reaction is run at −20 °C, the ratio of olefin isomers secured upon dehydration is improved to 9:1.[4] For the major olefin isomer **3**, further steps in its transformation to huperzine A were similar to those reported previously. In the present work, however, the PhSH/AIBN catalyzed isomerization of the 10:1 *Z*/*E* mixture of olefin isomers **4** proved less efficient.[5] After two repetitions of the isomerization reaction, the 10:1 mixture was converted to but a 1:1.4 *Z*/*E* mixture. After chromatographic separation, the *E* isomer was reacted with LAH (THF, room temperature, 7 h, 84%) to give alcohol **5** which was oxidized to acid **6** by Jones reagent (room temperature, 1 h, 90%). Subsequent Curtius rearrangement of the acid **6** ($SOCl_2$, $PhCH_3$, 75–80 °C, 1.5 h; NaN_3, $PhCH_3$, 75–80 °C, 8 h; MeOH, reflux, 14 h, 80% overall) then led to huperzine A which exhibited an $[\alpha]^{25}_D$ of −147°, a value nearly identical with that measured for natural (−)-huperzine A [$[\alpha]^{25}_D$ −150° (*c* 0.12, $CHCl_3$)].[6]

On taking the minor diastereomer **3'** through the same sequence of reactions, small amounts of (+)-huperzine A could be obtained. To obtain larger quantities of (+)-huperzine A, it was more efficient to react (±)-**7** with (*S*)-MTPA-Cl (Et_3N, CH_2Cl_2, room temperature, 2 h) and to separate the resulting diastereomers by column chromatography. The resulting optically pure ester was reduced with LAH/Et_2O to provide optically active **7**. Jones oxidation (acetone, 27 °C, 1.5 h) followed by esterification with methyl iodide (DBU, CH_3CN, room temperature, 2 h, 46% overall) provided ester **8**. Next, **8** was isomerized to the (*E*)-olefin with thiophenol/AIBN in toluene, and the ester hydrolyzed to acid **9** with 20% aqueous NaOH in MeOH–THF at reflux (73% overall). Acid **9** was transformed to the carbamate **10** [$(PhO)_2P(O)N_3$, Et_3N, $PhCH_3$, reflux, 2.5 h; MeOH, reflux, 18 h, 63% overall) which was deprotected in the standard way (TMSI; MeOH, 85%) to furnish (+)-huperzine A of $[\alpha]^{25}_D$ +147° (*c* 0.72, $CHCl_3$).[7]

To examine the in vitro biological activity of (+)-huperzine A, the compound was tested over a concentration range of 10–1000 nM for its ability to inhibit AChE from rat cortex.[8] The IC_{50} for (+)-huperzine A was found to be 1448 ± 62.4 nM (n = 5), which is 33-fold larger than that of (−)-huperzine A (IC_{50} = 44.5 ± 2.9 nM (n = 3)). Racemic huperzine A has an IC_{50} of 71.5 ± 2.4 nM (n = 7).

The difference in IC_{50}'s of the pure enantiomers demonstrates a reasonably large stereoselectivity of action for huperzine A. Nonetheless, this difference is not as great as that reported for physostigmine wherein the (+)-isomer is over 700 times less potent than its (−)-isomer in inhibiting AChE from the cortex.[9] Such differences probably reflect the more critical positioning required of the physostigmine molecule as a consequence of its inhibitory action being due to its ability to carbamoylate the enzyme, a feature not exhibited by the huperzine molecule.[10]

The present work has important implications for the use of huperzine A in the palliative treatment of Alzheimer's disease. Further applications of the chemistry described herein to the preparation of optically pure analogues of huperzine A for evaluation as cognition enhancers are being explored.

Acknowledgment. We are indebted to the National Institute on Aging (Grant No. 1RO1AG07591) for their generous support of our program.

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Supplementary Material Available: Table I containing relative populations and MM2 energies of tfs and bfs conformations and full experimental details including spectral data for the synthesis of (−)-huperzine A (13 pages). Ordering information is given on any current masthead page.

Use of Hydrogen Bonds to Control Molecular Aggregation. Self-Assembly of Three-Dimensional Networks with Large Chambers

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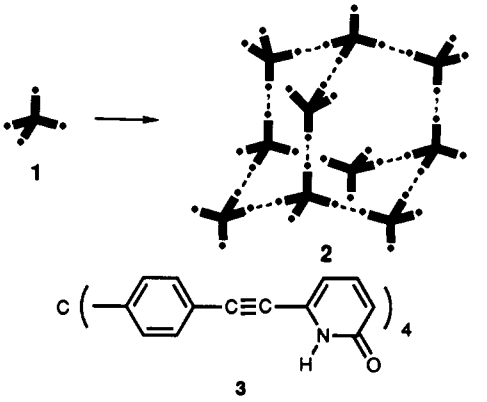
Noncovalent interactions that are selective, directional, and strongly attractive can induce the self-assembly of predictable supramolecular aggregates. We have shown that the tendency of 2-pyridones to form hydrogen-bonded dimers allows them to be used as sticky sites that compel molecules to associate, thereby driving the self-assembly of aggregates joined by extensive networks of hydrogen bonds.[1,2] This work suggested that the creative incorporation of multiple sticky sites in rigid frameworks might induce the self-assembly of three-dimensional networks with internal chambers. For example, hypothetical compound **1** should be forced by its tetrahedral geometry and the presence of four sticky sites (•) to form the cubic diamondoid network **2** or a related hexagonal lonsdaleite lattice. In this communication, we show



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that the self-assembly of such structures is possible; under suitable conditions, self-association of rigid tetrapyridone **3** produces an organic diamondoid network **2** with large internal chambers that selectively enclathrate molecules present during the self-assembly.[3,4]

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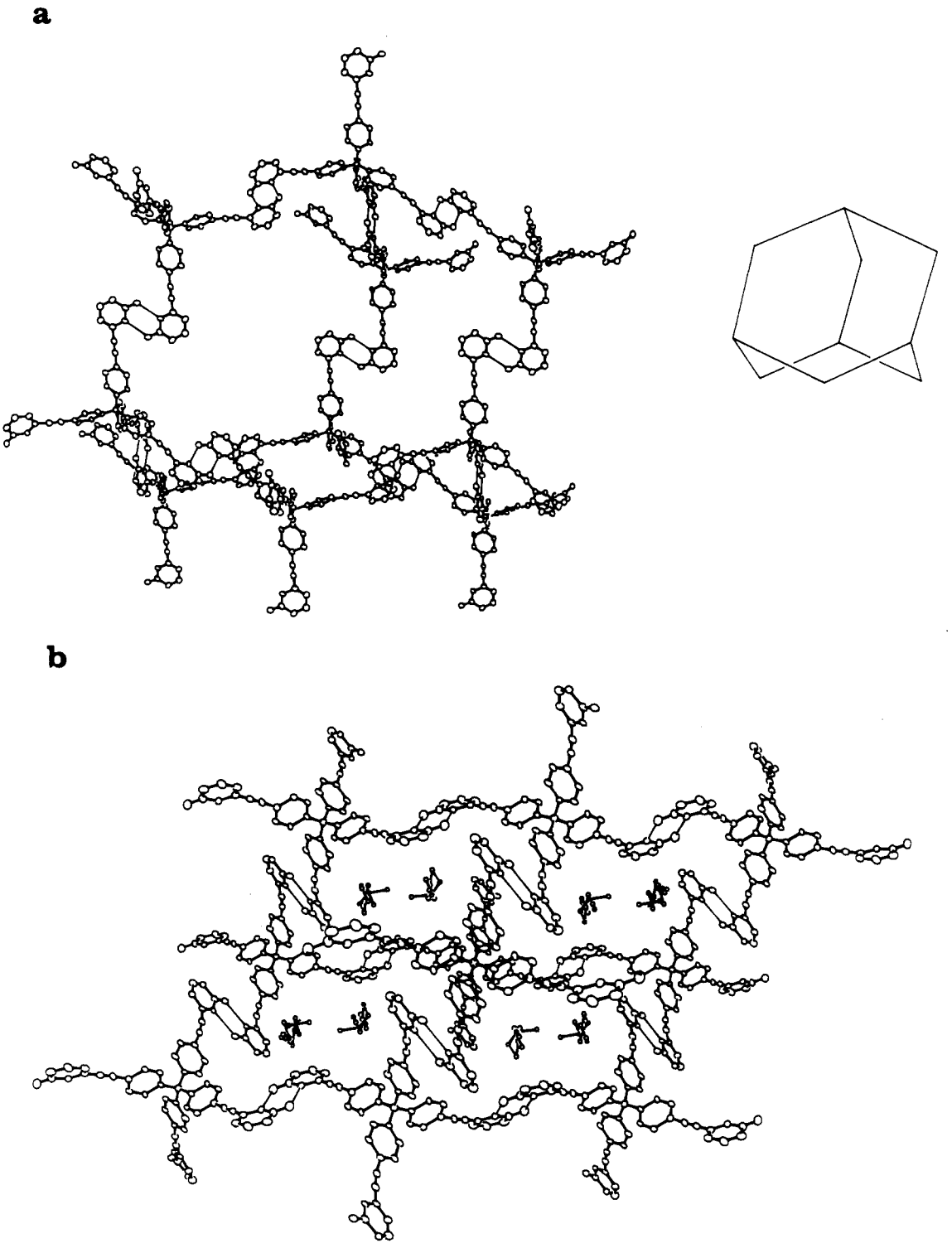

Figure 1. (a) ORTEP drawing of part of the infinite diamondoid network present in crystals of $3{\cdot}2CH_3CH_2CH_2COOH$. The tetrahedral centers of the 10 tectons in the drawing define a distorted adamantane, shown at the right at one-half scale. Non-hydrogen atoms are represented by ellipsoids corresponding to 50% probability. Butyric acid and all hydrogen atoms have been omitted for clarity. Hydrogen bonds are represented by narrow lines. (b) View along the *b* axis showing the channels containing parallel columns of butyric acid.

Tecton **3**[5] was synthesized from tetraphenylmethane[6] in three steps. Iodination (I_2, $PhI(OOCCF_3)_2$)[7] gave a 63% yield of tetraiodide **4**,[8] which was coupled[9] with 6-ethynyl-2-(phenylmethoxy)pyridine[1b] ($N(C_2H_5)_3$, $PdCl_2(PPh_3)_2$, CuI) to give pro-

(4) (a) Adamantane-1,3,5,7-tetracarboxylic acid self-associates to form diamondoid networks, but the networks interpenetrate and significant cavities are not present. Ermer, O.; Lindenberg, L. *Chem. Ber.* **1990**, *123*, 1111–1118. Ermer, O. *J. Am. Chem. Soc.* **1988**, *110*, 3747–3754. (b) For discussions of related hydrogen-bonded clathrates and engineered crystals, see: Weber, E. *Top. Curr. Chem.* **1987**, *140*, 1–20. Desiraju, G. R. *Crystal Engineering. The Design of Organic Solids*; Elsevier: New York, 1989.

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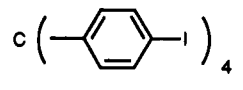
tected tetrapyridone **5** in 44% yield.[8] Deprotection (CF_3COOH)[10]



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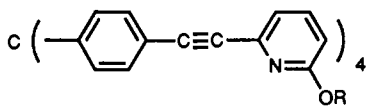
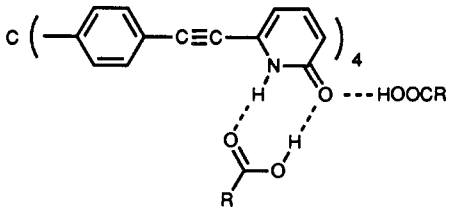


5 (R = CH_2Ph)

then provided tecton **3** in 100% yield.[8] Crystallization of compound **3** could be achieved only in mixtures containing significant amounts of carboxylic acids. Use of acetic acid or propionic acid in hexane or CH_3OH/hexane consistently produced needles of composition **3**·8RCOOH (R = CH_3, CH_3CH_2) in high yield. Unfortunately, an X-ray crystallographic study of **3**·8CH_3CH_2COOH revealed that self-assembly of a diamondoid network had been thwarted by association of the sticky pyridone sites with propionic acid, producing adduct **6**.[11]



6 (R = CH_2CH_3)

In contrast, crystallization of tecton **3** from butyric acid/CH_3OH/hexane provided plates of approximate composition **3**·2$CH_3CH_2CH_2COOH$ in 88% yield. In this case, an X-ray crystallographic study has confirmed that the sticky pyridone sites interact in the expected way[12] to induce self-assembly of the remarkable diamondoid network shown in Figure 1a.[13] Since the tetrahedral centers of adjoining tectons are separated by 19–20 Å, the network defines enormous chambers and interconnecting windows. The chambers enclathrate only butyric acid, even though crystallization occurred in a mixed solvent. The interstitial guests are surprisingly well ordered and form two parallel columns in channels aligned with the *b* axis (Figure 1b). Since the columns are retained within a porous host framework by van der Waals forces alone, loss of butyric acid occurs when the crystals are placed under vacuum.

Crystallization of tecton **3** from valeric acid/CH_3OH/hexane provided plates of approximate composition **3**·1$CH_3CH_2CH_2CH_2COOH$ in 76% yield. Again, an X-ray crystallographic study has confirmed that self-assembly occurs to give a closely similar diamondoid network with cavities that enclathrate only valeric acid.[14] In addition, crystals of tecton **3** obtained from isobutyric acid and isovaleric acid proved to have similar compositions. This indicates that the self-assembly of a diamondoid network is a phenomenon of considerable generality, not merely a curiosity limited to the case of butyric acid. Further investigation will reveal what other interstitial guests can be accommodated and whether or not the ordered diamondoid framework remains intact when the guests are removed or exchanged. The stickiness of the sites that create the hydrogen-bonded network can easily be amplified by using pyridones connected in series,[1b] so we are optimistic that the framework can be further strengthened to resist forces favoring close packing.

Self-assembly of the diamondoid network **2** suggests that cleverly designed tectons can give chemists the elements of a powerful molecular-scale construction set. We believe that this strategy can be used to build predictably ordered materials with useful properties, including selective enclathration, microporosity, high ratios of strength to density, and catalytic activity. A principal advantage of this strategy is that complex structures with specific architectural or functional features are formed reversibly by spontaneous self-assembly, not by tedious bond-by-bond syntheses.

Acknowledgment. This work was financially supported by the Natural Sciences and Engineering Research Council of Canada and by the Ministère de l'Éducation du Québec.

Supplementary Material Available: Spectroscopic and analytical data for compounds **4**, **5**, **3**·8CH_3CH_2COOH, and **3**·2$CH_3CH_2CH_2COOH$ and tables of crystallographic data, descriptions of the structure determinations, and tables of atomic coordinates and isotropic thermal parameters, bond lengths and angles, anisotropic thermal parameters, and refined and calculated hydrogen atom coordinates for compounds **3**·8CH_3CH_2COOH and **3**·2$CH_3CH_2CH_2COOH$ (20 pages); observed and calculated structure factors for **3**·8CH_3CH_2COOH and **3**·2$CH_3CH_2CH_2COOH$ (31 pages). Ordering information is given on any current masthead page.

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(11) Crystals of **3**·8CH_3CH_2COOH belong to the tetragonal space group $P4_2/n$ with $a = b = 21.977$ (2) Å, $c = 7.7866$ (9) Å, $V = 3760.7$ (6) Å^3, $D_{calcd} = 1.220$ g cm^{-3}, and $Z = 2$. A full description of the structure is provided in the supplementary material.

(12) For references to crystallographic studies of other 2-pyridones, see: Gallant, M.; Phan Viet, M. T.; Wuest, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 721–723.

(13) Crystals of **3**·2$CH_3CH_2CH_2COOH$ belong to the monoclinic space group $C2/c$ with $a = 31.249$ (7) Å, $b = 7.350$ (4) Å, $c = 23.145$ (6) Å, $\beta = 104.69$ (2)°, $V = 5142$ (3) Å^3, $D_{calcd} = 1.247$ g cm^{-3}, and $Z = 4$. A full description of the structure is provided in the supplementary material.

(14) Crystals of **3**·1$CH_3CH_2CH_2CH_2COOH$ belong to the monoclinic space group $P2_1/n$ with $a = 31.137$ (8) Å, $b = 7.290$ (2) Å, $c = 23.006$ (5) Å, $V = 5064$ (2) Å^3, $D_{calcd} = 1.303$ g cm^{-3}, and $Z = 4$.

Enzyme-Catalyzed Synthesis of Sialyl Oligosaccharide with in Situ Regeneration of CMP-Sialic Acid[1]

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Sugar nucleotide dependent glycosyltransferases have great potential for the stereocontrolled synthesis of oligosaccharides.[2,3] All glycosyltransferases in mammalian systems utilize nucleoside diphosphate sugars as activated donors with the exception of sialyl transferase, which requires CMP-sialic acid (or CMP-*N*-acetylneuraminic acid, CMP-NeuAc). Although small-scale (milligrams) enzymatic synthesis of oligosaccharides based on the stoichiometric reaction of a sugar nucleotide and a mono- or oligosaccharide acceptor has been well documented,[3,4] the procedure usually requires a separate preparation of expensive sugar nucleotides and often suffers from product inhibition caused by the released nucleoside di- or monophosphates.[4] A practical solution to these problems is to utilize catalytic amounts of sugar nucleotides and nucleoside phosphates that are regenerated in situ in glycosyltransferase reactions. Regeneration of nucleoside diphosphate sugars (UDP-Glc and UDP-Gal) has been developed by Wong et al.[5] for a large-scale (35–70 mmol) synthesis of

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