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Efficient Stereo- and Regiocontrolled Alkene Photodimerization through Hydrogen Bond Enforced Preorganization in the Solid State

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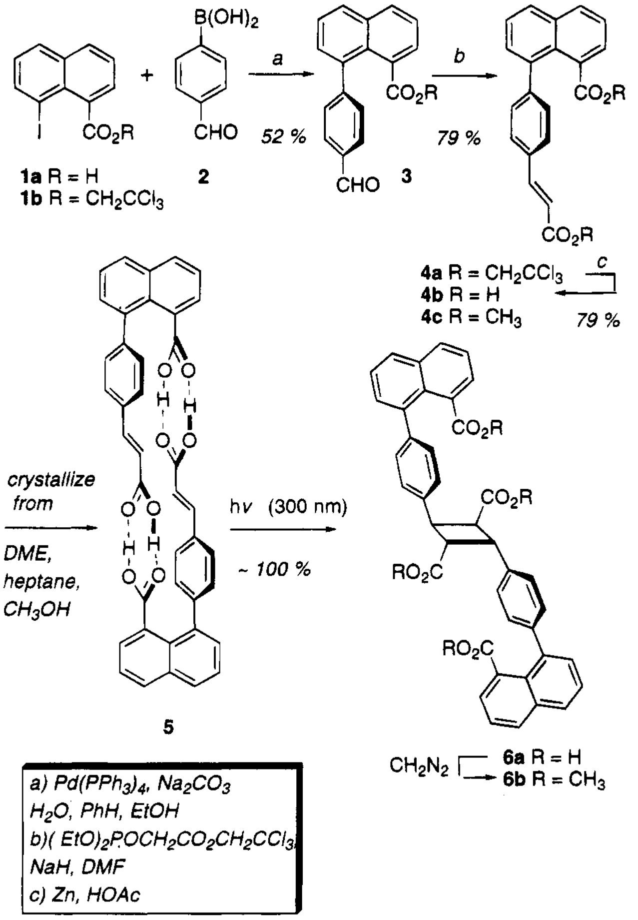
Hydrogen bond encoded molecular recognition has been a hallmark of innumerable studies probing ligand–receptor complexation in solution[1] and in the solid state.[2] However, the exploitation of these interactions to deliberately and predictably influence any subsequent chemistry of the bound partners has been much less explored in the liquid phase[3] and not at all in the latter environment.[4] In this paper we describe the solid state and comparative solution phase chemistry of a naphthoic acid-derived cinnamic acid which demonstrates that hydrogen bonding (1) can be used to enforce a particular and desirable stereo- and regiochemical outcome in a solid state transformation that otherwise might not follow this reaction course and (2) is directly responsible for providing product in a yield that exceeds the theoretical maximum for "independent-site" solid state reactions.[5] These attributes take on a measure of significance in the context of two- and three-dimensional carbon network synthesis, as the chemistry described herein may point to a strategy for fastening together various hub–spoke architectures en route to wholly organic materials that may be functionally analogous to zeolites.[6]

Scheme 1



The "U"-shaped diacid **4b** (Scheme 1) was chosen to test the premise that a carefully designed scaffold can satisfy the unrelated and not necessarily compatible geometric constraints imposed by both carboxyl hydrogen bonding patterns and by solid state alkene dimerization reactions (e.g., alkene–alkene distance ≤ 4.2 Å[7]). The parallel alignment of the acid groups on a single molecule ensures that proximity between the alkene moieties of different diacids can be achieved despite the fact that hydrogen bonding is by definition at the leading edge of intermolecular contact. This compound was readily available via Suzuki coupling[8] of the known boronic acid **2**[9] with 2,2,2-trichloroethyl 8-iodo-1-naphthoate (**1b**),[10] followed by Emmons–Horner homologation of the resultant aldehyde **3** and Zn-mediated deprotection of the ester moieties in **4a**. In addition, the dimethyl ester **4c** was

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[1] Leading references can be found in: (a) *Principles of Molecular Recognition;* Buckingham, A. D., Legon, A. C., Roberts, S. M., Eds.; Blackie Academic and Professional: London, 1993. (b) Mascal, M. *Contemp. Org. Synth.* **1994**, *1*, 31.

[2] (a) Etter, M. C. *J. Phys. Chem.* **1991**, *95*, 4601. (b) Leiserowitz, L.; Hagler, A. T. *Proc. R. Soc. London* **1983**, *A388*, 133. (c) Desiraju, G. R. *Crystal Engineering: The Design of Organic Solids*; Elsevier: Amsterdam, 1989. (d) Aakeroy, C. B.; Seddon, K. R. *Chem. Soc. Rev.* **1993**, *22*, 397.

[3] Leading references can be found in: (a) Wintner, E. A.; Conn, M. M.; Rebek, J., Jr. *Acc. Chem Res.* **1994**, *27*, 198. (b) von Kiedrowski, G.; Wlotzka, B.; Helbing, J.; Matzen, M.; Jordan, S. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 423. (c) Orgel, L. E. *Nature* **1992**, *358*, 203. (d) Kelly, T. R.; Bridger, G. J.; Zhao, C. *J. Am. Chem. Soc.* **1990**, *112*, 8024. (e) Goodwin, J. T.; Lynn, D. G. *J. Am. Chem. Soc.* **1992**, *114*, 9197. (f) Hirst, S. C.; Hamilton, A. D. *J. Am. Chem. Soc.* **1991**, *113*, 382.

[4] (a) Etter et al. describe a system which bears some conceptual resemblence to the approach described herein. Thus, they cocrystallize 4-chloro-3,5-dinitrobenzoic acid and 4-aminobenzoic acid into a solid which upon heating to 180 °C undergoes a nucleophilic aromatic substitution reaction with loss of HCl. Since this material was not characterized by X-ray diffraction, it remains unknown whether the hydrogen bond directed crystallization was responsible for orienting the reactive groups. See: Etter, M. C.; Frankenbach, G. M.; Bernstein, J. *Tetrahedron Lett.* **1989**, *30*, 3617. (b) See also: Wheeler, K. A.; Foxman, B. M. *Chem. Mater.* **1994**, *6*, 1330.

[5] Savion, Z.; Wernick, D. L. *J. Org. Chem.* **1993**, *58*, 2424 and references cited therein. This model, when applied to a stack crystal structure, predicts that the maximum attainable yield is 86.5%. A simplistic but useful interpretation of this model as applied to cinnamic acid photodimerization follows: for a given stack of five independent, adjacent cinnamic acid residues labeled 1–5, if 1 and 2 dimerize, and if 4 and 5 dimerize, acid 3 cannot react further. If this independent site model is propagated throughout the entire crystal, a limiting maximum yield is obtained.

[6] For leading references to work related to the assembly of periodic organic networks, see: (a) Venkataraman, D.; Lee, S.; Zhang, J.; Moore, J. S. *Nature* **1994**, *371*, 591. (b) Abrahams, B. F.; Hoskins, B. F.; Michail, D. M.; Robson, R. *Nature* **1994**, *369*, 727. (c) Fan, E.; Vicent, C.; Geib, S. J.; Hamilton, A. D. *Chem. Mater.* **1994**, *6*, 1113. (d) Mathias, J. P.; Simanek, E. E.; Whitesides, G. M. *J Am. Chem. Soc.* **1994**, *116*, 4326. (e) Shea, K. J.; Loy, D. A.; Webster, O. *J. Am. Chem. Soc.* **1992**, *114*, 6700. (f) Copp, S. B.; Subramanian, S.; Zaworotko, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 8719. (g) Ermer, O.; Lindenberg, L. *Helv. Chim. Acta* **1991**, *74*, 825. (h) Simard, M.; Su, D.; Wuest, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 4696.

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[9] (a) Torssell, K. *Arkiv. Kemi* **1956**, *10*, 507. (b) Torssel, K. *Acta Chem. Scand.* **1954**, *8*, 1779.

[10] Bailey, R. J.; Card, P. J.; Schechter, H. *J. Am. Chem. Soc.* **1983**, *105*, 6096.

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prepared by similar chemistry as a comparison compound both to aid in evaluating the ensuing photochemistry and to facilitate structural elucidation of the photoproduct of **4b**.

Irradiation of a recrystallized sample (10–50 mg) of **4b** (DME/heptane/CH_3OH) through Pyrex in a Rayonet carousel photoreactor (300 nm) led to clean conversion of the starting material into a single cyclobutane product over the course of 20–50 h. The original colorless crystals (typically rods 3 mm × 0.7 mm × 0.5 mm) visibly yellowed and lost definition around the sharp edges during irradiation but did not shatter or crumble. Treatment of the crude solid reaction product with ethereal diazomethane permitted isolation of the cyclobutane product **6b** which was shown to have the α-truxillate-type stereochemistry. The stereochemical and regiochemical assignment of **6b** was secured by comparison of its ^{13}C and ^{1}H NMR spectral data with those obtained from all four dimethyl esters (α-truxillate,[11a] ϵ-truxillate,[11b] β-truxinate,[11a] δ-truxinate[11c]) derived from irradiation and subsequent manipulation of cinnamic acid crystalline isomorphs. In addition, the isomeric β-truxinate and δ-truxinate analogs of photodimer **6b**, prepared by irradiation of dimethyl ester **4c** in dilute benzene solution, provided additional spectral comparison points to buttress the structural assignment of **6b** (see the supplementary material). Finally, it should be noted that *crystalline* dimethyl ester **4c** was completely unreactive under irradiation as described for diacid **4b**, while irradiation of a DME solution of **4b** resulted in consumption of diacid but afforded no characterizable materials.

Isolation of exclusively the cyclobutane stereo- and regioisomer **6b** provides permissive but not compelling evidence that dimerization proceeded through the "closed" dimer structure **5**. Alternative structures, such as an "open" dimer (e.g., two molecules of **4b** connected by a single hydrogen-bonded acid pair) or even no hydrogen-bonding connectivity between a reacting pair, could not be ruled out without further structural evidence. Fortunately, the crystals of **4b** proved suitable for X-ray diffraction,[12] and the derived structure (**5**, Figure 1) clearly demonstrates that our design criteria were met. The alkene carbon pairs destined to be joined each span a 3.62 Å gap.

The stereo- and regiochemical course of solid state photodimerizations of cinnamic acid derivatives is an inescapable consequence of the crystal packing of the precursor molecules, but that alignment is neither predictable a priori nor rationalizable a posteriori. Thus, variously substituted cinnamic acid derivatives crystallize (as hydrogen-bonded dimers) in either the α, β, or photostable γ forms, and subsequent irradiation affords the truxillic (from α) or truxinic (from β) isomers.[7a] However, our results show that at least in one particular case, a desired reaction selectivity can be imposed on this system via hydrogen bond directed alkene orientation. Apparently, formation of the *inter*molecular cinnamic acid hydrogen bond dimer,which contributes to substrate alignment with the simple derivatives noted above, is completely suppressed with **4b**. Furthermore, the high yield of this "dependent-site" photodimerization (essentially quantitative cyclobutane formation by examination of the ^{1}H NMR of the crude irradiation product) stands in sharp contrast to the limiting yields of all other (independent-site) solid state photodimerizations.[5] This feature may be particularly attractive for minimizing defects upon irradiation of a supramolecular lattice constructed from multidentate naphthoic acid/cinnamic acid connector-bearing hubs.

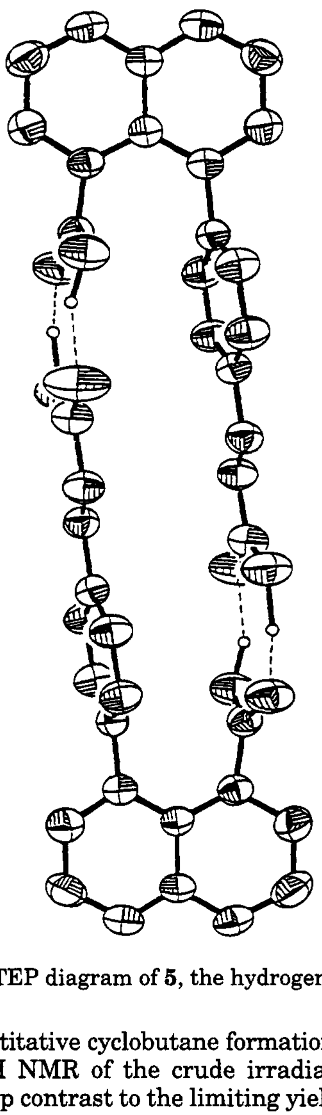

Figure 1. ORTEP diagram of **5**, the hydrogen-bonded dimer of **4b**.

In summary, we have demonstrated the feasibility of a novel strategy for covalently crosslinking organic fragments in the solid state which themselves already have been preorganized in a reactive orientation via hydrogen bond directed crystallization. Efforts to incorporate this connector assembly into a hub–spoke array as a prelude to the synthesis of periodic, covalently bound carbon networks are in progress.

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Supplementary Material Available: Experimental procedures, characterization data (^{1}H NMR, ^{13}C NMR, IR, MS, HRMS or comubstion analysis) for **1**, **3**, **4a**, **4b**, **4c**, **6b**, and the cyclobutane products derived from irradiation of **4c** in benzene solution, copies of key regions of the ^{1}H NMR spectra of **6b**, the cyclobutane products derived from **4c**, and the methyl esters of α-truxillic, ϵ-truxillic, β-truxinic, and δ-truxinic acids, and a labeled diagram for the X-ray crystallographic analysis of **5** (7 pages).

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(12) The author has deposited atomic coordinates for **5** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.