ORGANIC
LETTERS

2001
Vol. 3, No. 9
1257−1260

Coplanar Recognition by a Rebek Cleft Is Provided by Cooperative Structural Effects Involving a Combination of O–H···O, O–H···N, and C–H···O Forces

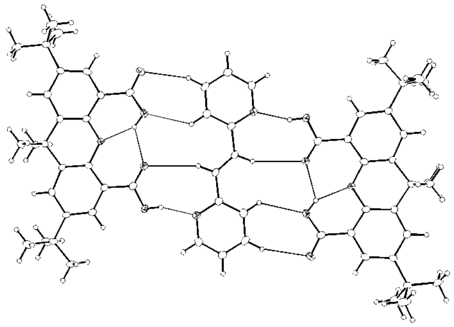
Leonard R. MacGillivray,* Michelle M. Siebke, and Jennifer L. Reid[†]

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242-1294

len-macgillivray@uiowa.edu

Received February 6, 2001

ABSTRACT



Reaction of 2,7-di-*tert*-butyl-9,9-dimethyl-4,5-xanthenedicarboxylic acid (1), a Rebek cleft, with 1,2-*trans*-bis(2-pyridyl)ethylene (2) yields a three-component organic assembly, 2(1)·2 (3), of nanoscale dimensions that is held together by 10 cooperative O–H···N, O–H···O, and C–H···O hydrogen bonds. The cleft adopts a planar conformation, by forming an intramolecular O–H···O hydrogen bond, which enables the host to recognize the guest in a coplanar orientation that facilitates the cooperativity displayed by the multiple forces.

Understanding how organic structures fit together continues to be the central paradigm of molecular recognition.[1] In this context, molecular assemblies that feature molecules that interact at the nanoscale,[2] and beyond,[3] represent intriguing synthetic targets which require the exploitation of forces responsible for recognition processes between organic molecules (e.g., hydrogen bonding) as part of the design strategy.[4] Although Nature readily utilizes such forces for the hierarchal design of complex chemical systems that exhibit multiple functions (e.g., viruses),[5] it is clear that an ability of chemists to reliably mimic such chemical behavior will rely upon development of a proper understanding of those less understood forces, and related structure phenomena,[6] which dictate the formation of nanoscale molecular assemblies of organized biological systems.[2]

One such phenomenon is hydrogen bond cooperativity.[7] Largely responsible for controlling folding and crystallization of nucleotides (e.g., DNA)[8] and proteins (e.g., collagen)[9] and structures of complexes based on such components (e.g., viral capsids),[5] cooperative effects involving hydrogen bonds

---

[†] Current address: Steacie Institute for Molecular Sciences, National Research Council of Canada, Ottawa, Ontario, Canada K1A 0R6.

[1] Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245.

[2] Whitesides, G. M.; Mathias, J. P.; Seto, C. T. *Science* **1991**, *254*, 1312.

[3] Seeman, N D. *Angew. Chem., Int. Ed.* **1998**, *37*, 3220.

[4] (a) Heinz, T.; Rudkevich, D. M.; Rebek, J., Jr. *Nature* **1998**, *394*, 764. (b) Jolliffe, K. A.; Timmerman, P.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 933. (c) Zimmerman, S. C.; Zeng, F.; Reichert, D. E. C.; Kolotuchin, S. V. *Science* **1996**, *271*, 1095. (d) MacGillivray, L. R.; Diamente, P. R.; Reid, J. L.; Ripmeester, J. A. *Chem. Commun.* **2000**, 359.

[5] Capar, D.; Klug, A. *Cold Spring Harbor Symp. Quantum Biol.* **1962**, *27*, 1.

[6] Desiraju, G. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2311.

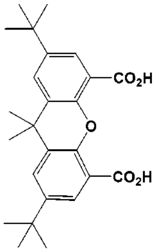
[7] (a) Cera, E. D. *Chem. Rev.* **1998**, *98*, 1563. (b) Missopolinou, D.; Panayiotou, C. *J. Phys. Chem. A* **1998**, *102*, 3574.

[8] (a) Iwataki, T.; Yoshikawa, K.; Kidoaki, S.; Umeno, D.; Kiji, M.; Maeda, M. *J. Am. Chem. Soc.* **2000**, *122*, 9891. (b) Silverman, S. K.; Cech, T. R. *Biochemistry* **1999**, *38*, 8691.

10.1021/ol0156695 CCC: $20.00

operate by exploiting an ability of hydrogen bonds located in close proximity to reinforce each other and, in doing so, stabilize secondary and tertiary structures of biomolecules and related assemblies.[10] Moreover, since formation of any one such stabilizing interaction depends, to a large extent, on whether nearest-neighbor bonds have formed,[10] it is difficult to delineate contributions of individual cooperative interactions to a final structure, which, consequently, has made it difficult to utilize such forces for the design of large synthetic systems.[11] Owing to their ability to facilitate multipoint interactions,[7] and enhance molecular association,[8] the ability to exploit cooperative hydrogen bonds for the rational design of large molecular assemblies is an attractive prospect.

With this in mind, we have embarked upon a program of study that focuses upon designing organic assemblies in the solid state that organize, by way of hydrogen bonds, reactive sites, in the form of olefins, in positions for [2 + 2] photoreaction.[12] A key feature of this approach lies in identifying bifunctional molecules that function as linear templates,[13] by forming hydrogen bonds with substituents attached to olefins, such that the template, which adopts an approximate orthogonal orientation with respect to the reactants,[12] preorganizes[14] two reactive sites in a solid for reaction. During studies aimed at elucidating the ability of 2,7-di-*tert*-butyl-9,9-dimethyl-4,5-xanthenedicarboxylic acid **1** (Figure 1), a Rebek cleft,[15] to serve as a hydrogen bond donor template, we have discovered the ability of **1** to undergo a conformational reorganization, in the presence of a suitable guest, such that the diacid forms a discrete ternary assembly, 2(**1**)·**2** (**3**) (where **2** = 1,2-*trans*-bis(2-pyridyl)-ethylene), of nanoscale dimensions, in which **1**, in a planar conformation, recognizes **2** in a coplanar orientation.[16] Recognition between **1** and **2** involves a structural modification of an established two-component supramolecular synthon,[17] giving rise to 10 cooperative hydrogen bonds, involving a combination of O−H···N, O−H···O, and C−H···O forces,[18] between constituent molecules. In addition to providing the first example of an organic molecular assembly based on **1** in the solid state, such observations provide insight into recognition processes involving hydrogen bond cooperativity,[7] where understanding the structure behaviors of such forces for the design of large molecular assemblies is of much interest.[4]



1

Figure 1.

Addition of **1** (0.042 g) to acetone (0.5 mL) and ethanol (1.0 mL) in the presence of **2** (0.009 g) yielded, upon slow cooling, colorless crystals of **3** suitable for X-ray analysis. The formulation of **3** was confirmed by ^{1}H NMR spectroscopy and single-crystal X-ray diffraction.[19]

An ORTEP perspective, as well as space-filling models, of **3** is shown in Figure 2. The components of **3** have assembled in the solid state such that they form a discrete three-component assembly, of dimensions ~14 × 24 Å, which sits around a crystallographic center of inversion, held together, in part, by two intermolecular O−H···N hydrogen bonds [O···N separation (Å): O(1)···N(1) 2.657(3)].[20] In this arrangement, the hydrogen bond functionality of **1**, in a similar way to free **1**, which assembles in the solid state to form a dimer held together by four intermolecular O−H···O forces,[21] is directed toward the center of the complex such that the *tert*-butyl groups of **1** lie along the periphery of the assembly. In contrast to free **1**,[21] however, both carboxyl groups of **3** lie approximately coplanar with the xanthene scaffold, as illustrated by twist angles of 11.4° and 9.1° made by carboxyl atoms C(1), O(1), O(2) and C(15), O(4), O(5) with respect to the aromatic plane, respectively,[22] such that the carboxyl group involving C(15) participates in a bifurcated intramolecular O−H···O hydrogen bond with the inner wall of the host [O···O separations (Å): O(4)···O(2) 2.681(3), O(4)···O(3) 2.661(3)].[23] Notably, such intramolecular bonding has been recently shown, using NMR spectroscopy, to position amide functionality in solution, in an orthogonal orientation, to facilitate aromatic stacking between a receptor based on **1** and aromatic guests for control

---

[9] (a) Griffiths-Jones, S. R.; Searle, M. S. *J. Am. Chem. Soc.* **2000**, *122*, 8350. (b) Olejniczak, E. T.; Hajduk, P. J.; Marcotte, P. A.; Nettesheim, D. G.; Meadows, R. P.; Edalji, R.; Holzman, T. F.; Fesik, S. W. *J. Am. Chem. Soc.* **1997**, *119*, 5828.

[10] Stryer, L. In *Biochemistry*; W. H. Freeman and Co.: New York, 1988.

[11] Gellman, S. H.; Schenck, H. L. *J. Am. Chem. Soc.* **1998**, *120*, 4869. (b) Gung, B. W.; Zhu, Z.; Everingham, B. *J. Org. Chem.* **1997**, *62*, 3436.

[12] MacGillivray, L. R.; Reid, J. L.; Ripmeester, J. A. *J. Am. Chem. Soc.* **2000**, *122*, 7817.

[13] Anderson, S.; Anderson, H. L. In *Templated Organic Synthesis*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 2000.

[14] Feldman, K. S.; Campbell, R. F. *J. Org. Chem.* **1995**, *60*, 1924.

[15] Nowick, J. S.; Ballester, P.; Ebmeyer, F.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 8902.

[16] Coplanar recognition forms the geometric basis for base-pairing in DNA (see ref 10).

[17] Sharma, C. V. K.; Zaworotko, M. J. *Chem. Commun.* **1996**, 2655.

[18] (a) Desiraju, G. R. *Acc. Chem. Res.* **1996**, *29*, 441. (b) For a discussion on the ability of C−H···O hydrogen bonds to stabilize coplanar recognition in nucleic acids, see: Wahl, M. C.; Sundaralingam *Trends Biochem. Sci.* **1997**, *22*, 97. (c) For a recent report that exploits C−H···O hydrogen bonding for the design of assemblies that parallel proteins, see: Meadows, E. S.; De Wall, S. L.; Barbour, L. J.; Fronzek, M.-S. K.; Gokel, G. W. *J. Am. Chem. Soc.* **2000**, *122*, 3325.

[19] Crystal data for **3**: crystal size 0.25 × 0.30× 0.40 mm, triclinic, space group $P\bar{1}$, $a = 7.3075(1)$ Å, $b = 13.222(2)$ Å, $c = 14.570(3)$ Å, $\alpha = 78.585(3)°$, $\beta = 78.318(4)°$, $\gamma = 79.489(4)°$, $U = 1336.4(4)$ Å^3, $2\theta = 45°$, Mo Kα radiation ($\lambda = 0.71070$ Å) for $Z = 2$ and $R = 0.049$.

[20] C−O bond distances of the carboxyl groups of **1** [C−O distances (Å): C(1)−O(1) 1.321(3), C(1)−O(2) 1.212(3), C(15)−O(4) 1.327(4), C(15)−O(5) 1.211(3)] indicate the acid exists in **3**.

[21] MacGillivray, L. R.; Siekbe, M. M. *J. Chem. Crystallogr.*, in press.

[22] The carboxyl groups of free **1** are rotated by 28.6° and 32.7° with respect to the xanthene core (ref 21).

[23] This hydrogen bond was initially observed during the original synthesis of **1** (see ref 15).

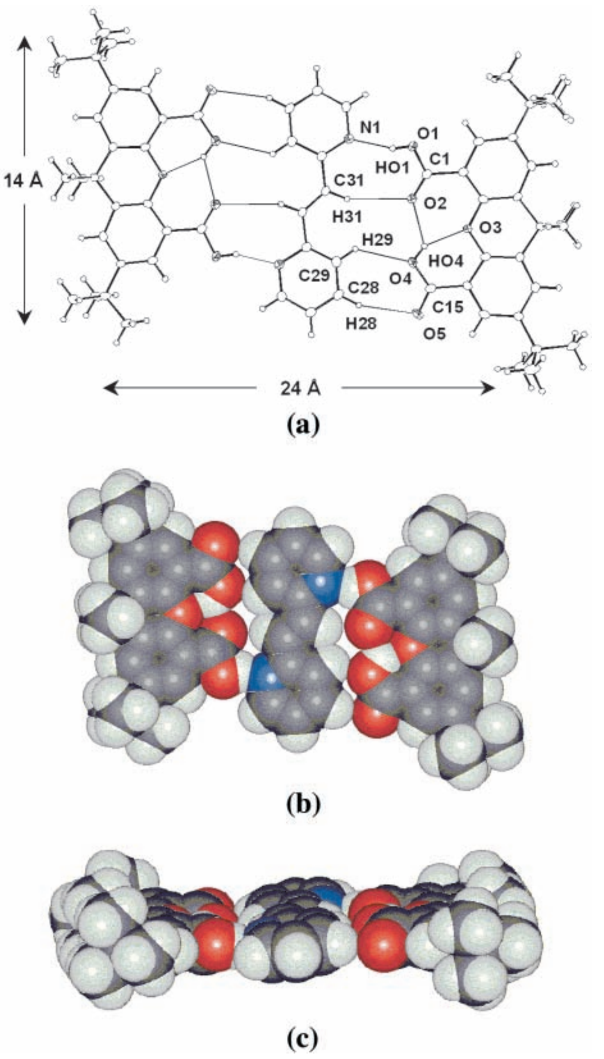


Figure 2. X-ray crystal structure of the three-component assembly **3**: (a) ORTEP perspective and (b) space-filling model displaying the cooperative forces and (c) space-filling model of a "side-on" view. Selected interatomic distances (Å): O(1)···N(1) 2.657(3), O(4)···O(2) 2.681(3), O(4)···O(3) 2.661(3), C(31)···O(2) 3.633(3), C(29)···O(4) 3.180(4), C(28)···O(5) 3.375(4).

of molecular switching and catalysis.[24] In the case of **3**, the pyridyl groups of **2**, in a similar way to the carboxyl groups of **1**, are approximately coplanar with the xanthene scaffold, as demonstrated by the twist angle of 10.1° made by the pyridyl group with respect to the aromatic plane. Moreover, whereas **1** typically recognizes aromatics in which host and guest adopt an approximate orthogonal orientation,[24] to our knowledge **3** represents the first example in which **1** has been observed to interact with an aromatic in a coplanar fashion.[16]

The recognition properties displayed by the cleft of **3** may be attributed to cooperative forces involving the intramolecular O−H···O bond of **1**.[7,15] Indeed, it is established[17] that pyridines tend to interact with carboxylic acids in organic solids by participating in a primary O−H···N interaction and a secondary C−H···O force,[18] involving an α-hydrogen atom of the pyridyl group, such that the pyridyl moiety adopts an approximate coplanar orientation, in the form of a two-component supramolecular synthon,[6] with the acid functionality. For **2**, such a synthon may, in principle, involve either the α-hydrogen atom of the pyridyl group **I** or a hydrogen atom of the ethylene moiety **II** (Figure 3). In **3**, **1** interacts with **2** such that a carboxyl group of each cleft, in addition to an O−H···N interaction, forms a C−H···O hydrogen bond [C···O separation (Å): C(31)···O(2) 3.633(3)] with a hydrogen atom of the olefin **II**. As a consequence of these forces, the second carboxyl group of the cleft participates in two C−H···O hydrogen bonds [C···O separation (Å): C(28)···O(5) 3.375(4), C(29)···O(4) 3.180(4)] with the "backside" of the second pyridyl unit such that the cleft, to permit formation of these forces, forms the intramolecular O−H···O hydrogen bond. Thus, **1** has, in effect, adapted its structure to a conformation that recognizes **2** in a "side-on" orientation by undergoing a structural reorganization that involves formation of an intramolecular bond (Figure 4).[25]

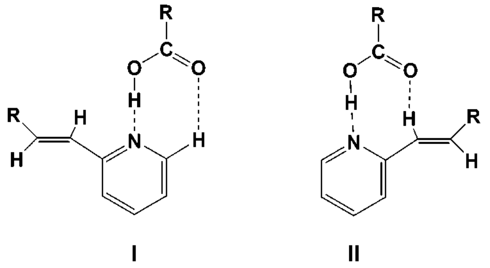


Figure 3.

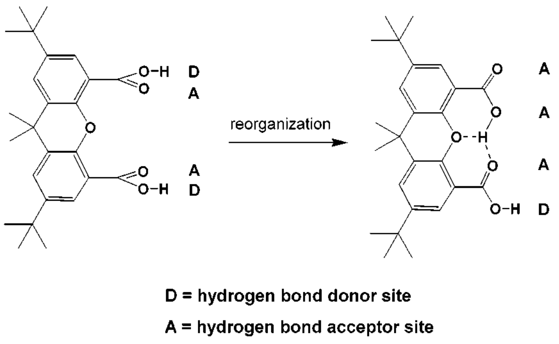


Figure 4.

As a result, the three-component assembly **3** is stabilized by two O−H···N and six C−H···O forces involving a single hydrogen bond donor and three hydrogen bond acceptor sites of each cleft, respectively,with the preference to form the C−H···O hydrogen bond with the olefin presumably arising,

---

[24] (a) Deans, R.; Niemz, A.; Breinlinger, E. C.; Rotello, V. M. *J. Am. Chem. Soc.* **1997**, *119*, 10863. (b) Park, T. K.; Schroeder, J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 5125.

in part, from stability gained by the cooperative nature of the 10 noncovalent bonds.[26] There is growing evidence that cooperative interactions involving combinations of strong (i.e., O−H···O) and weak (i.e., C−H···O) hydrogen bonds play a similar structural role stabilizing local structures of biomolecules[8,9,11] while **3** represents, to our knowledge, the first example in which a combination of cooperative hydrogen bonds has been observed to contribute to the structure of a molecular assembly involving **1**.[27]

A view along the crystallographic *b* axis depicting the crystal structure of **3** is shown in Figure 5. The assembly **3** organizes in the solid state to form a 2D layered structure where adjacent complexes are oriented, offset, in a tail-to-tail fashion, with the alkyl groups of **1** being positioned in close proximity. Interestingly, despite displaying a more elongated shape, **3** exhibits an extended structure virtually identical to that of free **1**,[21] neighboring layers lying offset, with interlayer olefins of **2** being separated by 7.31 Å,[28] such that the *tert*-butyl groups of the cleft form van der Waals interactions with the xanthene moiety.

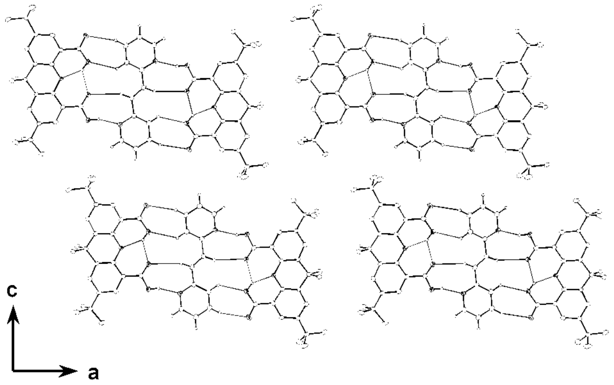


Figure 5. ORTEP perspective of the 2D layered structure of **3**.

In this report, we have demonstrated the ability of **1** to form a large organic assembly, with the appropriate guest **2**, such that the cleft, by undergoing a structural reorganization, displays a novel[21] mode of recognition,[24] involving a solid-state synthon based on recognition properties involving an olefin,[17] that is provided by a combination of cooperative[7] hydrogen bonds.[18] With these observations realized, experiments are underway to determine whether such cooperative forces may be exploited, by developing a library of hydrogen bond acceptor guests,[29] for the rational design of photoactive organic assemblies based on **1**.[12] Such studies should allow us to further delineate contributions of cooperative forces on the molecular assembly process such that the construction of organic assemblies akin to those of nanoscale biological complexes may be realized.

Acknowledgment. We are grateful for funding from the University of Iowa and the Natural Sciences and Engineering Research Council of Canada (doctoral scholarship, J.L.R.). We thank Dr. Charles L. Barnes (University of Missouri−Columbia) for collection of the X-ray data.

Supporting Information Available: Crystallographic reports and tables of positional and thermal parameters, bond lengths and angles, and NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0156695

---

[25] The reorganization of **1** in **3** is akin to the ability of a protein to recognize a substrate by way of an "induced-fit" (ref 10).

[26] The C−H groups that participate in the C−H···O interactions of **3** should exhibit comparable solid state acidities (see ref 18a).

[27] For an example where hydrogen bonds and $\pi-\pi$ interactions contribute to the structure of an assembly based on **1** see, ref 24a.

[28] For [2 + 2] photoreaction to occur in a solid, olefins should be aligned and separated by < 4.2 Å, see: Schmidt, G. M. J. *Pure Appl. Chem.* **1971**, *27*, 647.

[29] Cocrystallization of **1** with 1,2-*trans*-bis(4-pyridyl)ethylene yields a four-component assembly in which two hydrogen bond acceptors lie in an orthogonal, stacked arrangement (MacGillivray, L. R.; Siebke, M. M., unpublished results).