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HYDROGEN BONDING CONTROL OF SELF-ASSEMBLY: SIMPLE ISOPHTHALIC ACID DERIVATIVES FORM CYCLIC HEXAMERIC AGGREGATES

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Abstract: In this paper we demonstrate that six molecules of a functionalized isophthalic acid derivative form a cyclic aggregate stabilized by a network of 12 hydrogen bonds. The structure and stability of the aggregate were studied by X-ray crystallography, vapor phase osmometry and ^{1}H NMR.

The design of small molecular components that form well-defined and stable aggregates in solution is an area of intense current interest.[1,2] Some insight into how this might be achieved can come from consideration of the crystal structure packing patterns of hydrogen bonding molecules.[3,4] For example, the X-ray structure of trimesic acid shows an infinite sheet arrangement in which each molecule forms six hydrogen bonds to three neighboring residues (Figure 1).[5] The resulting hexagonal-lattice structure leads to large cavities each bounded by six trimesic acid molecules.

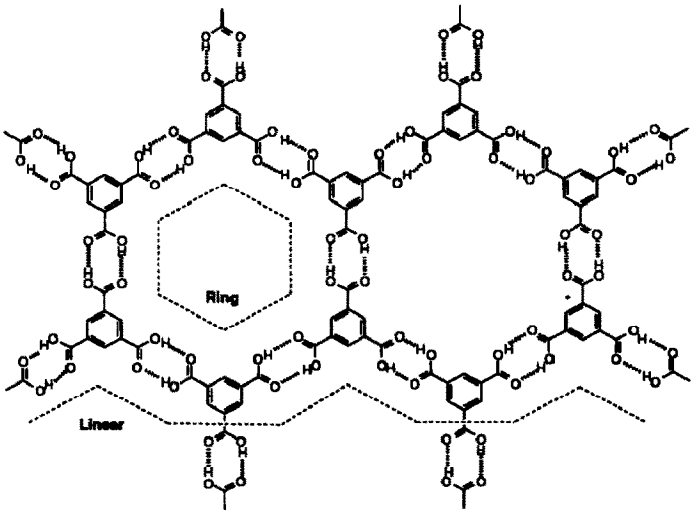
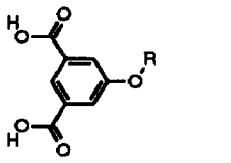


Figure 1. Extended sheet in X-ray structure of trimesic acid.

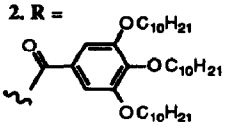
Simple isophthalic acid derivatives can form only partial elements of the sheet structure, such as the linear or ring motifs indicated in Figure 1.[6] The ring structure is particularly interesting as a basis for the design of novel aggregates in solution and our goal was to determine how substitution on the isophthalic acid might direct its

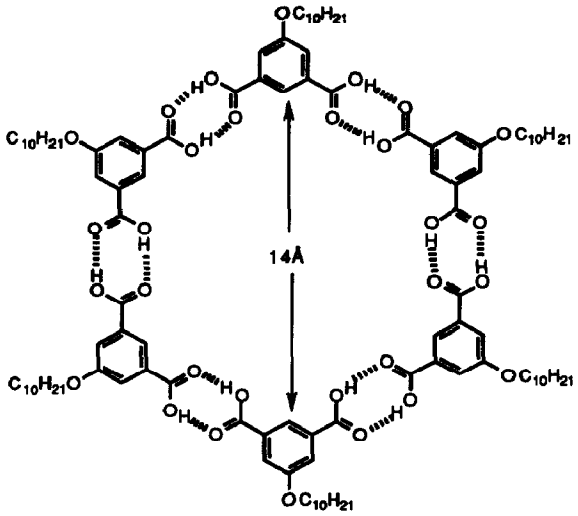
formation over the linear form. The parent, isophthalic acid, is known[7] to form the ribbon motif with a planar arrangement of phenyl and carboxylic acid groups. This preference for formation of hydrogen bonded ribbon or



1. R = $C_{10}H_{21}$

2. R =





sheet structures is well precedented in the solid state literature.[8] In the case of isophthalic acid, the ribbon motif allows both optimal formation of the bidentate hydrogen bonds and efficient packing interactions between the ribbons in vertical and horizontal directions. In order to direct formation of the cyclic motif in the solid state it is necessary to disrupt the linear packing arrangement. We reasoned that this might be achieved by placing a bulky substituent in the 5-position of isophthalic acid, thus preventing easy alignment of the hydrogen bonded ribbons.[9] The X-ray structure of 5-decyloxyisophthalic acid **1** (crystallized from THF/hexane; Figure 2) shows the formation of a cyclic hexameric aggregate corresponding to the ring motif in Figure 1.[10] The six isophthalic acid molecules define a macrocyclic cavity that is 14 Å in diameter (from opposite isophthaloyl-2H sites) and is stabilized by 12 hydrogen bonds (O-O distance, 2.65 Å). The isophthalate core of the structure is planar with only a 4° angle between phenyl and carboxylate planes, while the decyloxy chains maintain an alternating up-down arrangement.

A critical question is whether these cyclic aggregates form in solution and what would be the relative stability of the linear vs. cyclic motifs. Despite the absence of crystal packing effects, the cyclic aggregate should still be favored entropically in solution since it allows the formation of 12 hydrogen bonds by six particles rather than the seven that would be necessary in a linear aggregate. In initial experiments we have investigated the solution aggregation properties of a more soluble 5-substituted isophthalic acid derivative **2** using vapor phase osmometry, and ^{1}H NMR. VPO measurements were carried in toluene at 40°C and gave molecular weights for the aggregate of 4600 (against a benzil standard) and 4900 (against a polystyrene standard) over a concentration range of 12-35 mM. The calculated MW for hexameric **2** is 4531. These results are consistent with the preferential formation of a hexameric aggregate in toluene at concentrations above 10 mM. Below these concentrations there appears to be significant dissociation resulting in non-linear VPO plots.

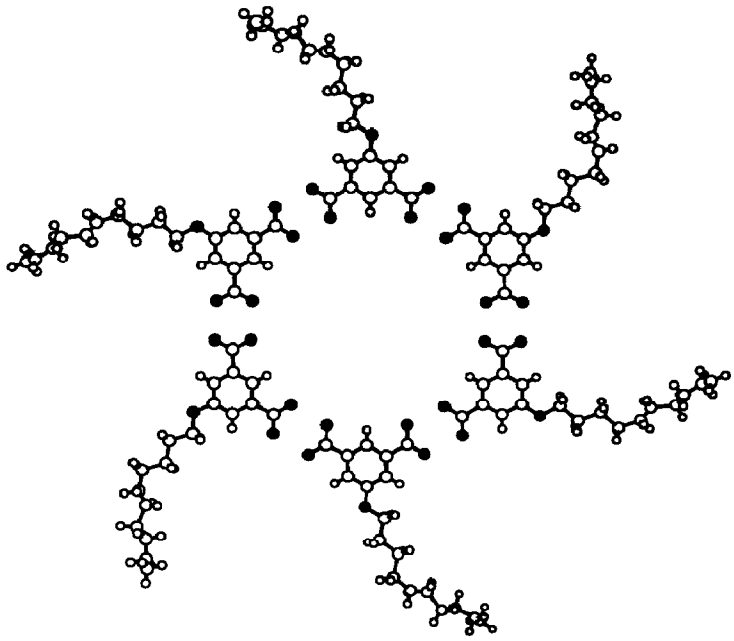


Figure 2. X-ray structure of 5-decyloxyisophthalic acid showing cyclic motif.

Diacid **2** is very soluble in benzene and toluene (up to 100 mM). The ^{1}H NMR spectrum of **2** in C_6D_6 (25 mM) at 55°C shows three sharp resonances at 8.89, 8.21 and 7.51 ppm from the isophthaloyl-2H and -4/6H and benzoyl-H, respectively. The position of the isophthaloyl-2H resonance is strongly dependent on concentration, shifting upfield by 0.26 ppm over a 15-0.1 mM range. Above 15 mM, however, there is little change, reflecting the formation of a discrete and stable aggregate at higher concentrations. At 25°C a 25 mM solution of **2** in C_6D_6 gives a more complex ^{1}H NMR spectrum with several peaks in the aromatic region (7.3-8.9 ppm), suggesting some higher order aggregation possibly involving π-stacked hexamer structures.[11,12]

In summary, we have shown that simple 5-substituted isophthalic acid derivatives can form well defined cyclic hexameric aggregates in solution and in the solid state, stabilized by 12 hydrogen bonds. We anticipate that appropriate substitution of the interior or exterior of the isophthalic acid monomer will lead to larger aggregates with cavities capable of including small organic and inorganic substrates.

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9. The strategy of controlling aggregate structure by steric crowding of the subunits has been elegantly demonstrated by Whitesides with his melamine-barbiturate systems.[4]
10. Crystal Data for $C_{18}H_{24}O_5$: rhombohedral, *R* $\bar{3}$; a = 30.559(4) , c = 10.251(2) Å, V = 8289(6) Å^3 , Z =18, D_c = 1.166 g cm^{-3} , 296K. A Rigaku AFC5R diffractometer was used to collect 2403 data points of which 1244 data with ($F > 4.0\sigma(F)$) were used in the solution and refinement. X-ray data were corrected for absorbtion (λ(CuKα) =1.54178 Å). Structure was solved by direct methods which located all non-hydrogen atoms. Hydrogen atom positions were calculated (d(C-H) = 0.96 Å). Structure refined to R_F = 9.26% and R_{WF} = 10.97%; *GOF* = 2.22, highest final difference peak, 0.71 e/Å^3.
11. A covalent hexa(phenylacetylene) macrocycle, analogous in shape to hexameric **2**, has been shown to aggregate in $CDCl_3$ via π-π stacking interactions; Zhang, J.; Moore, J. S. *J. Am. Chem. Soc.* **1992**, *114*, 9701.
12. At lower concentrations of **2** or higher temperatures the aromatic region of the NMR spectrum simplifies to three singlets.

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