Binding of Heptanedioic Acid to a Threefold Pyridine Arylamide Receptor. Enhancement of the Stability of Supramolecular Solution Structures by Multiple Binding Sites

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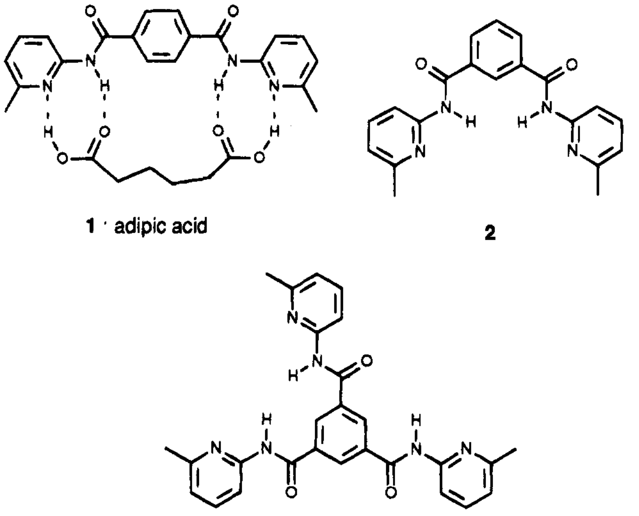
The formation of two hydrogen bonds between carboxylic acids and *N*-2′-(6′-methylpyridyl)arylamides in nonpolar organic solvents, such as chloroform, is well documented and has been used to design synthetic receptors for carboxylic acids.[1] Whereas the binding constants of monocarboxylic acids to a pyridylamide moiety are small (normally $\sim 2 \times 10^2$ L M^{-1}), dicarboxylic acids of appropriate lengths bind to ditopic receptors, forming, e.g., **1**, with association constants up to 10^5 L M^{-1}.[2] Hamilton has shown that, by increasing the length of the dicarboxylic acid beyond the optimum, the formation of ribbon,[3] or, as in the case of the related isophthalate receptor **2**, helical supramolecular structures[4] is observed (see Chart 1).

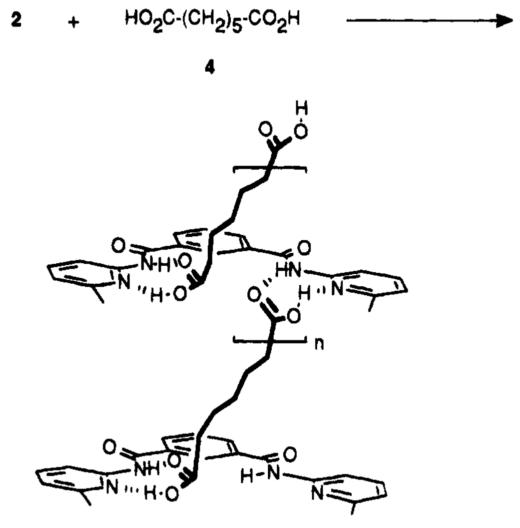
Chart 1



1 · adipic acid **2**

3

Scheme 1



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Self-assembled structures represent thermodynamic minima because they are formed by reversible association of a number of individual molecules. While the reaction entropy is usually of secondary importance in reactions that form a covalent bond irreversibly, the contribution of $T\Delta S$ from the loss of translational, rotational, and conformational freedom to the free energy (ΔG) is essential in all self-assembly processes.[5] The effect of unfavorable conformational constraints might be diminished by the symmetrical incorporation of an additional binding site into the receptor **2**. The dynamic supramolecular solution structure **6**, obtained from **3** and **4**, should therefore have a larger association constant than the analogous assembly,[4] **5**, if the same type of association occurs and only two binding sites of **3** are used.[6] The movement of an associated carboxyl group to the free pyridine−amide moiety will induce no change in the assembly.[7] In statistical thermodynamic terms the system is degenerate: there is more than one way to form the supramolecular structure from the components (see Schemes 1 and 2).

Compound **3** was synthesized from trimesic acid (benzene-1,3,5-tricarboxylic acid) and 2-amino-6-picoline *via* the acyl chloride in 54% yield.[8] The ^{1}H NMR spectra of 2×10^{-3} M CDCl$_3$ solutions of **3** and **4** show large

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(1) (a) Yang, J.; Fan, E; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 5314−5315 and references cited therein. For reviews of hydrogen bonding in molecular recognition, see: (b) Diederich, F. in *Cyclophanes*; Royal Society of Chemistry: Cambridge, England, 1991. (c) Hamilton, A. D. *Advances in Supramolecular Chemistry*; Gokel, G., Ed.; Jai Press: Greenwich, CT, 1990. (d) Rebek, J. *Acc. Chem. Res.* **1990**, *23*, 399−404. For a review on self-assembly see: (e) Lindsey, J. S. *New J. Chem.* **1991**, *15*, 153−180.

(2) (a) Garcia-Tellado, F.; Goswami, S; Chang, S.-K.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1990**, *112*, 7393−7394. (b) Self-assembled receptor for dicarboxylic acids: Goodman, M. S.; Weiss, J.; Hamilton, A. D. *Tetrahedron Lett.* **1994**, *35*, 8943−8946.

(3) Garcia-Tellado, F.; Geib, S. J.; Goswami, S; Hamilton, A. D. *J. Am. Chem. Soc.* **1991**, *113*, 9265−9269.

(4) Geib, S. J.; Vicent, C.; Fan, E.; Hamilton, A. D. *Angew. Chem.* **1993**, *105*, 83−85; *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 119−121.

(5) Whitesides, G. M.; Mathias, J. P.; Seto, C. T. *Science* **1990**, *254*, 1312−1319.

(6) The thermodynamic model assumes equal enthalpies from hydrogen-bonding interactions for each assembly, which is probably, but not necessarily, the case.

(7) If a helical structure similar to **6** exists in solution, the right-handed segment changes into a left-handed segment by this movement. Previously reported results indicate that the exchange between the enantiomeric helical forms of **5** is fast; see ref 4, reference 17 therein.

(8) For other amide derivatives of benzene-1,3,5-tricarboxylic acid see: (a) Curtius, T. *J. Prakt. Chem.* **1915**, *91*, 39−102. (b) Seha, Z.; Weis, C. D. *Helv. Chim. Acta.* **1980**, *63*, 413−419. (c) Seto, C. T.; Whitesides, G. M. *J. Am. Chem. Soc.* **1993**, *115*, 1330−1340. (d) Sieger, H.; Vögtle, F. *Liebigs Ann. Chem.* **1980**, 425−440. (e) Ried, W.; Königstein, F.-J. *Chem. Ber.* **1959**, *92*, 2532−2537. (f) Wang, W.; Lown, W. *J. Med. Chem.* **1992**, *35*, 2890−2897. (g) Yoon, S. S.; Still, W. C. *Tetrahedron Lett.* **1994**, *35*, 8557−8560.

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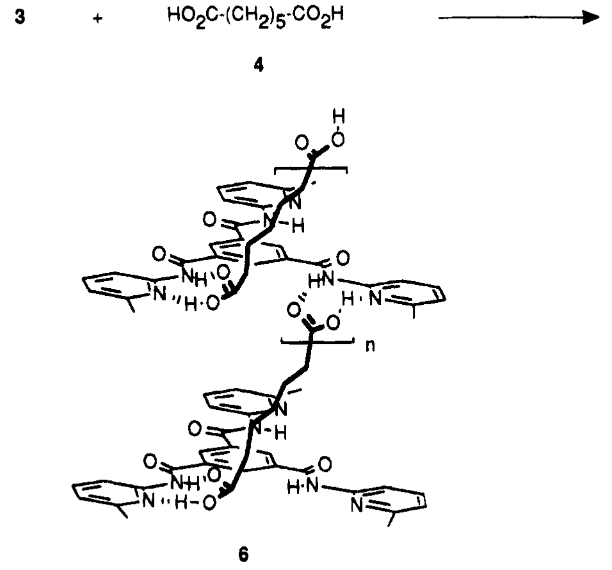
Scheme 2



downfield shifts for the pyridine N−H protons indicative of hydrogen-bond formation in solution.[9] Jobs plot analysis[10] of the δ_{N-H} shift with a sharp maximum at $X_3 = 0.5$ proved the formation of an assembly with a 1:1 stoichiometry (see Figure 1).

Figure 2 shows the change in chemical shift of the N−H protons for **2** and **3** when titrated with **4** in CDCl$_3$. The break in the curves as the C_{guest}/C_{host} of 1.0 is reached is again good evidence for 1:1 binding stoichiometry. The macroscopic association constants for both processes were derived by nonlinear fitting of the experimental data points to theory.[11] Whereas the binding constant of **2** and **4** was calculated to be 7×10^3 L M^{-1}, the value for **3** and **4** with K_a ~2.5×10^5 L M^{-1} is significantly larger.[12] Although not conclusive, the formation of similar solution structures for **2** and **3** with **4** seems likely.[13]

The thermodynamic parameters for both association processes were estimated from van't Hoff analysis[14] of K_a at different temperatures. Although the number of data points recorded does not allow the calculation of exact values for ΔH and ΔS, similar enthalpies of the order of $\Delta H = -55$ kJ M^{-1} K^{-1} and a significant difference in ΔS[15] are observed for the association of **2** or **3** with **4**. The larger association constant in the case of **3** can be attributed to a more favorable ΔS for this process.

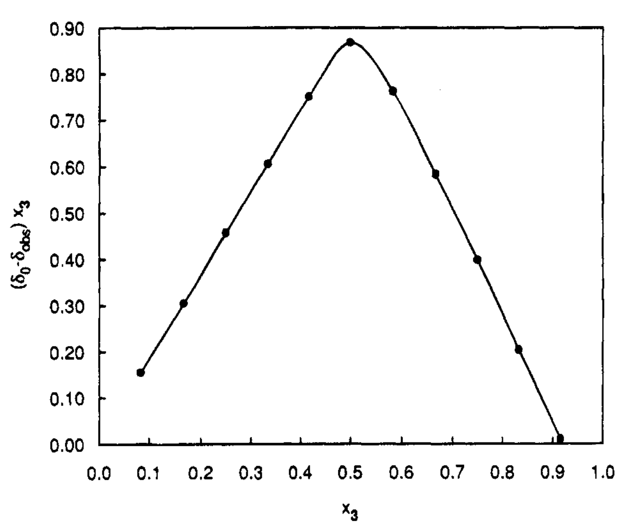


Figure 1. Jobs plot analysis of δ_{N-H} in different mixtures of **3** and **4**.

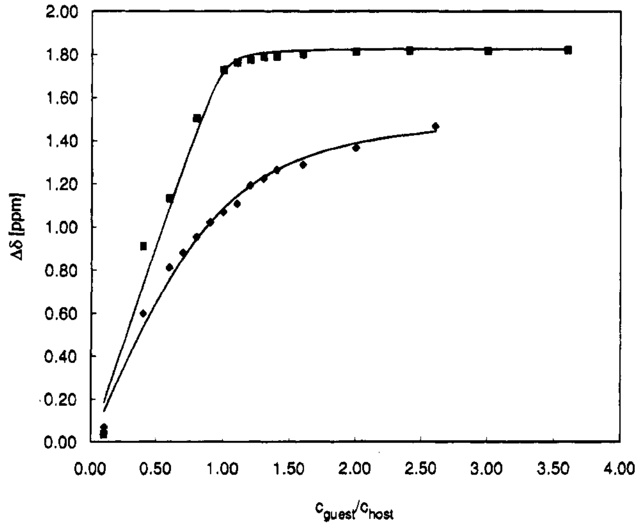


Figure 2. Plot of the observed (◆, ■) and calculated (—) upfield chemical shifts of the δ_{N-H} resonances of **2** and **3** as a function of added **4**.

We have shown that the stability of dynamic supramolecular structures can be enhanced by an entropic effect if additional binding sites are present in the host molecule. This effect might be useful in the design of components for the synthesis of extended molecular structures in solution by self-assembly.

X-ray Crystallographic Analysis.[16] A single crystal of **3** was obtained from ethyl acetate/petroleum ether solution. The X-ray crystal structure analysis shows a

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[9] A shift of the N−H resonance of less than 0.2 ppm was observed in the ^{1}H NMR spectra of solutions of **3** in a concentration range from 10^{-2} to 3×10^{-4} mol/L. The self-association of **3** in CDCl$_3$ can therefore be neglected compared to the association with **4** (shift of the N−H resonances in this process, approximately 1.7 ppm). The self-association constant of mono- and dicarboxylic acids in nonpolar organic solvents have been previously determined to be of the order of 0.01−5 L M^{-1}. The self-association of **4** is therefore a negligible process compared to the association with **3**. (a) Wolf, K. L.; Metzger, G. *Justus Liebigs Ann. Chem.* **1949**, *563*, 157−175. For the use of pimelic acid in noncovalent binding studies see: (b) Tanaka, Y.; Kato, Y.; Aoyama, Y. *J. Am. Chem. Soc.* **1990**, *112*, 2807−2808. (c) Rebek, J., Jr.; Nemeth, D; Ballester, P.; Lin, F.-T. *J. Am. Chem. Soc.* **1987**, *109*, 3474−3475. (d) Lehn, J.-M.; Meric, R.; Vigneron, J.-P.; Bkouche-Waksman, I.; Pascard, C. *J. Chem. Soc., Chem. Commun.* **1991**, 62−64. (e) Hosseini, M. W.; Lehn, J.-M. *J. Am. Chem. Soc.* **1982**, *104*, 3525−3527. (f) Breslow, R.; Rajagopalan, R.; Schwarz, J. *J. Am. Chem. Soc.* **1981**, *103*, 2905−2907. (g) Kimura, E.; Sakonaka, A.; Yatsunami, T.; Kodama, M. *J. Am. Chem. Soc.* **1981**, *103*, 3041−3045.

[10] For a recent example of Jobs plot analysis in noncovalent binding see: Blanda, M. T.; Horner, J. T.; Newcomb, M. *J. Org. Chem.* **1989**, *54*, 4626−4636.

[11] Analysis performed by nonlinear regression analysis using the HOSTEST5 program. Wilcox, C. S. In *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H. J., Dürr, H., Ed.; VCH: Weinheim, Germany, 1990, pp 123−143. We thank Prof. C. S. Wilcox, who provided us a copy of this program.

[12] The association constant is too high to be measured accurately by NMR methods.

[13] The stoichiometry and geometry of both dynamic supramolecular solution structures are definite, while the extension of the aggregates is variable.

[14] Horman, I.; Dreux, B. *Helv. Chim. Acta.* **1984**, *67*, 754 −764.

[15] The value of ΔS for the association of **3** and **4** was estimated from a ln K_a *vs* T^{-1} graph to be in the order of $\Delta S = -70$ J M^{-1} K^{-1} [±30 J M^{-1} K^{-1}], while ΔS for the association of **2** with **4** is in the order of 150 J M^{-1} K^{-1} [±30 J M^{-1} K^{-1}].

[16] The authors have deposited atomic coordinates for **3** 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, U.K.

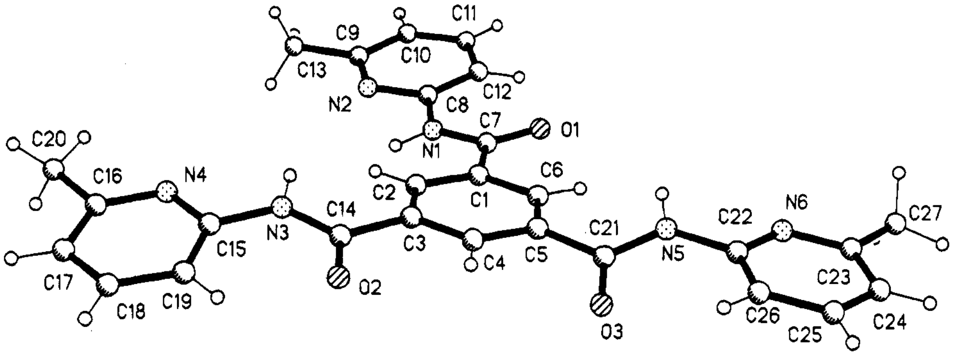

Figure 3. Structure of **3** in the crystal (water molecules omitted).

conformation of **3** in which pairs of phenyl−CO bonds can be described as *syn,syn*, *syn,anti*, and *anti,anti*.[17] Two molecules of water cocrystallize with **3** and form hydrogen bonds between the molecules. The structure shows that two pyridylamide binding sites can be occupied simultaneously without distortion of the amide geometry (see Figure 3).

Crystal Data for 3·H$_2$O. $C_{27}H_{28}N_6O_5$, $M = 516.56$, triclinic, space group $P\bar{1}$, $a = 806.2(3)$ pm, $b = 1221.6(4)$ pm, $c = 1394.6(5)$ pm, $\alpha = 111.54(2)°$, $\beta = 96.40(2)°$, $\gamma = 98.33(2)°$, $V = 1.2436(8)$ nm^3, $Z = 2$, λ(Mo $K\alpha$) = 0.710 73 Å, $\mu = 0.1$ mm^{-1}, $D_x = 1.379$ Mg m^{-3}, $F(000) = 544$, $T = 143$ K. A total of 8742 intensities (4392 unique, $R_{int} = 0.0796$) were measured to $2\theta = 50°$ on a Stoe STADI-4 diffractometer. The structure was solved by direct methods and refined anisotropically on F^2 (program SHELXL-93, G. M. Sheldrick, University of Göttingen). Hydrogen atoms were included with a riding model. The final wR(F^2) for all reflections was 0.110, with a conventional R(F) of 0.052, for 358 parameters.

Experimental Section

NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C) in CDCl$_3$ solutions.

Benzene-1,3,5-tricarboxylic Acid Tris-2′-(6′-methylpyridyl)amide (3). A 1 g (4.8 mmol) amount of benzene-1,3,5-tricarboxylic acid was refluxed in 20 mL of SOCl$_2$ with a catalytic amount of pyridine. Excess SOCl$_2$ was removed *in vacuo*, 100 mL of chloroform, 5 mL of NEt$_3$ and 3.1 g (29 mmol) of **2** were added, and the mixture was stirred for 12 h at room temperature. The reaction mixture was hydrolyzed with ice, and the organic phase was washed with aqueous NH$_4$Cl (2 × 50 mL) and brine (1 × 50 mL), dried over MgSO$_4$, and evaporated *in vacuo*. The crude product was chromatographed on silica gel (petroleum ether/ethyl acetate 1:1) to yield 1.2 g (54%) of **3** (R_f = 0.45) as a white solid, mp 236 °C; ^{1}H NMR δ 2.50 (s, 9 H), 6.90 (d, $^3J = 8.0$ Hz, 3 H), 7.70 (m, 3 H), 8.15 (d, $^3J = 8.1$ Hz, 3 H), 8.70 (s, 3 H), 8.90 (bs, 3 H); ^{13}C NMR δ 23.95 (+), 111.03 (+), 119.87 (+), 129.15 (+), 135.73 (C$_{quart}$), 138.87 (+) 150.29 (C$_{quart}$), 157.08 (C$_{quart}$), 163.27 (C$_{quart}$); IR (KBr) ν = 3399, 1684, 1629, 1454 cm^{-1}; MS (70 eV), m/z (%) 480 (M$^+$, 100). Anal. Calcd. for $C_{27}H_{28}N_6O_5$: C, 62.78, H, 5.46, N, 16.27. Found: C, 62.51, H, 5.49, N, 16.28.

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Supplementary Material Available: ^{1}H NMR spectra of **3** at different concentrations and mixtures of **3** and **4**, ln K_a vs T^{-1} graph for **2**−**4** and **3**−**4**, δ_{N-H} vs concentration graph for **3**, and experimental details of Jobs plot analysis and NMR titration (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[17] An analogous description of the primary conformations of **2** has been used by Hamilton, see ref 4.