A Synthetic Receptor for Dinucleotides

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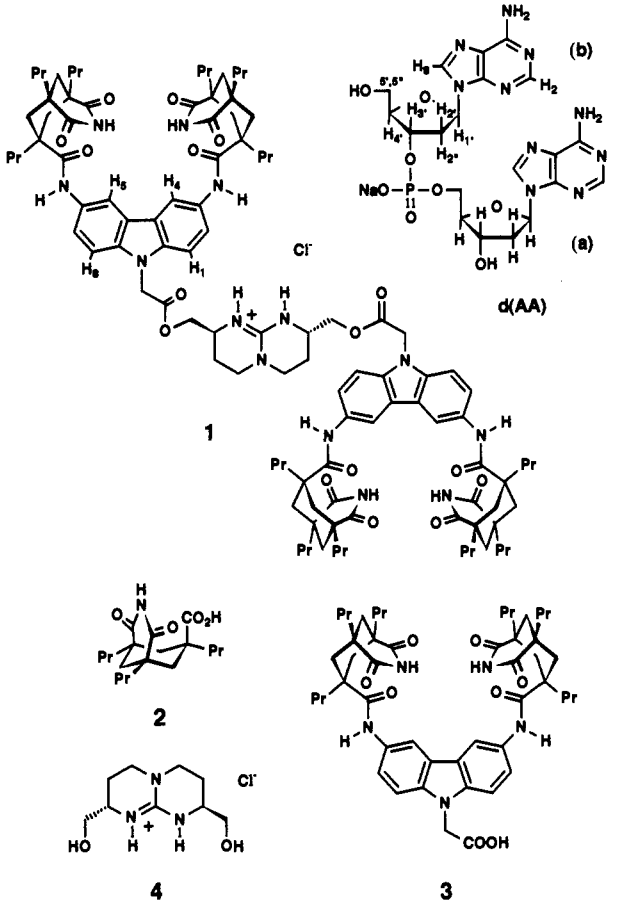
Received August 2, 1991

Complexation of biorelevant targets with synthetic receptors continues to provide information regarding recognition at the molecular level.[2] One tactic involves the concatenation of modular subunits with complementarity to specific domains of the target. Here we apply this means to develop a system (receptor **1**) for the complexation of 2′-deoxyadenylyl(3′→5′)-2′-deoxyadenosine (*d*(AA)) and give evidence of its success.

Chart I



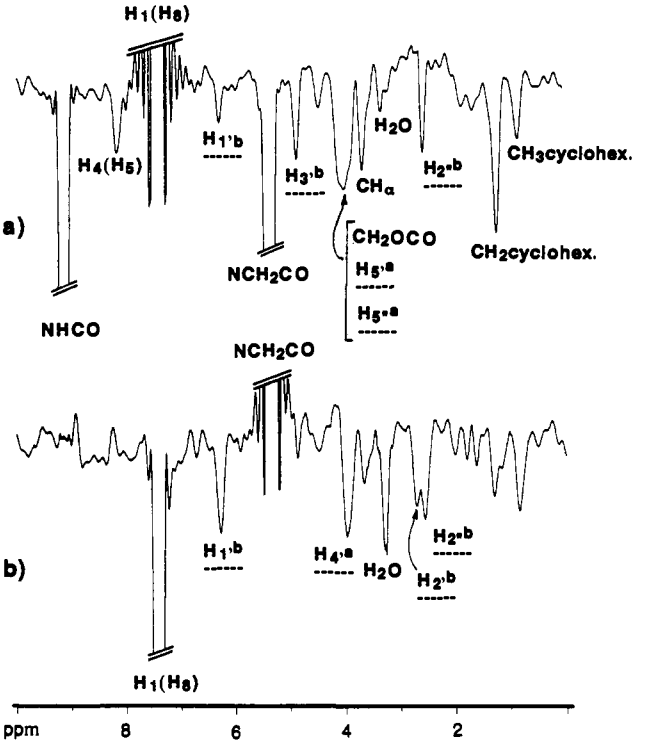


Figure 1. Column cross sections in the ROESY spectrum of the complex in DMSO-d_6 corresponding to (a) $H_1(H_8)$ carbazole protons and (b) NCH_2CO protons. NOE contacts between these receptor resonances and deoxyribose protons of the substrate are underlined.

The adenine binding domains were assembled using a carbazole spacer and two imides derived from the highly soluble and lipophilic version of the Kemp triacid **2**.[3] Alkylation (K_2CO_3, DMF, $BrCH_2CO_2Me$, 99%) then reduction (H_2, Pd/C, EtOH, HOAc, 61%) of 3,6-dinitrocarbazole afforded *N*-((methyloxycarbonyl)-methyl)-3,6-diaminocarbazole. Its coupling with the acid chloride of **2** (pyridine, 39%) and subsequent saponification (1 M NaOH, CH_3OH, 95%) gave the scorpion-shaped subunit **3**. This structure features nearly ideal spacing of the imides for simultaneous Watson-Crick and Hoogsteen base-pairing to the purine nucleus of adenine.[4]

For the phosphodiester complement, the bicyclic guanidinium ion **4** previously developed[5] for binding to carboxylic acids[6] and phosphates[2c,d] was used. Receptor **1** (mp 248-250 °C) was thus assembled by coupling modules **3** and **4** (1,1′-carbonyldiimidazole, DMF, 31%).[7]

Extraction experiments permitted the assessment of the high affinity of the receptor for *d*(AA): *a full equivalent of the dinucleotide was extracted from aqueous solutions of its sodium salt into organic solvents such as dichloromethane.*[8] The complex obtained from the extraction showed broadened NMR spectra

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(2) For recent examples of molecular recognition of nucleotides, see: (a) Furuta, H.; Magda, D.; Sessler, J. L. *J. Am. Chem. Soc.* **1991**, *113*, 978. (b) Hosseini, M. W.; Blacker, A. J.; Lehn, J.-M. *J. Am. Chem. Soc.* **1990**, *112*, 3896. (c) Schmidtchen, F. P. *Tetrahedron Lett.* **1989**, *30*, 4493-4496. (d) Galán, A.; Pueyo, E.; Salmerón, A.; de Mendoza, J. *Tetrahedron Lett.* **1991**, *32*, 1827. For amino acids, see: (e) Liu, R.; Sanderson, P. E. J.; Still, W. C. *J. Org. Chem.* **1990**, *55*, 5184. (f) Pirkle, W. H.; Pochapski, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 5975. (g) Galán, A.; Andreu, D.; Echavarren, A.; Prados, P.; de Mendoza, J. *J. Am. Chem. Soc.* **1991**, *113*, submitted. For carbohydrates, see: (h) Kikuchi, Y.; Kato, Y.; Tanaka, Y.; Toi, H.; Aoyama, Y. *J. Am. Chem. Soc.* **1991**, *113*, 1349. (i) Bonar-Law, R. P.; Davis, A. P.; Murray, B. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1407.

(3) Jeong, K. S.; Tjivikua, T.; Muehldorf, A.; Deslongchamps, G.; Famulok, M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 201.

(4) Deslongchamps, G.; Galán, A.; de Mendoza, J.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.*, in press.

(5) (a) Echavarren, A.; Galán, A.; de Mendoza, J.; Salmerón, A.; Lehn, J.-M. *Helv. Chim. Acta* **1988**, *71*, 685. (b) Kurzmeier, H.; Schmidtchen, F. P. *J. Org. Chem.* **1990**, *55*, 3749-3755.

(6) Echavarren, A.; Galán, A.; Lehn, J.-M.; de Mendoza, J. *J. Am. Chem. Soc.* **1989**, *111*, 4994.

(7) New compounds were characterized by a full complement of analytical and/or spectroscopic data (high-resolution MS, ^1H and ^{13}C NMR).

(8) Extraction conditions: a solution of **1** (2×10^{-3} mmol) in CH_2Cl_2 (2 mL) was shaken for 2 min with a solution of *d*(AA) (1.6×10^{-2} mmol) in water (0.5 mL). The mixture was centrifuged, the organic layer was evaporated, and the residue was taken up in DMSO-d_6 for NMR analysis. Control experiments using ApA with hexadecyltrimethylammonium bromide under these conditions showed no extraction of the dinucleotide into the organic phase.

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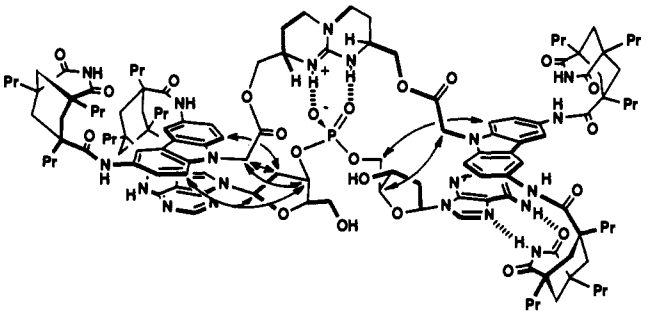


Figure 2. Proposed structure for the complex. Arrows illustrate intermolecular NOE contacts shown in Figure 1.

in $CDCl_3$ so its structure was examined in DMSO-d_6, where rapid exchange exists between free and bound components. Assignments for the signals were made through COSY and TOCSY methods. Fifteen intermolecular NOE's were observed in a ROESY experiment, and the cross-sections for $H_1(H_8)$ and $N-CH_2$ are shown in Figure 1. The negative peaks observed are labelled in the proposed structure for the complex (Figure 2).

The NOE information points to the following: (i) Base pairing is dominantly Hoogsteen (NOE's from the imide N–H of the receptor are seen to H_8 of the adenines but not to H_2) and (ii) the conformation of nucleotide a is syn ($N-CH_2-CO$ contact to $H_{4'}$ but not to $H_{2'}$) and that of nucleotide b is anti ($N-CH_2-CO$ contact to $H_{2'}$ but not to $H_{4'}$). The data best fit a structure in which most of the driving force for binding is provided by the salt bridge. In less polar solvents, such as CH_2Cl_2 used in the extraction, magnification of hydrogen bonding is expected and both Watson–Crick and Hoogsteen base-pairing are likely.

It is expected that cleft-like structures such as defined here can find use in transporting nucleotides across membranes and may even be suitable to bind to single-stranded nucleic acids. We will report on these developments in due course.

Acknowledgment. We thank the National Institutes of Health for support of this work. We are also indebted to Dr. Ramôn Eritja, CSIC, Barcelona, Spain, for a sample of *d*(AA).

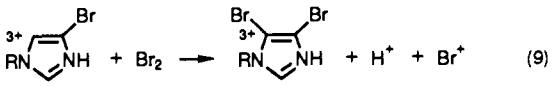
Supplementary Material Available: 600-MHz ^1H NMR spectra of **1**, *d*(AA), and complex, including an NOE list (9 pages). Ordering information is given on any current masthead page.

Additions and Corrections

Bromination of Imidazoles Coordinated to Cobalt(III). Kinetics and Mechanism of Bromination of $RImH^{3+}$ Systems (R = $(NH_3)_5Co$), Wheland Intermediates, and Preassociation or Diffusion Control [*J. Am. Chem. Soc.* **1991**, *113*, 2656]. ALLAN G. BLACKMAN, DAVID A. BUCKINGHAM,* and CHARLES R. CLARK

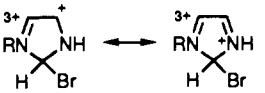
Page 2657: For "imidazolinium cation" read "imidazolium cation".

Page 2659: Equation 9 should rad



(9)

Page 2661, Scheme I: The C-2 addition product equation should read



Page 2662, Table III: The rate (M^{-1} s^{-1}) for RIm^{2+} should be 3.6×10^9, not 3.0×10^9.

Page 2663, Table IV: The rates (k_2, M^{-1} s^{-1}) for the following *N*-$Co(NH_3)_5^{3+}$ systems should be 1.1×10^8 for 4-BrIm, 2.7×10^8 for 5-BrIm, and 3.6×10^9 for Im.