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Toward an Artificial Oxidative DNA Photolyase

Mickaël Pauvert, Patrick Laine, Marco Jonas, and Olaf Wiest*

Department of Chemistry & Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556-5670

owiest@nd.edu

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The design, synthesis, structure, and binding affinity of two dioptic receptors for the selective molecular recognition of the cis,syn cyclobutane pyrimidine dimer are reported. The design is based on two 2,6-di(acetamino)pyridine recognition units that are covalently linked via triple bonds to an anthraquinone functional spacer unit. The convergent synthesis uses a modified Sonogashira reaction involving a zinc transmetalation as the key step. The crystal structure of one of the receptors reveals a supramolecular 1D polymer with strong interactions mediated by shape self-complementarity, π-stacking, and hydrogen bonding between adjacent molecules. Hydrogen bonding between adjacent strands enforces a parallel orientation, which leads to a noncentrosymmetric crystal structure of the highly polar compound. The receptor has an association constant of $K_a = 1.0 \times 10^3$ M^{-1} with the cis,syn pyrimidine dimer, whereas binding of the trans,syn isomer is approximately 1 order of magnitude weaker.

Introduction

Upon irradiation of DNA with UV light of wavelengths between 260 and 320 nm, two adjacent pyrimidines undergo a photochemical [2+2] cycloaddition, leading to the formation of cyclobutane pyrimidine dimers (CPD), the most important among several possible photoproducts.[1] These photolesions are mutagenic and cause all of the three major types of skin cancer.[2] Many organisms, but not humans, have developed a protection mechanism to regenerate the damaged genetic information by using enzymes called CPD photolyases that use a unique photoinduced electron-transfer-catalyzed mechanism to achieve DNA repair. Although CPD photolyase uses a reductive single electron transfer to initiate the cycloreversion, it was shown that the cycloreversion of the CPD can also be achieved in vitro through an oxidative pathway.[3] The development of artificial models for this reaction has been a very active and attractive field of research in recent years and has yielded valuable information about CPD photolyase.[4]

The first step toward a successful CPD photolyase model is the selective molecular recognition of CPD. This is a particularly interesting problem in supramolecular chemistry because one can envision hydrogen bonding patterns that are related to the molecular recognition phenomena that play a key role in maintaining genetic integrity (e.g. Watson−Crick pairing). Consequently, the use of noncovalent interactions for the nucleotide bases of DNA, based mainly on hydrogen bonding, has become an important field of research and the development of new receptors for the binding of molecules of biological interest is a main focus of supramolecular chemistry.[5−7] The structure of the biologically relevant cis,syn CPD would allow an extension of these concepts by using more than three hydrogen bonds for molecular recognition by appropriately positioned multiple receptor units.

There have been a number of different approaches to the problem of molecular recognition of CPD. Several research groups have developed artificial receptors for CPD and the corresponding TpT dinucleotide. Rebek and co-workers[8] achieved a binding constant of 4800 M^{-1} for

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(7) Tecilla, P.; Jubian, V.; Hamilton, A. D. *Tetrahedron* **1995**, *51*, 435−448.

(8) Park, T. K.; Schroder, J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 5125−5127. It is possible that the cis,syn derivative has in fact a higher association constant than the reported value because the procedure used for the synthesis of the CPD derivative used was later shown to yield the trans,syn derivative: (b) Cochran, A. G.; Sugasawara, R.; Schultz, P. G. *J. Am. Chem. Soc.* **1988**, *110*, 7888−7890. (c) Jacobsen J. R.; Cochran, A. G.; Stephans, J. C.; King, D. S.; Schultz, P. G *J. Am. Chem. Soc.* **1995**, *117*, 5453−5461.

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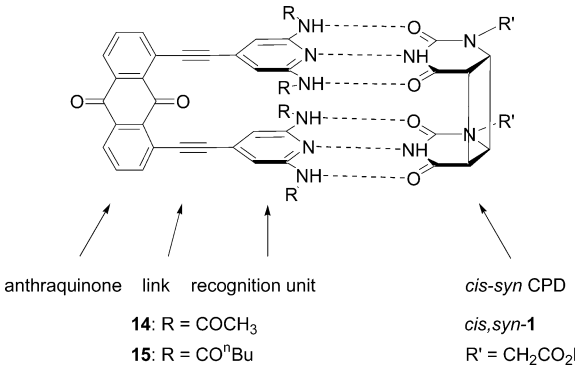
a CPD derivative in chloroform by covalently linking the widely used 2,6-bis(acetamino)pyridine recognition unit to a xanthene spacer. Hamilton used the same recognition unit for binding of thymines and CPD with binding constants between 520 and 2200 M^{-1}.[9] By linking 2,6-bis(acetamino)pyridine with indoles, which can induce a reductive electron transfer upon irradiation with visible light, Rose and co-workers[10] obtained the first artificial photolyase. More recently, Inouye et al. measured a binding constant of 45 M^{-1} for a dioptic receptor, originally designed for the binding of TpT, to a CPD derivative in chloroform/DMSO 85:15.[11]

The structural similarity of some of these receptor units to the approach studied in our laboratories as well as our recent results on the very interesting crystal structure of one of our receptors prompted us to report the design, synthesis, X-ray analysis, and binding studies for two new receptor units that are selective for the binding of *cis*,*syn*-CPD (*cis*,*syn*-**1**) at this time.

Results and Discussion

Design The 2,6-bis(acylamino)pyridine unit is well-known in the literature and has been widely used for the molecular recognition of pyrimidine bases, as discussed above.[7,10−13] By modifying the alkyl side chain of the acyl group, the solubility of the molecule can be fine-tuned. The binding affinity is mediated through three hydrogen bonds in a DAD/ADA system, leading to the formation of a strong pyridine−pyrimidine complex. The search for the ideal spacer unit to link the two recognition units led to the 1 and 8 positions of an anthracene moiety. This specific linkage provides a rigid framework for a bidentate ligand, with an ca. 0.5 nm bridging distance with minimal steric interference from the anthracene ring.[14,15] This distance between these positions is very close to the distance between the two pyrimidine units in *cis*,*syn*-CPD (∼0.51 nm). An entropically favorable, rigid preorientation can be achieved by using ethynyl linker units to position the DAD recognition unit. The anthracene-triple bond assembly has been previously used for the rigid positioning of receptor units.[6,11] It was then envisioned that the previously described anthracene spacer can be modified to provide the desired function, i.e., the ability to serve as an electron-transfer catalyst in the excited state. This can be achieved by oxidation to the anthraquinone, which was shown to be efficient in inducing cycloreversion of CPD, using an oxidative, photoinduced electron transfer.[16,17] The overall design concept is summarized in Scheme 1.

SCHEME 1. Design of the System for Molecular Recognition



Synthesis The formal retrosynthesis of **14** and **15** leads to 1,8-diethynylanthracene **11** and 2,6-diamino-4-halogenopyridine, followed by a Sonogashira-type coupling of those units in the key step of the convergent synthesis. The 2,6-diaminopyridine units **6**, **7**, and **8** were prepared in four steps from **2** or **3**[18] according a modified literature procedure.[11,13,19,20] Conversion of **2** and **3** to the di(carboxylic acid chloride) is followed by nucleophilic substitution under phase transfer conditions with 2 equiv of sodium azide, which gave the di(acyl azide) intermediate. This unstable intermediate undergoes a Curtius rearrangement[19−21] and alcohol capture of the reactive isocyanate intermediate with *tert*-butyl alcohol leads to the formation of the bis(Boc-protected) diaminopyridine **4**. The bis-Boc derivatives **4** and **5** was then treated with TFA to obtain the 2,6-diamino-4-halopyridine. It was found that the electron-rich unprotected diamino pyridine is prone to oxidation and electrophilic attack. These unwanted side reactions made it necessary to quench the *tert*-butyl cation formed during deprotection and to reprotect the free amine without isolation. Therefore, anisole was added and the diamino pyridine, without isolation, was reprotected as the desired acylamino derivatives, using either Ac_2O or valeryl chloride in the presence of pyridine, leading to the formation of three different 2,6-diaminopyridine recognition units **6**, **7**, and **8** (Scheme 2). The total yields for this five-step pathway from commercially available starting material chelidamic acid range from 40% for **8** to 66% for **7**.

The 1,8-diethynylanthracene moiety was prepared in five steps from 1,8-anthraquinonedisulfonicacid potassium salt according to a modified literature procedure.[15] After reduction of the 1,8-anthraquinone disulfonicacid potassium salt with zinc dust,[22] the new anthracene compound is melted with KOH pellets under an argon atmosphere to lead to the formation 1,8-dihydroxyanthracene **9**.[23] Activation of the two hydroxyl substituents by reaction with triflate anhydride gave the corresponding triflate derivatives that were suitable for Sonogashira

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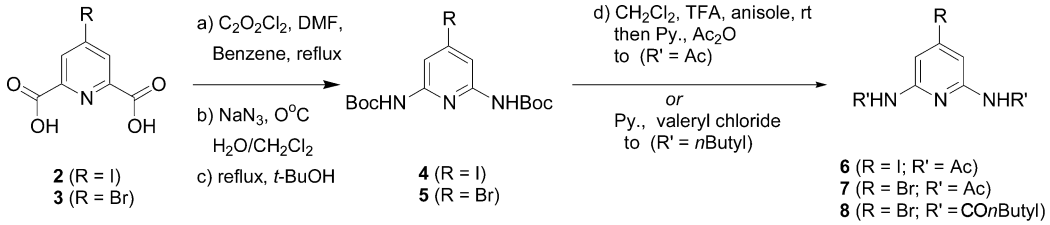
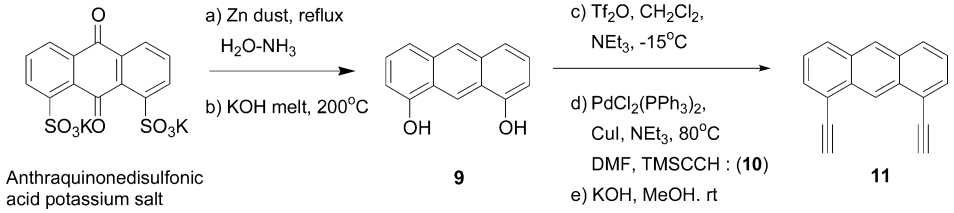
(23) Lampe, B. *Chem. Ber.* **1909**, *42*, 1413−1418.

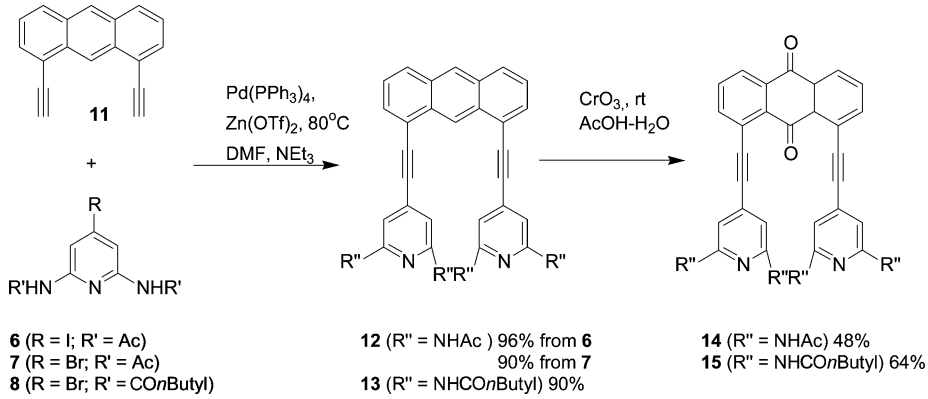
SCHEME 2



SCHEME 3



SCHEME 4



coupling with trimethylsilylethyne in the presence of $PdCl_2(PPh_3)_2$, CuI, and Et_3N, yielding the 1,8-bis-trimethylsylilethynylanthracene building block **10**.[14] The two TMS protective groups were removed under basic condition to give the desired 1,8-diethynylanthracene **11** (Scheme 3).

The key step of the convergent synthesis of the designed model is a modification of a Sonogashira coupling, using a zinc acetylide prepared in situ, which yields compounds **12** and **13** in 90−96% yield. Although reaction of the 1,8-diethynylanthraquinone should directly yield the desired product, a direct coupling of 2,6-diaminopyridine **6** and 1,8-diethynylanthaquinone was not successful due to copper-catalyzed self-coupling of the acceptor-substituted acetylenes. Similarly, coupling of the anthracene-1,8-bistriflate with 2,6-bis(acetamino)-4-ethynylpyridine was not successful. Although the self-coupling of acetylenes under copper or palladium catalysis is of course well documented,[24] evidence of this reaction as a side reaction of Shonogashira couplings of acceptor substituted alkynes appears to be mostly anecdotal. Several examples of palladium-coupling reactions with zinc acetylides have been published recently.[25,26] Although this modification needs stoichiometric quantities of zinc (in contrast to the Sonogashira protocol, which proceeds by catalytic in situ metalation), this modification gave us the desired compounds **12** and **13** with excellent yields in a case where the classical Sonogashira reaction failed.

Final oxidation of the anthracene derivatives **12** and **13** with chromium oxide in aqueous acetic acid yielded the two desired models **14** and **15**[27] with 48−64% yield depending on the protective group (Scheme 4). The surprisingly large difference between the two yields is due to the poor solubility of **12**.

X-ray Structure During our synthetic studies, we noted the extremely poor solubility of **12**, which could be rationalized by strong intermolecular interactions mediated by either hydrogen bonding in the DAD recognition unit or π-stacking of the electron-rich anthracene and the electron-poor pyridine moieties. Although the poor solubility of **12** prevented the growth of suitable crystals, gas diffusion of diethyl ether into a DMF solution of **14** yielded single crystals that revealed the highly unusual structure of **14**, cocrystallized with one molecule of solvent (DMF). Three views of the structure of **14** are shown in Figure 1.

(24) For recent publications, compare e.g.: (a) Liao, Y.; Fathi, R.; Yang, Z. *Org. Lett.* **2003**, *5*, 909−912. (b) Russell, J. M.; Sabat, M.; Grimes, R. N. *Organometallics* **2002**, *21*, 4113−4128. (c) Zhao, Y.; McDonald, R.; Tykwinski, R. R. *J. Org. Chem.* **2002**, *67*, 2805−2812.

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(27) Inbasekaran, M.; Witiak, D. T. *J. Med. Chem.* **1980**, *23*, 278−281.

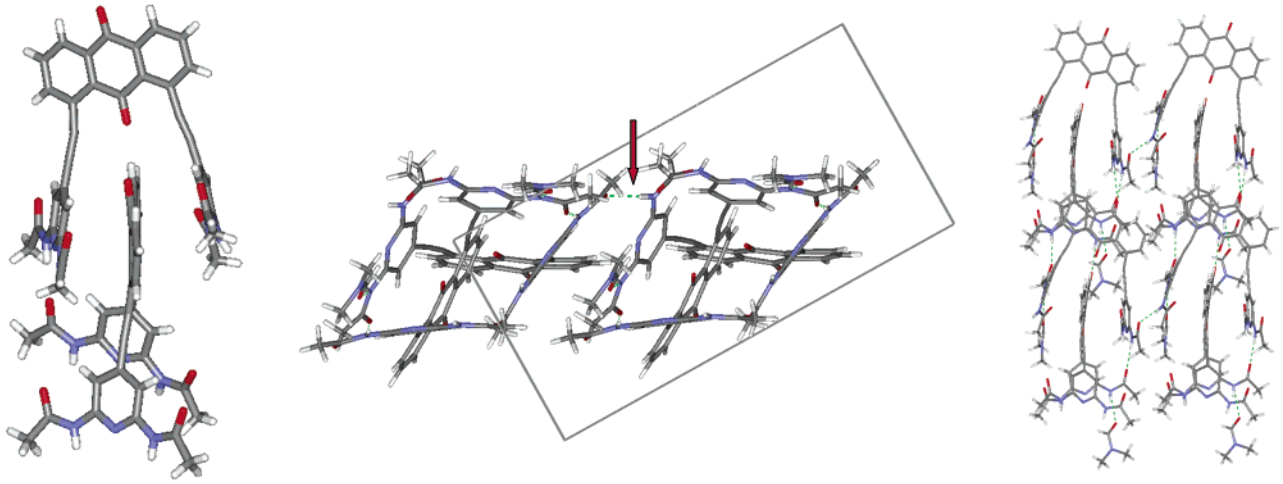

FIGURE 1. Three views of the crystal structure of **14**: (left) repeating unit of two molecules; (middle) view down the *c* axis showing unit cell and two infinite bands; and (right) view down the *b* axis.

The crystal structure indeed confirms an intercalation of the electron-rich benzene portion of anthraquinone into the cleft formed by the two pyridines, as shown on the left in Figure 1. To allow for this intercalation, the two triple bonds have to be distorted from linearity by 14°. It can be expected that the π-stacking interaction would be even stronger in **12**, which is consistent with the lower solubility of **12** compared to **14**.[28] Additionally, there is one hydrogen bond with an O−H distance of 1.97 Å between the carbonyl carbon of an acetamide of one molecule to the N−H of the next molecule. Because of the shape and functionality of **14**, the intercalation and the hydrogen bonding lead to the formation of the infinite 1D-band in the solid that most likely is responsible for the poor solubility of **12** and **14**. This strong, noncovalent interaction between repeating, self-complementary monomers can be considered a new example of a supramolecular polymerization.[29]

The pyridine rings in **14** are not exactly parallel to each other, but are at angles of 48° and 68° relative to the anthraquinone moiety. The two molecules of the repeating until are therefore rotated against each other by ~65°. The shape of each of the infinite bands is that of a parallelogram, as can be seen in the middle of Figure 1. Adjacent bands are connected in the *a* and *b* directions by one C═O−HN hydrogen bond per unit, enforcing a parallel orientation of the bands, as shown in Figure 1 on the right. In light of the high dipole moment of **14** of 8.65 D,[30] the parallel arrangement of the adjacent directional bands is unusual and leads to a highly polar, noncentrosymmetric crystal. Materials with such properties are of considerable interest because of their potential as piezoelectrics or second-order harmonic generators in nonlinear optics.[31] Although the formation of noncentrosymmetric material based on 1D-networks is more commonly achieved by using metalorganic coordination compounds,[32] the use of purely organic materials may lead to improved properties such as high optical nonlinearity, fast response times, and the possibility of rational modification of the physical properties through targeted synthesis of derivatives.[33] The combination of π-stacking interaction, shape self-complementarity, and hydrogen bonding[34] in the crystal structure of **14** is to the best of our knowledge a new and promising, albeit unexpected, motif for the design of polar, noncentrosymmetric organic crystals based on 1D-networks. Given the relatively efficient synthesis, future studies will investigate the optical properties on these interesting compounds.

Binding Affinity The interactions of the receptor **14** or **15** with the *cis*,*syn*-**1** were investigated by ^{1}H NMR in different solvents.[35] Titration of the receptor with the *cis*,*syn*-**1** led to the formation of hydrogen-bonded complexes that resulted in several characteristic changes in the ^{1}H NMR spectrum: the signals for the NH protons of both receptor **14** and **15** and *cis*,*syn*-**1** are shifted downfield, thus allowing the measurement of the binding affinity of these systems. When **14** (4.3 mM) is treated with *cis*,*syn*-**1** (4.3 mM) in 10/90 DMSO-d_6/$CDCl_3$, the NH protons on both compounds were shifted downfield by 0.12 and 0.34 ppm, respectively. In pure DMSO-d_6, no complex was observed. When **15** (1.4 mM) is treated with *cis*,*syn*-**1** (1.4 mM) in CD_2Cl_2/acetone-d_6 50/50, the NH protons were shifted downfield by 0.11 and 0.44 ppm, respectively. In pure acetone-d_6, shifts are significantly smaller (<0.01 and 0.04 ppm, respectively). Figure 2 shows the plot of the chemical shift of the NH of model

(28) This is also in agreement with our observation that addition of veratrole to a solution of **12** in hot DMF inhibits the normally observed crystallization upon cooling.

(29) Würthner, F.; Yao, S.; Beginn, U. *Angew. Chem., Intl. Ed.* **2003**, *42*, 3247−3250. (b) Ishada, Y.; Aida, T. *J. Am. Chem. Soc.* **2002**, *124*, 14017−14019.

(30) Calculated at the B3LYP/6-31G* level of theory, using the coordinates from the X-ray structure

(31) E.g.: (a) Curtin, D. Y.; Paul, I. C. *Chem. Rev.* **1981**, *81*, 525−541. (b) Evan, O. R.; Lin, W. *Acc. Chem. Res.* **2002**, *35*, 511−522.

(32) (a) Jouaiti, A.; Hosseini, M. W.; Kyritsakas, N. *Chem. Commun.* **2002**, 1898−1899. For an example of a purely organic material, compare: (b) Martz, J.; Graf, E.; Hosseini, M. W.; DeCian, A.; Fischer, J. *J. Chem. Soc., Dalton Trans.* **2000**, 3791−3795.

(33) (a) Marder, S. R.; Sohn, J. E.; Stucky, G. D. *Materials for Nonlinear Optics*; ACS Symp. Ser. 445; American Chemical Society: Washington, DC, 1991. (b) *Nonlinear Optical Properties of Organic Molecules and Crystals*; Chemla, D. S., Zyss, J., Eds.; Academic Press: New York, 1987; Vols. 1 and 2.

(34) For examples of two-component complexes with hydrogen bonding in aromatic compounds, compare also: Muthuraman, M.; Masse, R.; Nicoud, J.-F.; Desiraju, G. R. *Chem. Mater.* **2001**, *13*, 1473−1479.

(35) Foster, R.; Fyfe, C. A. *Prog. Nucl. Magn. Reson. Spectrosc.* **1969**, *4*, 1−89.

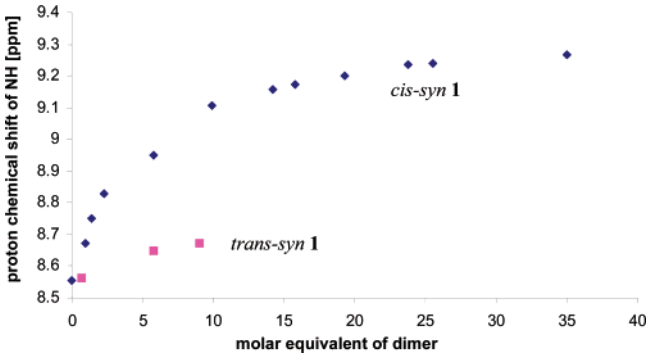

FIGURE 2. Plot of ^{1}H chemical shift of NH model **15** against total equivalent of dimers *cis*,*syn*-**1** and *trans*,*syn*-**1** in solution of CD_2Cl_2/acetone-d_6 (50/50) at 25 °C.

15 (1.4 mM) as a function of the amount of dimer *cis*,*syn*-**1** in solution in a mixture of $CDCl_2$/acetone-d_6 (50/50) at 25 °C. We observed a significant characteristic chemical shift reflecting the formation of a multipoint hydrogen-bonded complex. The association constant was estimated to be 1.0×10^3 M^{-1} for this system (**15**∗*cis*,*syn* **1**).[36]

To probe for the selectivity of the molecular recognition, we also studied the binding of the isomer *trans*,*syn*-**1** using the same methodology. Due to the lower solubility of this isomer, only a 9-fold excess of the dimer could be used. However, it is clear from the data shown in Figure 2 that binding of *trans*,*syn*-**1** is significantly weaker than that for *cis*,*syn*-**1**. Although no quantitatively accurate determination of the binding constant can be performed with the small number of datapoints in a limited concentration range, the difference of binding constants can be estimated to be approximately one order of magnitude smaller than that for *cis*,*syn*-**1**.

The same binding constant estimate was made in pure acetone-d_6 with the complex (**15**∗*cis*,*syn*-**1**) but the association constant obtained was too small to be considered further. Those results are in accordance with the presence of a solvent competing for binding at both **15** and *cis*,*syn*-**1**.[37] Hydrogen bond acceptor solvents such as DMF and DMSO dramatically decrease the association constant. The same effect is observed here for the case of acetone, a competitive hydrogen bond acceptor that is necessary in our case to enhance solubility. The use of cosolvent as CD_2Cl_2 or more commonly $CDCl_3$ decreases the competitive character of the solvent, and using higher CD_2Cl_2 percentage should dramatically increase the binding affinity to the association constant. In agreement with previous findings, determination of the binding constant was not possible for the system (**14**∗*cis*,*syn*-**1**) in $CDCl_3$/DMSO-d_6 (90/10) due to the very low solubility of the dimer *cis*,*syn*-**1** in this mixture of solvent.

(36) The equation used to this estimation needs extrapolation to a solution of high concentration. This is why this equation was used because of the saturation of donor solubility observed after 25 equiv of donor was added during the collection of data. But according to Foster and Fyfe[35] if we consider an extrapolation to infinitely dilute solution, the new equation is $\Delta/[D]_0 = -K^{AD}\Delta + \Delta_0 K^{AD}$ and the plot of Δ against $\Delta/[D]_0$ gave good linearity and the association constant was estimated to be 4.3×10^3 M^{-1}.

(37) Kondo, S.; Utsumi, K.; Yano, Y. *Internet J. Sci.: Biol. Chem.* [*Electronic Publication*] **1997**, *1*, http://www.netsci-journal.com/97v1/97012/index.htm.

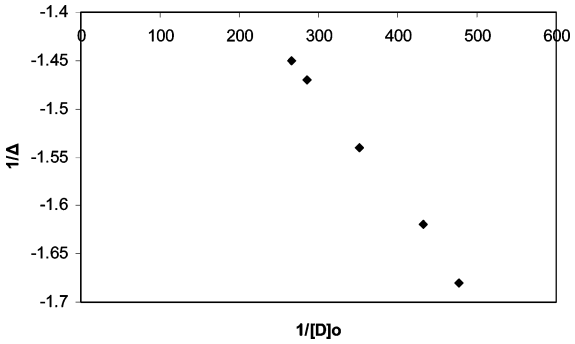

FIGURE 3. Plot of $1/\Delta$ (ppm^{-1}) against $1/[D]_0$ (M^{-1}) from equation $1/\Delta = 1/K^{AD} \times 1/\Delta_0 \times 1/[D]_0 + 1/\Delta_0$ in conditions of in the system (**15**∗*cis*,*syn*-**1**) in a mixture of CD_2Cl_2/acetone-d_6 (50/50) at 25 °C.

Conclusions and Outlook

In summary, two new receptors **14** and **15** for the selective binding of cis,syn cyclobutane pyrimidine dimers (CPD, *cis*,*syn*-**1**) in organic solvents were synthesized. The modified Sonogashira coupling, using zinc acetylides in the key step of a convergent synthesis, provides a useful alternative to the traditional methods for the case of acceptor-substituted acetylenes. The final compound **14** was shown to have a fascinating, if unexpected, three-dimensional structure where 1D-polymers are formed through supramolecular interactions and are oriented by interstrand hydrogen bonding in a parallel fashion to form a noncentrosymmteric material of a highly polar material. This could have potential implications for piezoelectric or NLO materials. The binding constant of *cis*,*syn*-**1** to **15** in CD_2Cl_2/acetone-d_6 was estimated as 1000 M^{-1}.

Current studies investigate the use of the functional spacer unit as a sensitizer for photoinduced oxidative electron transfer, leading to the cycloreversion of CPD. If successful, the systems described would be the first artificial photolyase using an oxidative pathway. This will require the study of different solvent systems to balance the solubility of the functional receptors, the lower binding constants in hydrogen bond acceptor solvents, and the solvent-dependent driving force for electron transfer and might make further fine-tuning and development of the receptors necessary. These studies are currently in progress and will be reported in due course.

Experimental Section

Methods for Estimation of the Association Constant. The association constant were estimated from a plot of $1/\Delta$ against $1/[D]_0$ from the equation $1/\Delta = 1/K^{AD} \times 1/\Delta_0 \times 1/[D]_0 + 1/\Delta_0$ under the condition of $[D]_0 \gg [A]_0$ according Foster and Fyfe[35] {$[D]_0$ = concentration of the donor (dimer **1**); $[A]_0$ = concentration of the acceptor (models **14**, **15**); K^{AD} = association constant; Δ = chemical shift of $NH_{acceptor-donor}$ − chemical shift of $NH_{acceptor\ alone}$; Δ_0 = chemical shift for the pure complex (not measurable)}. The form of this equation is analogous to the Benesi−Hildebrand equation,[39] which has frequently been used in the determination of association constants from the analysis of optical data. The plot of $1/\Delta$ against $1/[D]_0$ from

(38) Carell, T.; Epple, R.; Gramlich, V. *Helv. Chim. Acta* **1997**, *80*, 2191−2203.

(39) Benesi, H. A.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703−2707.

the previous equation in the range of 14 to 25 equiv of dimer *cis,syn*-**1** for the system **15**∗*cis,syn*-**1** (i.e. under conditions where $[D]_0 \gg [A]_0$) gave good linearity as shown in Figure 3 and the association constant was estimated to be 1.0×10^3 M^{-1}.

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Supporting Information Available: Experimental procedures for the synthesis and spectral characterization of some new compounds as well as X-ray data for **14** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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