complex with a bridging μ-C=PR ligand. The atoms C(1), Cl(a), Cl(b), P(4), P(1), C(2), Pt(1), and Pt(2) are all coplanar within 0.134 Å; of the coordinated atoms, only P(2) and P(3) are out of this plane, the Pt(1)-P(2) and Pt(1)-P(3) bond vectors being approximately perpendicular to this plane. The C(1)-P(1) distance (1.67 (1) Å) in the μ-C=PR ligand is the same as the length of the C=P double bond in Ph(H)C=PR, where R = 2,4,6-tri-*tert*-butylphenyl.[10] It is substantially longer than the C≡P triple bond (1.516 (13) Å)[11] in RC≡P (R = 2,4,6-tri-*tert*-butylphenyl) but is shorter than the C(sp^2)—P single bond C(2)—P(1) (1.89 (1) Å) in **2**.

The Pt-C distances to the bridging C=PR from the inequivalent Pt atoms are significantly different; Pt(2)-C(1) (1.89 (1) Å) is 0.22 Å shorter than Pt(1)-C(1) (2.107 (9) Å). Also the Pt-C(1)-P(1) angles are vastly different; the Pt(2)-C(1)-P(1) angle (164.1 (6)°) approaches linearity while Pt(1)-C(1)-P(1) (112.0 (5)°) is sharply bent. Thus, the geometry of the C=PR ligand shows that it is not an analogue of a symmetrically bridging isocyanide as occurs in such compounds as the triangular $Pt_3(\mu\text{-}CNR)_3(CNR)_3$[12] or dinuclear $Cp_2Fe_2(\mu\text{-}CNR)_2(CNR)_2$.[13] The long nonbonding Pt(1)-P(1) distance (3.15 Å) eliminates the possibility that the C=PR ligand is a four-electron donor with π-donation from the C=P bond to Pt(1). Therefore, the most reasonable description of μ-C=PR in this complex is that of a semibridging group, which is strongly coordinated to Pt(2) and interacts more weakly with Pt(1) by accepting at C(1) electron donation from the more electron rich Pt(1) (with two PEt_3 donor ligands) (structure E, Chart II).

Structure E of compound **2** is very similar to that (F) of $(Cl)(PPh_3)Pt(\mu\text{-}CO)Pt(PPh_3)_2(Cl)$[14] and $(Br)(PPh_3)Pt(\mu\text{-}CO)Pt(PPh_3)_2(Br)$,[15] both of which have been described as containing a semibridging CO ligand. As in **2**, the Pt(2)-C-O angle (156 (1)°) is very open and the Pt(2)-C bond distance (1.901 (13) Å) is shorter than that of Pt(1)-C (2.218 (13) Å).[15] In the absence of a semibridging interaction with Pt(1), the C≡PR ligand in **2** would be terminal and have structure G. It is not clear why the C≡PR ligand in **2** and the CO in F prefer the semibridging structure.

In summary, we describe the first example of a metal complex containing a C≡PR ligand. In the reported complex $(Cl)(PEt_3)Pt(\mu\text{-}C{=}PR)Pt(PEt_3)_2Cl$ (**2**), the C≡PR is semibridging, a type of bridging that has not been observed for isocyanide ligands. The synthesis of **2** demonstrates that C≡PR groups can be stabilized in transition-metal complexes.

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Supplementary Material Available: Description of the data collection and structure solution, completely labeled ORTEP drawing of **2**, and tables of crystal data, positional and thermal parameters, complete bond distances and angles, and least-squares planes for **2** (14 pages); listing of calculated and observed structure factors for **2** (20 pages). Ordering information is given on any current masthead page.

(9) Crystallographic data for **2**: mol wt 1103.95; space group $P2_12_12_1$; a = 14.4639 (9) Å, b = 16.152 (2) Å, c = 19.343 (2) Å, V = 4518.8 (9) Å^3, d_{calcd} = 1.62 g/cm^3 for Z = 4 at −50 ± 1 °C, μ = 68.2 cm^{-1} (Mo Kα). Diffraction data were collected at −50 ± 1 °C with an Enraf-Nonius CAD4 automated diffractometer. A total of 8196 reflections were collected. Of the 4227 unique data, 3548 were considered observed, having $F_o^2 > 2.5\ \sigma(F_o^2)$. R = 0.029 and R_w = 0.035. Details of data collection and refinement are given in the supplementary material.

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Molecular Recognition of a Pyrimidine Dimer and Photosensitized Dimer Splitting by a Macrocyclic Bis(diaminopyridine)

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Enzyme-substrate binding is an example of molecular recognition[1] par excellence. Such recognition is a prerequisite for photorepair of pyrimidine dimers in DNA by photolyases, enzymes that bind to dimer-containing DNA in a dark reaction and subsequently split the dimer in a light-dependent step that employs a reduced flavin cofactor.[2] The mode of dimer recognition by photolyases is unknown but is thought to involve contacts of the enzyme, bound across the major groove of DNA, with the cyclobutyl group of the dimer and the phosphates of the DNA backbone.[2a,f,h,i,k] To explore the possible utility of the unique hydrogen-bonding pattern of the dimer's splayed dihydropyrimidine rings in dimer recognition and binding, we have prepared macrocycle **1a**[3] (Figure 1) and found that it has a high affinity for pyrimidine dimer **2** (Chart I). Analogues of the macrocycle **1a** were found to photosensitize pyrimidine dimer splitting.

Binding of **1a** to pyrimidine dimer **2** (1,1′-di-*n*-butylthymine *cis-syn*-photodimer)[4] in $CHCl_3$ resulted in a red shift in UV absorbance (λ_{max} = 291 → 296 nm). Complex formation was also monitored by ^{1}H NMR spectroscopy. A typical titration curve is shown in Figure 1 (upper curve). The largest shift changes occurred in the N-H hydrogens, as a consequence of hydrogen bonding in the complex (e.g., $\Delta\delta$ = 1.23 ppm downfield for **1a** and 3.05 ppm for **2**). Binding of **1a** to **2** was clearly of 1:1 stoichiometry. The association constant[5] was estimated by curve fitting to be on the order of 1.5 ± 0.4 × 10^4 M^{-1}. Repeated titrations gave values on the same order of magnitude. Methyl

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(3) The syntheses of the macrocycles will be presented elsewhere (see supplementary material). For all compounds, high-resolution FAB MS, EI MS, and/or high-resolution (400 or 500 MHz) ^{1}H NMR spectra were consistent with the assigned structures (e.g., high-resolution FAB MS of **1a**: theoretical exact mass for $C_{36}H_{40}N_8O_8S_2 + H^+$ 777.2489, found 777.2485).

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(5) K_{assoc} may be underestimated due to self-association of **2**. Also, these values may exceed the limit for accurate determination by this method.[11f]

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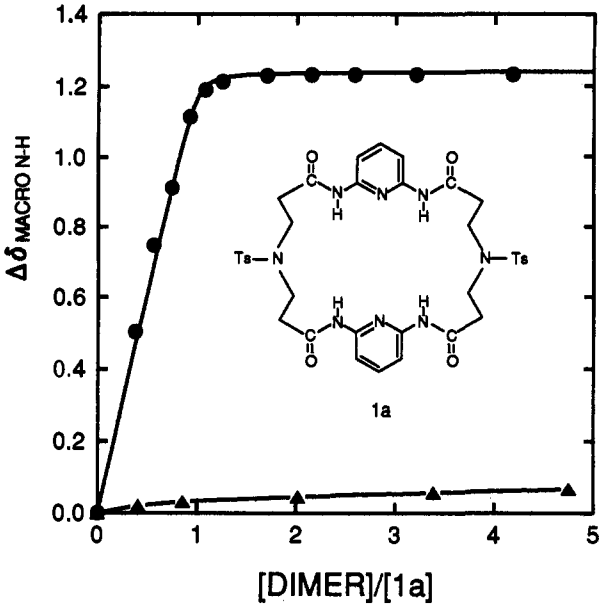
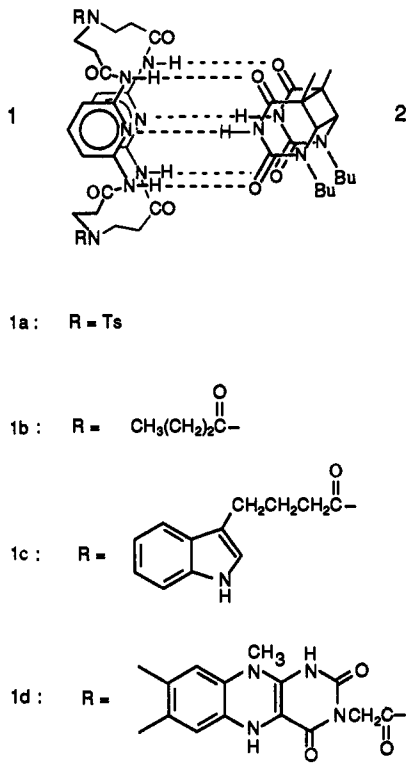


Figure 1. NMR titration of **1a** with **2** (circles) and with *N*(3),*N*(3′)-dimethyl-substituted **2** (triangles) in $CDCl_3$.

Chart I



substitution at the N(3) and N(3′) positions of **2** prevented association (Figure 1, lower curve). *Escherichia coli* photolyase binds TpT with somewhat lower affinity ($K_{assoc} = 4 \times 10^3\ M^{-1}$),[2i] but dimer-containing DNA is more tightly bound ($K_{assoc} = 10^8$–$10^9\ M^{-1}$).[2a,j,k] A catalytic antibody generated against a pyrimidine dimer also binds dimers more tightly ($1/K_m \simeq 1.5 \times 10^5$ and $>10^6\ M^{-1}$).[6]

The structure of **1a** was also determined by single-crystal X-ray diffraction,[7] and the two preorganized[8] diaminopyridine moieties were found oriented parallel to each other. This motif, in which

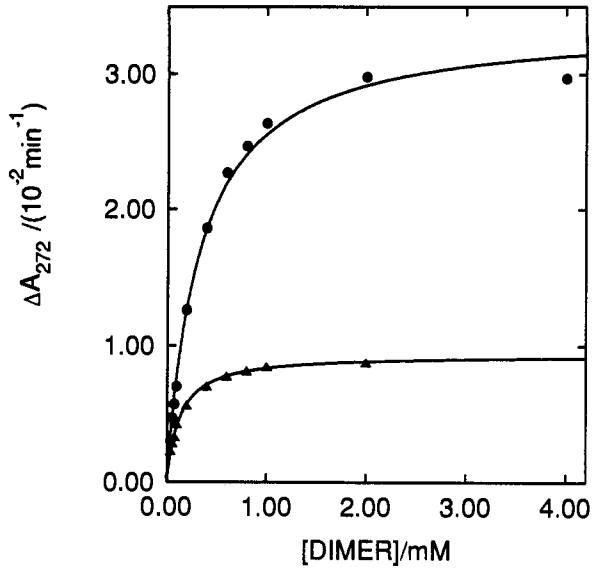


Figure 2. Photosplitting of **2** by 19 μM **1b** (triangles) or 23 μM **1c** (circles) in argon-purged CH_3CN (λ_{irrad} = 313 nm). Each point is the average of two determinations, which agreed within 5%. The principal light absorber is the 1:1 complex ($K_{assoc} \simeq 6.8 \pm 0.3 \times 10^3\ M^{-1}$ for **1b** and $2.5 \pm 0.2 \times 10^3\ M^{-1}$ for **1c**, determined by curve fitting to the data shown). Thus, the indolyl groups of **1c** do not enhance binding, in contrast with the effect of Trp277 in *E. coli* photolyase.[2h]

the diaminopyridines are part of a macrocyclic ring, differs from the thymine dimer receptors recently reported by Hirst and Hamilton,[9] which consist of two linked diaminopyridines ($K_{assoc} = 2.2 \times 10^3\ M^{-1}$), and the receptor of Rebek and co-workers,[10] which consists of two diaminopyridine moieties separated by a rigid spacer ($K_{assoc} = 4.8 \times 10^3\ M^{-1}$). Improvements in **1** can be imagined.[11]

The analogues **1b** and **1c** were found to photosensitize pyrimidine dimer splitting (Figure 2). Acetonitrile was used because of light-induced spectral changes of the macrocycle in $CHCl_3$. Macrocycle binding clearly showed saturation, as expected for complex formation. Splitting probably occurs as a result of photoinduced electron transfer involving the diaminopyridine and/or indolyl moieties.[12] It was found that **1b** functioned photocatalytically, splitting approximately five dimers during an extended irradiation. The quantum efficiency of splitting by **1c** was estimated by HPLC of 1-butylthymine to be approximately 0.01, lower than that for covalently linked dimer–indole systems ($\Phi = 0.4$),[12d] a catalytic antibody with an indole sensitizer (Φ = 0.08),[6] and photolyases themselves (Φ = 0.2–0.75).[2d,e,l] Analogue **1d**, which bears reduced flavin chromophores (prepared from the oxidized flavin analogue by photoreduction with 1,4-cyclo-

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hexadiene[13]), was ineffective at dimer splitting in preliminary experiments (CH_3CN; λ_{irrad} = 436 nm), possibly because of a need for the deprotonated form of the reduced flavin.[14]

Dimer photosplitting by **1b** and **1c** in low-polarity environments demonstrates the feasibility of pyrimidine dimer recognition for the purpose of dimer repair. Dimers apparently engage in Watson-Crick hydrogen bonding to their complementary bases when formed in double-stranded DNA,[15] but there is currently no evidence regarding hydrogen bonding of photolyases to dimers in single- or double-stranded DNA. Whether photolyases utilize hydrogen bonding in the recognition, orienting, and splitting of thymine dimers in DNA awaits further studies of the natural system.

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Supplementary Material Available: Experimental details for the synthesis of **1a** and structure representation of **1a** determined by single-crystal X-ray diffraction (2 pages). Ordering information is given on any current masthead page.

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X-ray Crystal Structure of the HIV Protease Complex with L-700,417, an Inhibitor with Pseudo C_2 Symmetry

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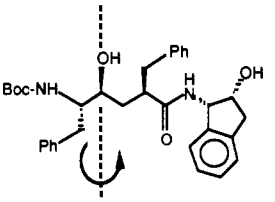
The human immunodeficiency virus type 1 protease (HIVP) is responsible for the processing of the polyprotein products of the *gag* and *pol* genes into their mature forms.[1,2] The enzyme is an aspartyl protease and is active as a dimer with the active site shared between subunits.[3-5] If the action of the protease is inhibited or blocked genetically, virus infection can be arrested.[6-8] Because of the essential role that the protease plays in virus maturation, it appears to be an excellent target for the development of an antiviral agent.

Among the most potent inhibitors of aspartyl proteases are compounds containing a central secondary alcohol which interacts with two catalytic Asp residues,[9] and inclusion of such a hydroxyl group into any inhibitor design would be desirable. Other desirable features in an HIVP inhibitor would include hydrophobic substituents to project into the specificity pockets of the enzyme[10] and hydrogen-bond donors to interact with the carbonyl of Gly 27 which projects up from the floor of the active site from each subunit.[11,12] Because the native enzyme can adopt a conformation in which a 2-fold symmetry axis extends through the active site,[3-5] it might also be desirable to include approximate C_2 symmetry through the central alcohol of inhibitors. Compounds which take advantage of this C_2 symmetry have recently been reported by Erickson et al.[13] Using a similar strategy, we have designed a new set of pseudosymmetric inhibitors based upon L-685,434,[14] (**1**), a hydroxyethylene-containing HIVP inhibitor which utilizes the novel 2-hydroxy-1-aminoindan as a P_2' amino acid[15] replacement. Rotation of the C-terminal half of **1** around the central hydroxyl-bearing carbon led to the design of L-700,417[16] (**2**). Compound **2** inhibits HIVP activity[17] with an IC_{50} of 0.67 nM and was active in halting the spread of HIV-1 (IIIB) infection in human T-lymphoid cell culture[18] with a minimal 100% inhibitory concentration of 100 nM. To further evaluate and improve on the inhibitor design, we have determined the high-resolution crystal structure of the complex of **2** with HIVP.



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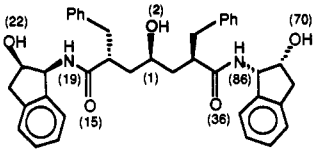

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