Exploiting modularity in template-controlled synthesis: a new linear template to direct reactivity within discrete hydrogen-bonded molecular assemblies in the solid state

Giannis S. Papaefstathiou, Alex J. Kipp and Leonard R. MacGillivray*

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242-1294, USA.
E-mail: len-macgillivray@uiowa.edu

Co-crystallization of 1,8-naphthalenedicarboxylic acid (1,8-nap) with *trans*-1,2-bis(*n*-pyridyl)ethylene (*n,n*′-bpe) (*n* = 2 or 4) yields a discrete four-component molecular assembly, 2(*n,n*′-bpe)·2(1,8-nap) 1, that is held together by four O–H···N hydrogen bonds where the dicarboxylic acid, serving as a linear template, directs alignment of olefins in the solid state for [2 + 2] photoreaction.

Molecules that function as linear templates[1,2] are emerging as tools for applying principles of molecular recognition,[3] supramolecular chemistry,[4] and self-assembly[5] for the control of covalent-bond-making processes that lead to the design of molecules,[6] oligomers,[7] and polymers[8] in solution[6a,d,7] and the solid state.[6b,c,8] In addition to facilitating stereo- and regio-controlled positioning of reactive sites with atomic-level precision, linear templates are promising tools for gaining control of reactivity that approaches the nanometer-scale level, and beyond (*i.e.* > 10 Å),[9] owing to an ability of such molecules to enforce predetermined topologies upon reactants, circumventing problems of molecular entanglement[10] that can lead to poor selectivities and product yields. Indeed, to extend linear templates beyond the reach of current synthetic methodologies,[1] it will be necessary to exploit the inherent modularity of such a template approach[9] by devising templates, reactants, and reactions that may be readily interchanged. Moreover, by establishing such synthetic flexibilities, ready access to molecules and materials not accessible using traditional approaches to synthesis may be realized.[6–8]

We are utilizing linear templates to control reactivity in molecular solids.[6b] In particular, we have revealed the ability of resorcinol, and derivatives, to function as linear templates in the solid-state by organizing, by way of hydrogen bonds, olefins attached to symmetrically substituted bipyridines in position for [2+2] photoreaction.[11] By enforcing reaction to occur within a discrete molecular assembly,[5] this approach eliminates many vexatious problems of intermolecular forces that have made such topochemical designs unreliable,[11] providing a reliable means to make covalent bonds in solids. Such an ability to deliberately control chemical reactivity offers a prospect of eliminating waste organic solvent in molecular synthesis (*i.e.* green chemistry)[12] and gaining access to molecules less obtainable, or completely inaccessible, in solution.

We are currently identifying molecules that function as linear templates. Owing to the modularity of the approach, we reasoned that it should be possible to engineer molecules that possess structures largely preorganized,[13] in a similar way to resorcinol, to align olefins within discrete assemblies, giving rise to template libraries.[8] Here, we reveal the ability of 1,8-naphthalenedicarboxylic acid (1,8-nap), in 2(4,4′-bpe)·2(1,8-nap) **1a** and 2(2,2′-bpe)·2(1,8-nap) **1b** (where 4,4′-bpe = *trans*-1,2-bis(4-pyridyl)ethylene, 2,2′-bpe = *trans*-1,2-bis(2-pyridyl)ethylene), to function, in a similar way to resorcinol, as a linear hydrogen bond donor template. Following work of Feldman and Campbell,[14] we anticipated that co-crystallization of 1,8-nap with either 4,4′-bpe or 2,2′-bpe would yield a four-component molecular assembly held together by

four O–H···N hydrogen bonds (Scheme 1) where 1,8-nap, owing to the proximity of the carboxylic acid groups along the naphthalene scaffold,[14] would juxtapose two bipyridines in the solid for [2 + 2] photoreaction. To our knowledge, 1,8-nap represents the second example of a molecule that functions as a linear template by controlling reactivity within a discrete hydrogen-bonded molecular assembly in the solid-state.[6b]† In addition to increasing the synthetic flexibility of this approach, such observations provide structure criteria for controlling reactivity that approaches the nanometer-scale level,[6–8] which is of growing interest.

Addition of 1,8-nap (0.017 g) to methanol (2 mL) in the presence of either 4,4′-bpe (0.015 g) or 2,2′-bpe (0.015 g) yielded, upon slow cooling, colorless crystals of **1a** and **1b**, respectively, suitable for X-ray analysis. The formulations of **1a** and **1b** were confirmed by ¹H NMR spectroscopy and single-crystal X-ray diffraction.‡

ORTEP perspectives of **1a** and **1b** are shown in Fig. 1. The components of **1a** and **1b** have assembled, in a similar way to 2(4,4′-bpe)·2(resorcinol) and 2(2,2′-bpe)·2(resorcinol),[6b] to form discrete molecular assemblies, of dimensions ~ 5.5 × 6.4 × 26.3 and 5.5 × 11.1 × 19.3 Å, respectively, held together by four O–H···N hydrogen bonds. In addition to a primary O–H···N interaction, each carboxylic acid group, each of which is twisted out of the plane of the naphthalene unit, participates in a C–H···O hydrogen bond with each pyridyl ring.[15,16] In this arrangement, two molecules of 4,4′-bpe and 2,2′-bpe lie stacked adjacent to 1,8-nap where the olefins of each complex are separated by 3.73 and 3.91 Å, respectively. These separations
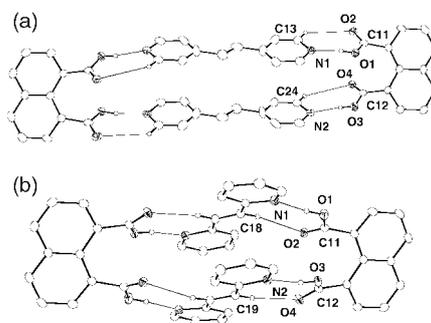

2(4,4′-bpe)·2(1,8-nap)
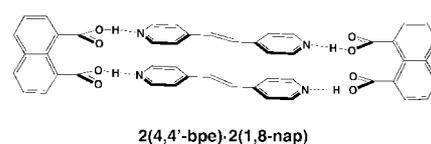
Scheme 1

Fig. 1 ORTEP perspectives of molecular assemblies: (a) **1a** and (b) **1b**. Selected interatomic distances (Å) for **1a**: O(1)···N(1) 2.598(4), O(3)···N(2) 2.612(4), C(13)···O(2) 3.497(5), C(24)···O(4) 3.562(4); for **1b**: O(1)···N(1) 2.658(2), O(3)···N(2) 2.601(2), C(18)···O(2) 3.396(2), C(19)···O(4) 3.287(2). Twist angles of carboxylic acid groups (°): **1a**, 51.2 (C11), 50.9 (C12); **1b**, 53.0 (C11), 52.2 (C12).

are within the distance criterion of Schmidt for [2 + 2] photoreaction.[11] Notably, in the case of **1a**, the olefins are disordered across two sites (occupancies: 70:30) while the olefins of **1b** are ordered and parallel. Olefins of nearest-neighbor molecular assemblies of **1a** and **1b** are offset and separated by 4.81 and 4.09 Å, respectively. Indeed, UV irradiation of powdered crystalline samples of **1a** and **1b**, each for a period of 7 h (Rayonet reactor, 300 nm Hg lamp), produces, stereospecifically (100% yield), *rctt*-tetrakis(4-pyridyl)cyclobutane (4,4′-tpcb) and *rctt*-tetrakis(2-pyridyl)cyclobutane (2,2′-tpcb), respectively, as determined by ^{1}H NMR spectroscopy.

To confirm the structure of each product, a portion of each photolyzed solid (0.0010 g) was dissolved in methanol (5 mL) and single crystals of (4,4′-tpcb)·2(1,8-nap) **2a** and (2,2′-tpcb)·2(1,8-nap) **2b** were grown, after a period of approximately three days, by way of slow solvent evaporation. The formulations of **2a** and **2b** were confirmed by ^{1}H NMR spectroscopy and single-crystal X-ray diffraction.‡

ORTEP perspectives of **2a** and **2b** are shown in Fig. 2. As in the case of **1a** and **1b**, the components of **2a** and **2b** assemble by way of O–H···N and C–H···O hydrogen bonds, the carboxylic acid groups being twisted out of the plane of the naphthalene unit. For **2a**, one carboxylic acid group participates in an O–H···O hydrogen bond, in the form of a carboxylic acid dimer, with a neighboring diacid. As a consequence of these forces, the components of **2a**, in contrast to **1a**, assemble to form a one-dimensional hydrogen-bonded polymer along the crystallographic *a*-axis. This contrasts (4,4′-tpcb)·2(resorcinol)[6b] where the template, owing to the flexibility of the hydroxy groups, forms a discrete assembly with 4,4′-tpcb. We attribute the formation of the polymer **2a** to the rigidity of the diacid which, presumably, is less able to participate, in a similar way to (4,4′-tpcb)·2(resorcinol), in two O–H···N interactions with two *cis*-pyridyl groups of the product. In the case of **2b**, the components assemble, in a similar way to **1b**, to form a discrete molecular assembly held together by four O–H···N and four C–H···O hydrogen bonds where the O–H···N forces involve, in contrast to **1b**, two *trans*-pyridyl groups of the photoproduct.§

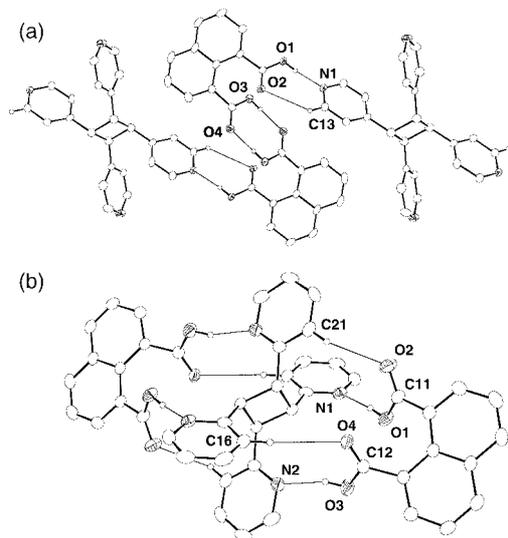In this report, we have identified the ability of 1,8-nap to function as a linear template in the solid state, controlling reactivity within a discrete molecular assembly held together by hydrogen bonds. With these observations realized, we are currently utilizing the molecule as a template for conducting solid-state synthesis by design.[6b] With a library of linear templates now emerging,[8] it may be possible to utilize this approach for the designed synthesis of molecules of increasing complexity (*e.g.* nanosystems).[7] In the case of the solid state, our observations suggest an ability to organize molecules with precision and flexibility that rivals the liquid phase, providing routine access to molecular species less available in solution.[9]

Notes and references

† A conceptually similar approach has been described that has involved infinite assemblies (see ref. 6c).

‡ *Crystal data*: for **1a**: monoclinic, space group $P2_1/c$, $a = 7.599(2)$, $b = 29.271(6)$, $c = 9.106(2)$ Å, $\beta = 106.611(4)°$, $U = 1941.0(8)$ Å^3, $D_c = 1.36$ g cm^{-3}, Mo-Kα radiation ($\lambda = 0.71070$ Å) for $Z = 4$. Least-squares refinement based on 1412 reflections with $I_{net} > 2.0\sigma(I_{net})$ (out of 2539 unique reflections) led to a final value of $R = 0.053$. For **1b**: monoclinic, space group $P2_1/c$, $a = 7.303(1)$, $b = 23.187(3)$, $c = 11.425(1)$ Å, $\beta = 98.070(3)°$, $U = 1915.4(4)$ Å^3, $D_c = 1.38$ g cm^{-3}, Mo-Kα radiation ($\lambda = 0.71070$ Å) for $Z = 4$. Least-squares refinement based on 2325 reflections with $I_{net} > 2.0\sigma(I_{net})$ (out of 2500 unique reflections) led to a final value of $R = 0.031$. For **2a**: triclinic, space group $P\bar{1}$, $a = 8.377(2)$, $b = 11.294(2)$, $c = 11.685(2)$ Å, $\alpha = 99.45(3)$, $\beta = 105.12(3)$, $\gamma = 109.73(3)°$, $U = 965.1(3)$ Å^3, $D_c = 1.37$ g cm^{-3}, Mo-Kα radiation ($\lambda = 0.71070$ Å) for $Z = 1$. Least-squares refinement based on 2182 reflections with $I_{net} > 2.0\sigma(I_{net})$ (out of 2509 unique reflections) led to a final value of $R = 0.049$. For **2b**: monoclinic, $P2_1/n$, $a = 10.059(2)$, $b = 15.456(3)$, $c = 12.414(3)$ Å, $\beta = 97.39(3)°$, $U = 1914.0(7)$ Å^3, $D_c = 1.38$ g cm^{-3}, Mo-Kα radiation ($\lambda = 0.71070$ Å) for $Z = 2$. Least-squares refinement based on 2405 reflections with $I_{net} > 2.0\sigma(I_{net})$ (out of 2493 unique reflections) led to a final value of $R = 0.043$. CCDC reference numbers 172617–172620. See http://www.rsc.org/suppdata/cc/b1/b106584j/ for crystallographic data in CIF or other electronic format.

§ The photoproduct of **2b** adopts a conformation where the nitrogen atoms of *cis*-pyridyl groups point in opposite directions which, in addition to the rigidity of 1,8-nap, may account for the discrete assembly.

1 T. R. Kelly, C. Zhao and G. J. Bridger, *J. Am. Chem. Soc.*, 1989, **111**, 3744.
2 S. Anderson and H. L. Anderson, in *Templated Organic Synthesis*, ed. F. Diederich and P. J. Stang, Wiley-VCH, New York, 2000, pp. 1–38.
3 J. Rebek Jr., *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 245.
4 J.-M. Lehn, *Supramolecular Chemistry*, Wiley-VCH, Weinheim, 1995.
5 M. C. T. Fyfe and J. F. Stoddart, *Acc. Chem. Res.*, 1997, **30**, 393.
6 (*a*) D. M. Bassani, X. Sallenvae, V. Darcos and J.-P. Desvergne, *Chem. Commun.*, 2001, 1446; (*b*) L. R. MacGillivray, J. L. Reid and J. A. Ripmeester, *J. Am. Chem. Soc.*, 2000, **122**, 7817; (*c*) S. Ohba, H. Hosomi and Y. Ito, *J. Am. Chem. Soc.*, 2001, **123**, 6441; (*d*) D. M. Bassani, V. Darcos, S. Mahony and J.-P. Desvergne, *J. Am. Chem. Soc.*, 2000, **122**, 8795.
7 (*a*) E. A. Archer, N. T. Goldberg, V. Lynch and M. J. Krische, *J. Am. Chem. Soc.*, 2000, **122**, 5006; (*b*) E. A. Archer, A. E. Sochia and M. J. Krische, *Chem. Eur. J.*, 2001, **7**, 2059.
8 (*a*) J. Xiao, M. Yang, J. W. Lauher and F. W. Fowler, *Angew. Chem., Int. Ed.*, 2000, **39**, 2132; (*b*) J. J. Kane, J. John, R.-F. Liao, J. W. Lauher and F. W. Fowler, *J. Am. Chem. Soc.*, 1995, **117**, 12003.
9 K. E. Drexler, *Proc. Natl. Acad. Sci. USA*, 1981, **78**, 5275.
10 C.-T. Chen, P. Gantzel, J. S. Siegel, K. K. Baldridge, R. B. English and D. M. Ho, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2657.
11 G. M. J. Schmidt, *Pure Appl. Chem.*, 1971, **27**, 647.
12 P. T. Anastas and J. C. Warner, in *Green Chemistry: Theory and Practice*, Oxford University Press, New York, 1998.
13 D. J. Cram, *Science*, 1988, **240**, 760.
14 K. S. Feldman and R. F. Campbell, *J. Org. Chem.*, 1995, **60**, 1924.
15 C. V. K. Sharma and M. J. Zaworotko, *Chem. Commun.*, 1996, 2655.
16 L. R. MacGillivray, M. M. Siebke and J. L. Reid, *Org. Lett.*, 2001, **3**, 1257.

Fig. 2 ORTEP perspectives of the photoproducts: (a) **2a** and (b) **2b**. Selected interatomic distances (Å) for **2a**: O(1)···N(1) 2.607(3), O(3)···O(4) 2.619(3), C(13)···O(2) 3.474(4); for **2b**: O(1)···N(1) 2.651(2), O(3)···N(2) 2.667(2), C(21)···O(2) 3.196(3), C(16)···O(4) 3.722(3). Twist angles of carboxylic acid groups (°): **2a**, 48.5 (C11), 50.2 (C12); **2b**, 41.0 (C11), 48.8 (C12).