ESI mass spectra were recorded on a Perkin-Elmer Sciex API-I mass spectrometer (Ontario, Canada) equiped with a nebulizer-assisted electrospray and calibrated with poly(propylene glycol) ions. The solvents CH_3CN (Baxter; B&J, High Purity) and C_2H_5OH (AAPER Alcohol and Chemical Co, Absolute) were used as received. [N(n-$C_4H_9)_4$](PF$_6$) or TBAH (Aldrich; 98%) was recrystallized twice from ethanol. Indium oxide (ITO: In_2O_3, Sn) coated glass slides were purchased from Delta Tech. Ltd (Stillwater, MN). The ITO slides were scored with a diamond tipped stylus and cleaved with pressure into 1 cm strips. Before surface attachment, ITO electrodes were washed with ethanol and thoroughly rinsed with purified water. They were then placed in solutions 1 x 10^{-5} M in metal complex as PF_6^- salts in CH_3CN for 48 hours. TiO_2 electrodes were prepared by a literature procedure.[22] They were derivatized with a metal complex by first heating the electrodes to 400 °C for 30 minutes over O_2 after which the electrodes were cooled and placed in solutions 1 x10^{-5} M in metal complex as PF_6^- salts in CH_3CN for 48 hours.

Electrochemistry and surface-binding measurements. For surface electrochemistry, cyclic voltammetric experiments were conducted with a PAR 273 potentiostat by using the standard three-electrode configuration in a three-compartment cell. The medium was 0.1 M TBAH in CH_3CN. The reference electrode was Ag/$AgNO_3$ (0.1 M TBAH and 0.01 M $AgNO_3$ in CH_3CN), which was 315 mV more positive than SCE. The counter electrode was Pt and the working electrode was the derivatized ITO. Surface coverage of electroactive complex was calculated from cyclic voltammograms. Using an in-house written program, the area under the voltammetric waves was integrated after correction for background current and divided by the scan rate and electron charge. As measured, the electrode areas were between 2 to 3 cm^2 and used without correction for surface roughness. For solution electrochemistry, cyclic voltammetric experiments were conducted by using the standard three-electrode configuration in a one-compartment cell. The medium was 0.1 M TBAH in CH_3CN. The reference electrode was Ag/$AgNO_3$ and the counter and working electrodes were Pt. UV-visible absorbance

measurements were made on a HP-8452 diode array spectrophotometer and referenced against a solvent blank (CH_3CN). The TiO_2 electrodes were placed in a 1-cm cuvette containing CH_3CN and positioned against the side of the cell for each measurement. Surface coverages of the metal complexes on the electrode, Γ in mol/cm^2, were calculated from the absorbance measurements after subtraction of a blank TiO_2 electrode. Surface coverage was measured by absorption spectroscopy, and the relationship, $A(\lambda) = 1000\Gamma\varepsilon(\lambda)$, in which $A(\lambda)$ and $\varepsilon(\lambda)$ are the absorbance and molar extinction coefficient in $M^{-1}cm^{-1}$. The molar extinction coefficient was measured in CH_3CN for $[Ru^{II}(b)_2(4,4'\text{-}(CO_2H)_2b)](PF_6)_2$, ($\varepsilon$(464nm) = 13000 $M^{-1}cm^{-1}$) and the same value was used for $[Bpb\text{-}Pra(Ru^{II}b_2m)\text{-}OCH_3]^{2+}$(**12**).

3,5-Bis(dimethoxyphosphinylmethyl)benzoic acid (5, Me_4Bpb-OH). 3,5-Bis(bromomethyl)benzoic acid (**4**, 4.6 g, 14.9 mmol, 1.0 equiv) was dissolved in trimethyl phosphite (35.2 mL, 298 mmol, 20 equiv). The clear mixture was heated at reflux for 16 h under argon. Excess trimethyl phosphite was removed by rotary evaporation under high vacuum. Carbon tetrachloride (5 mL) was added to the reaction mixture and rotary evaporated to remove any excess trimethyl phosphite. TLC and ^{1}H NMR show that the resulting oil contained no starting material but only a mixture of Me_4Bpb-OH (**5**) and Me_4Bpb-OCH_3 (**6**). The crude mixture was dissolved in H_2O and washed 4 times with CH_2Cl_2 to remove the Me_4Bpb-OCH_3. The aqueous layer was acidified to pH 2 by dropwise addition of HCl, extracted five times with CH_2Cl_2, dried over Na_2SO_4, and rotary evaporated to yield Me_4Bpb-OH as a white solid. The solid was dried overnight under high vacuum to afford the TLC and NMR-pure Me_4Bpb-OH as a white solid (2.2 g, 40 % yield). The residual Me_4Bpb-OCH_3 (2.7 g, 7.1 mmol, 1.0 equiv) solution was rotary evaporated and dissolved in 2:1 (v/v) CH_3OH/H_2O (200 mL). Solid LiOH (600 mg, 14.2 mmol, 2.0 equiv) was added and the reaction mixture stirred in an ice bath for 7 h. The solvent was removed by rotary evaporation under high pressure, redissolved in water, and washed four times with CH_2Cl_2. The aqueous layer was acidified to pH 2 by dropwise addition of HCl and washed five times with CH_2Cl_2. The organic washes were combined, dried over Na_2SO_4, rotary evaporated, and dried overnight in a vacuum dessicator to afford Me_4Bpb-OH (**5**, 1.90 g, 73% yield for the saponification reaction) as a white solid: mp 155.2-156.8°C; R_f 0.21 (85/15 (v/v) $CHCl_3/CH_3OH$); ESI MS (calcd for $C_{13}H_{21}O_8P_2$ (Me_4Bpb-OH+H$^+$): 367.2 Da) 367 Da; ^{1}H NMR (Me_4Bpb-OH, D_2O, pH 3, 500 Mhz) δ 3.40 (d, J = 22 Hz, 4 H, PCH_2), 3.72 (d, J = 11 Hz, 12 H, $POCH_3$), 7.47 (br s, 1 H, C^4H), and 7.82 ppm (d, J = 1.8 Hz, 2 H, $C^{2,6}H$); ^{31}P NMR (500 MHz, D_2O, pH 2.6) δ 62.5-63.0 ppm (m).

Methyl 3,5-bis(dimethoxyphosphinylmethyl)benzoate (6, Me_4Bpb-OCH_3). Me_4Bpb-OCH_3 (**6**) was isolated from the crude Me_4Bpb-OH reaction as described above: mp 109.5-112.0°C; R_f 0.55 (85/15 (v/v) $CHCl_3/CH_3OH$); ESI MS (calcd for $C_{14}H_{22}O_8P_2$ (Me_4Bpb-OCH_3+H$^+$): 381.3 Da) 381 Da; ^{1}H NMR (Me_4Bpb-OCH_3, 500 Mhz, D_2O) δ 3.45 (d, J = 21.7 Hz, 4 H, PCH_2), 3.75 (d, J = 11.0 Hz, 12 H, $POCH_3$), 3.94 (s, 3 H, $COCH_3$), 7.52 (br s, 1 H, C^4H), and 7.87 ppm (d, J = 1.8 Hz, 2 H, $C^{2,6}H$).

[Boc-Pra($Ru^{II}b_2$m)-OCH_3]$(PF_6)_2$ (10). A solution of Boc-Pra(m)-OCH_3 (**8**, 400 mg, 0.91 mmol, 1.0 equiv.) and $Ru^{II}b_2Cl_2$ (880 mg, 1.82 mmol, 2.0 equiv., Aldrich) in methanol (10 mL) was heated at reflux for 24 h until Boc-Pra(m)-OCH_3 was no longer observed by TLC. The reaction was also followed by UV/VIS spectroscopy. During the course of the reaction, the two visible-light absorption peaks for $Ru^{II}b_2Cl_2$ (364 nm and 526 nm) converged into a single absorption peak corresponding to the product

(456 nm). The solvent was removed by rotary evaporation. Cold water (10 mL) was added to the black solid and the reaction mixture was filtered through a 0.45 um filter to remove the water insoluble $Ru^{II}b_2Cl_2$. After NH_4PF_6 was added to the aqueous solution, an orange precipitate was formed and collected by filtration. The residue was dried overnight in a vacuum desiccator to afford [Boc-Pra($Ru^{II}b_2$m)-OCH_3]$(PF_6)_2$ (**9**) as an orange solid (680 mg, 66% yield): R_f 0.48 (85/10/5 (v/v) $CHCl_3/CH_3OH/CH_3CO_2H$, alumina); ^{1}H NMR (CD_3CN, 500 Mhz) δ 1.39 and 1.43 (2s, 9 H, $(CH_3)_3CO$), 2.58-2.67 (m, 1 H, Pra β), 2.56 (s, 3 H, m 4' CH_3), 3.12-3.21 (m, 1 H, Pra β), 3.46-3.53 (m, 1 H, Pra δ), 3.73 and 3.74 (2s, 3 H, Pra OCH_3), 3.69-3.76 (m, 1 H, Pra δ), 4.33 (d, J = 10 Hz, d, J = 4 Hz, 1 H, Pra γ or α), 4.62-4.67 (m, 1 H, Pra γ or α), 7.32 (d, J = 6 Hz, 1 H, m 5'), 7.37-7.43 (m, 4 H, 4xb5), 7.57 (d, J = 6 Hz, 1 H, m 5 or m 6'), 7.61 (d, J = 5 Hz, m 5 or m 6'), 7.70-7.78 (m, 5 H, 4xb6 and m 6), 7.86-7.90 (m, 1 H, CONH), 8.07 (t, J = 8 Hz, 4 H, 4xb4), 8.51 (s, 1 H, m 3'), 8.51 (d, J = 8 Hz, 4 H, 4xb3) and 8.75 ppm (s, 1 H, m 3).

[H_2-Pra($Ru^{II}b_2$m)-OCH_3]$(PF_6)_3$ (10). The complex [Boc-Pra($Ru^{II}b_2$m)-OCH_3]$(PF_6)_2$ (**9**, 300 mg, 0.26 mmol) was dissolved in 1/1 (v/v) trifluoroacetic acid/methylene chloride (10 mL) and stirred for 30 min at room temperature. The solvent was removed by rotary evaporation, redissolved in 1/1 (v/v) trifluoroacetic acid/methylene chloride, stirred for another 30 min at room temperature, and dried by rotary evapoartion to yield a dark brown solid. The residue was dissolved in 2/1 (v/v) water/acetonitrile, concentrated HPF_6 (100 uL) was added, and lyophilized overnight to afford [H_2-Pra($Ru^{II}b_2$m)-OCH_3]$(PF_6)_3$ (**10**) as an orange solid (220 mg, 80% yield): ESI MS (calcd for $C_{38}H_{36}N_8O_3Ru^+$: 753.8 Da) 753.2 Da; ^{1}H NMR (D_2O/CF_3CO_2D, pH 1.6, 500 Mhz) δ 2.37-2.44 (m, 1 H, Pra β), 2.48 (s, 3 H, m 4' CH_3), 2.84-2.92 (m, 1 H, Pra β), 3.56-3.61 (m, 5 H, Pra δ), 3.75 (d, J = 11 Hz, d, J = 8 Hz, 1 H, Pra δ), 3.79 and 3.80 (2s, 3 H, Pra OCH_3), 4.61-4.71 (m, 2 H, Pra γ & α), 7.20 (d, J = 6 Hz, 1 H, m 5'), 7.27-7.34 (m, 4 H, 4xb5), 7.53 (d, J = 6 Hz, 1 H, m 5), 7.58 (d, J = 6 Hz, m 6'), 7.70-7.78 (m, 4 H, 4xb6), 7.93 (d, J = 6 Hz, 1 H, m 6), 7.95-8.02 (m, 4 H, 4xb4), 8.41 (s, 1 H, m 3'), 8.47 (d, J = 8 Hz, 4 H, 4xb3) and 8.72 ppm (s, 1 H, m 3).

[Me_4Bpb-Pra($Ru^{II}b_2$m)-OCH_3]$(CF_3CO_2)_2$ (11). A solution of Me_4Bpb-OH (**5**, 9.2 mg, 0.025 mmol, 1.0 equiv), [H_2-Pra($Ru^{II}b_2$m)-OCH_3]$(PF_6)_3$ (**10**, 30.0 mg, 0.025 mmol), PyBOP (13.1 mg, 0.025 mmol, 1.0 equiv), DMAP (1.5 mg, 0.013 mmol, 0.5 equiv), HOBt (3.4 mg, 0.025 mmol, 1.0 equiv), and NMM (8.3 μL, 0.075 mmol, 1.0 equiv) in DMF (200 μL) was stirred for 20 h at room temperature. The solvent was removed by rotary evaporation under high vacuum to yield a black oil. The latter was dissolved in CH_2Cl_2 and a solution of water containing several drops of HPF_6 and NH_4PF_6 (50 mg), and washed five times with 5% citric acid, once with saturated NaCl, twice with 1 M $NaHCO_3$, once with saturated NaCl, dried over anhydrous Na_2SO_4, and rotary evaporated to a dark brown solid which still contained trace impurities. The crude was dissolved in 3/1 (v/v) water/acetonitrile (5 mL) and purified by RP HPLC using an octadecyl-silica column (Vydac C18, 1.0 x 25.0 cm) eluted at 5.0 mL/min with a linear gradient of 13-27% acetonitrile and 0.08% trifluoroacetic acid over 60 min. The fractions corresponding to the clean product were combined, placed on the Speedvac for 60 min to remove the acetonitrile, and lyophilized overnight to yield NMR-pure complex **11** as a red trifluoroacetate salt (7 mg, 25 %yield): R_f 0.20 (6/3/1 (v/v/v) $CHCl_3/CH_3OH/NH_4OH$); ESI MS (calcd for $C_{51}H_{54}N_8O_{10}P_2Ru$ ([Me_4Bpb-Pra(Rub_2m)-OCH_3]$^{2+}$): 1102.0 Da) 1102.0 Da; ^{1}H NMR (D_2O, 500 Mhz, isomer A/isomer B = 4/1) δ 2.30-2.39 (m, 1 H, Pra β, A&B), 2.54 (s, 3 H, m 4' CH_3, A&B), 2.81-2.89 (m, 1 H, Pra β, A&B), 3.37-3.47 (m, 5 H, Pra δ &

PCH_2, A&B), 3.65-3.77 (m, 12 H, $POCH_3$, A&B), 3.82 (s, 3 H, Pra OCH_3, A&B), 3.99 (d, J = 11 Hz, d, J = 6 Hz, 1 H, Pra δ, A), 4.13-4.18 (m, 1 H, Pra δ, B), 4.60-4.82 (m, 2 H, Pra γ & α, A&B), 7.26 (d, J = 6 Hz, 1 H, m 5', A&B), 7.31-7.41 (m, 5 H, 4xb5 & Bpb C^4H, A&B), 7.43 (s, 2 H, Bpb C^2H, A&B), 7.54-7.58 (d, 1 H, m 5, A&B), 7.64 (d, J = 6 Hz, m 6', A&B), 7.76-7.83 (m, 4 H, 4xb6, A&B), 7.96-7.99 (m, 1 H, m 6, A&B), 8.04 (t, J = 8 Hz, 4 H, 4xb4, A&B), 8.46 (s, 1 H, m 3', A&B), 8.52 (d, J = 8 Hz, 4 H, 4xb3, A&B) and 8.74 ppm (s, 1 H, m 3, A&B); ^{31}P NMR (D_2O, 500 Mhz) δ 62.4-62.9 ppm (m).

[Bpb-Pra($Ru^{II}b_2m$)-OCH_3]$(CF_3CO_2)_2$ (12). A solution of [Me_4Bpb-Pra($Ru^{II}b_2m$)-OCH_3]$^{2+}(CF_3CO_2)_2$ (**11**, 5 mg, 4 μmol) and TMSI (1 M) in acetonitrile (1 mL) was stirred for 2 h in an ice bath under argon and in the absence of light. The reaction mixture was quenched with water (1 mL) and lyophilized overnight. The solid was redissolved in water, washed through a 0.45 um filter, and relyophilized overnight to afford the crude product **12** as an orange trifluoroacetate salt. Proton NMR spectroscopy showed minor impurities, so it was dissolved in 3/1/0.1 (v/v) water/acetonitrile/trifluoroacetic acid (5 mL) and purified by RP HPLC by using an octadecyl-silica column (Vydac C18, 1.0 x 25.0 cm) eluted at 5.0 mL/min with a linear gradient of 13-22% acetonitrile and 0.08% trifluoroacetic acid over 60 min. The fractions corresponding to the clean product were combined, placed on the Speedvac for 60 min to remove the acetonitrile, and lyophilized overnight to yield NMR-pure complex **12** as a red trifluoroacetate salt (3 mg, 60% yield): R_f 0.0 (85/15 (v/v) $CHCl_3/CH_3OH$); ESI MS (calcd for $C_{47}H_{44}N_8O_{10}P_2Ru$ ([Bpb-Pra($Ru^{II}b_2m$)-OCH_3]$^{2+}$): 1043.9 Da) 1044 Da; ^1H NMR (D_2O, pH 2.1, 500 Mhz) δ 2.27-2.34 (m, 1 H, Pra β), 2.54 (s, 3 H, m 4' CH_3), 2.80-2.87 (m, 1 H, Pra β), 3.04-3.12 (d, J = 21 Hz, 4 H, PCH_2); 3.69-3.85 (m, 4 H, Pra δ & Pra OCH_3), 4.01-4.07 (m, 1 H, Pra δ), 4.60-4.75 (m, 2 H, Pra α & Pra γ), 7.25 (d, 1 H, m 5'), 7.32-7.39 (m, 5 H, 4xb5 & Bpb C^4H), 7.53-7.57 (d, 1 H, m 5), 7.63 (d, J = 6 Hz, 1 H), 7.75-7.84 (m, 4 H, 4xb6), 7.96 (d, J = 6 Hz, 4 H, m 6), 8.04 (t, J = 8 Hz, 4 H, 4xb4), 8.24 (s, 2 H, Bpb $C^{2,6}H$), 8.47 (s, 1 H, m 3'), 8.52 (d, J = 8 Hz, 4 H, 4xb3) and 8.74 ppm (s, 1 H, m 3).

3,5-Bis(phosphonomethyl)benzoic acid (7, Bpb-OH)) [Method 1, HCl deprotection]. Me_4Bpb-OH (**5**, 5.0 mg, 0.014 mmol) was added to 12 N HCl (1 mL) and the mixture heated at reflux overnight. After allowing the reaction mixture to cool to room temperature, several drops of concentrated NaOH was added until the solution was at pH 2. The mixture was extracted six times with ethyl acetate and the organic layer was dried over Na_2SO_4 and filtered. The solvent was removed by rotary evaporation and the sample dissolved in 4/1 (v/v) water/acetonitrile and lyophilized overnight to afford deprotected acid **7** as a white solid (3.5 mg, 83% yield): R_f 0.0 (6:3:1 (v/v/v) $CHCl_3/CH_3OH/NH_4OH$); ^1H NMR (D_2O, pH 2.1, 500 Mhz) δ 3.21 ppm (d, J = 21.3 Hz, 4 H, PCH_2), 7.50 (br s, 1 H, C^4H), and 7.83 (d, J = 1.8 Hz, 2 H, $C^{2,6}H$).

3,5-Bis(phosphonomethyl)benzoic acid (7, Bpb-OH) [Method 2, TMSI deprotection]. Five different conditions involving TMSI were applied to Me_4Bpb-OH (10 mg, 0.027 mmol): 1 M TMSI (213 μL) in acetonitrile (1.29 mL); 1 M TMSI (213 μL) in acetonitrile (1.26 mL) and ethanedithiol (10 equiv.); 1 M TMSI (213 μL) in acetonitrile (1.25 mL) and thioanisole (10 equiv.); 1 M TMSI (213 μL) in acetonitrile (1.29 mL) and dithiothreitol (10 equiv.); and 1 M TMSI (1.46 mL) in trifluoroacetic acid (7.36 mL), thioanisole (1.17 mL), and m-cresol (10 equiv.). All five reactions were stirred under argon, in the absence of light, and in an ice bath. Aliquots (10 μL) of the reaction mixtures were taken out at 1 min, 5 min, 1 h, and 24 h. Each

aliquot was immediately dissolved in 100 μL water, and placed in the refrigerator until each was analyzed by analytical RP HPLC (octadecyl-silica column) at 270 nm. After four days, each of the reaction mixtures was quenched with water (1 mL each), rotary evaporated to remove the acetonitrile, and extracted with CH_2Cl_2 (3 times each) to remove the scavengers. The aqueous phase of each of the five reactions was frozen and lyophilized and the resulting solids were analyzed by ^1H NMR, which were all consistent with the ^1H NMR spectrum from the HCl hydrolysis reaction detailed above. One of the cleavage reactions was purified by RP HPLC (Vydac C18, 1.0 x 25.0 cm, eluted at 5.0 mL/min with a linear gradient of 0-70% acetonitrile and 0.08% trifluoroacetic acid over 60 min) and analyzed by ^1H NMR in order to verify that the analytical RP HPLC peak we thought corresponded to the fully deprotected product was indeed the fully deprotected product: R_f 0.0 (6:3:1 (v/v/v) $CHCl_3/CH_3OH/NH_4OH$).

Boc-Aba-Me$_4$Bpb (14). A solution of Me$_4$Bpb-OH (**5**, 200 mg, 0.55 mmol, 1.0 equiv), Boc-Aba-H (104 μL, 0.55 mmol), BOP (289 mg, 0.66 mmol, 1.2 equiv), DMAP (80 mg, 0.66 mmol, 1.2 equiv), HOBt·H_2O (88 mg, 0.66 mmol, 1.2 equiv), and NMM (72 μL, 2.62 mmol, 4.8 equiv) in DMF was stirred at room temperature for 24 h. The solvent was removed by rotary evaporation under high vacuum to yield an oil, which was dissolved in ethyl acetate, washed five times with 10% citric acid, once with saturated NaCl, twice with 1 M $NaHCO_3$, once with saturated NaCl, dried over anhydrous Na_2SO_4, and rotary evaporated to afford the protected amino phosphonate **14** (110 mg, 38% yield) as a solid: R_f 0.54 (85/15 (v/v) $CHCl_3/CH_3OH$); ^1H NMR ($CDCl_3$, 500 Mhz) δ 1.432 (s, 9 H, Boc), 1.557 and 1.635 (2 p, J = 5.6 Hz, CCH_2CH_2C), 3.11-3.16 (m, 2 H, CH_2N), 3.157 (d, J = 21.7 Hz, 4 H, PCH_2), 3.417 (q, J = 6.5 Hz, 2 H, CH_2N), 3.681 (d, J = 10.6 Hz, 12 H, $POCH_3$), 5.07-5.16 (m, 1 H, CONH), 7.37 (m, 1 H, Bpb C^4H), and 7.641 ppm (br s, 2 H, Bpb $C^{2,6}H$).

Aba-Bpb (16). A solution of Boc-Aba-Me$_4$Bpb (**14**, 110 mg) in 1/1 (v/v) trifluoroacetic acid/dichloromethane (4 mL) was stirred at room temperature for 30 min. The solvent was removed by rotary evaporation at 35°C and placed in a vacuum dessicator overnight to afford Aba-Me$_4$Bpb (**15**) as an oil, which was used without further purification. Then Aba-Me$_4$Bpb (**15**) was dissolved in a solution of 1 M TMSI in acetonitrile and stirred in an ice bath under argon and in the absence of light for 1 h. Two volumes of water were added to the reaction mixture, which was stirred for 5 min and then lyophilized overnight to yield a brown solid. The solid was dissolved in water, filtered through a 0.2 μm filter, and purified by RP HPLC (Vydac C18, 1.0 x 25.0 cm) eluted at 5.0 mL/min with a linear gradient of 0-14 % acetonitrile and 0.08% trifluoroacetic acid over 60 min to yield NMR-pure amino diphosphonate **16** as a white solid: R_f 0.0 (85/15 (v/v) $CHCl_3/CH_3OH$); ^1H NMR (D_2O, pH 2.3, 500 Mhz) δ 1.71-1.84 (m, CCH_2CH_2C), 3.09 (t, 2 H, CH_2N), 3.19 (d, J = 21.3 Hz, 4 H, PCH_2), 3.48 (t, J = 6.5 Hz, 2 H, CH_2N), 7.44 (br s, 1 H, Bpb C^4H), and 7.55 ppm (d, J = 1.8 Hz, 2 H, Bpb $C^{2,6}H$).

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