Self-Assembly of 1,3,5-Benzenetricarboxylic (Trimesic) Acid and Its Analogues

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Abstract: A crystalline inclusion complex between 1,3,5-benzenetricarboxylic acid (trimesic acid, **1**) and pyrene was grown from diethyl ether/ethanol and its structure was determined by X-ray analysis. Trialkyltrimesic acids **4b–4e** were synthesized in seven steps from 1,3,5-trichlorobenzene (**5**). Trimethyltrimesic acid (**4a**) was synthesized in four steps from mesitylene. All five substituted trimesic acids were crystallized to determine their potential as clathrate hosts and to compare their solid-state structures with the parent trimesic acid. The X-ray structures of **4a–4d** were resolved and are reported. A covalent analogue of a trimesic acid dimer (**13**) was synthesized in seven steps from 2-butylisophthalic acid and its solid-state structure determined.

Introduction

Considerable effort over the last several decades has been devoted to the understanding of relationships between molecular structure and crystal structure, such as crystal engineering.[1–6] Despite many successful attempts towards crystal engineering, it remains difficult at best to predict how a particular molecule will pack in the solid-state. For this reason a significant portion of research on crystal engineering has concentrated on the design of hydrogen-bonded or coordination networks.[7–10] This type of supramolecular synthesis relies primarily on the directional and often predictive nature of these intermolecular cohesive (sticky) interactions to control short- and long-range packing. Of particular relevance to the work described here are the efforts to create new clathrates or nanoporous solids,[7–11] in which the target network is porous, contrary to Kitaigorodski's principle of close crystal packing.[12] In this regard the 1,3,5-benzenetricarboxylic (trimesic) acid system is particularly illustrative.

The crystal structure of the α-polymorph of trimesic acid was reported by Duchamp and Marsh in 1969.[13] It contains the infinite chicken-wire motif of Figure 1. The approximately

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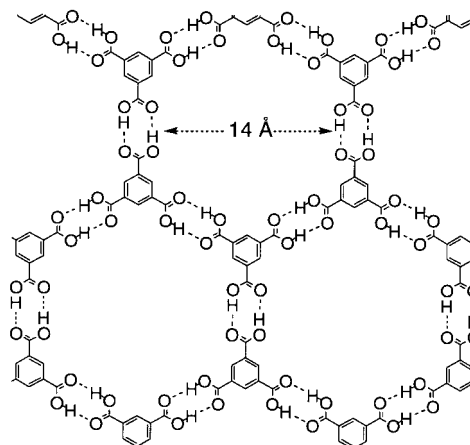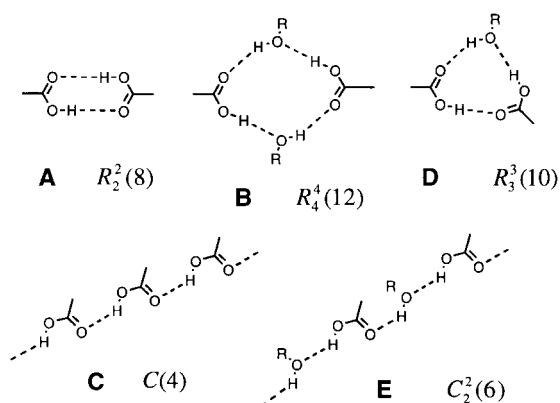WWW: http://ludwig.scs.uiuc.edu

Figure 1. Extensively hydrogen-bonded chicken-wire network formed by $R_2^2(8)$ dimerization of carboxylic acid groups in trimesic acid (TMA). Concatenation of independent networks leads to extensive interpenetration which fills the holes.

14 Å diameter holes in this structure present an obvious obstacle to close packing. Nonetheless, each carboxylic acid group forms a centrosymmetric carboxylic acid dimer (graph set $R_2^2(8)$[4] Scheme 1, **A**). The packing density problem is solved by triple concatenation of each hole, which leads to infinite interpenetration of independent networks. Interpenetration of networks is a common way for open networks to increase packing density and prevent clathrate formation.[14]

In 1987, after a 17 year effort, Herbstein et al. reported[15] the first noncatenated trimesic acid structures, again contain-

Scheme 1. Different graph sets for carboxylic acids.

ing carboxylic acid dimers of the $R_2^2(8)$ graph set.[4] These structures featured stacked chicken-wire networks—either two, three, or five layers in the stacking-axis period—and channels containing disordered alkane guests. Herbstein's investigations revealed numerous structures of trimesic acid and its inclusion complexes, some of which contain non-$R_2^2(8)$ dimers.[15] Because the 14 Å channel in trimesic acid is significantly larger than that found in other, more commonly formed channel clathrates, one might speculate that this greater porosity increases the likelihood that alternative structures will form.

In a recent communication we described[16a] three strategies to generate clathrates from trimesic acid and its analogues: a) crystallization of trimesic acid and organic guests, by direct analogy to Herbstein's work,[15] b) synthesis and crystallization of substituted analogues of trimesic acid, and c) replacement of a putative carboxylic acid dimer with a covalent linkage of similar geometry. Herein we present a full account of these efforts and describe the synthesis and solid-state structures of three new trialkyltrimesic acids. What is remarkable in the new results is the lack of any pattern in the structures of the trialkyltrimesic acids, as a result of a striking variation in the carboxylic acid packing motifs. The findings bear directly on the reliability of the $R_2^2(8)$ carboxylic acid dimer under the condition of programmed voids.

Results and Discussion

Expanded carboxylic acid dimers—a trimesic acid pyrene structure: In an effort to obtain stacked chicken-wire networks of trimesic acid with ordered guests in the channels, the steric fit of various aromatic compounds was examined by Corey-Pauling-Koltun (CPK) models. Nonvolatile aromatic compounds were chosen because of their rigidity and tendency to stack into columns in the solid-state. Although coronene showed a nearly perfect steric match with the 14 Å channel diameter when tilted along the channel axis, it was poorly soluble in solvents useful for crystallizing trimesic acid. Of the several smaller aromatic systems examined, only pyrene readily formed a cocrystal with trimesic acid.

The crystal was grown by slow evaporation of solution of the compound in diethyl ether. Unexpectedly, the X-ray analysis revealed the incorporation of molecules of ethanol,

suggesting that the diethyl ether was contaminated with a small amount of ethanol, a fact subsequently confirmed by NMR analysis. The stoichiometry of the crystal is $(\mathbf{1})_2 \cdot$ pyrene $\cdot (EtOH)_2$, with eight such units in a large monoclinic unit cell (ca. $28 \times 17 \times 15$ Å). Although the structure (Figure 2) contains stacks of noninterpenetrated hydrogen-bonded networks that superficially resemble the chicken-wire network of Figure 1, closer examination reveals few of the desired crystal packing features. Most significantly, the pyrene molecules are not stacked into channels, rather they alternate in stacks with trimesic acid molecules (Figure 2B).
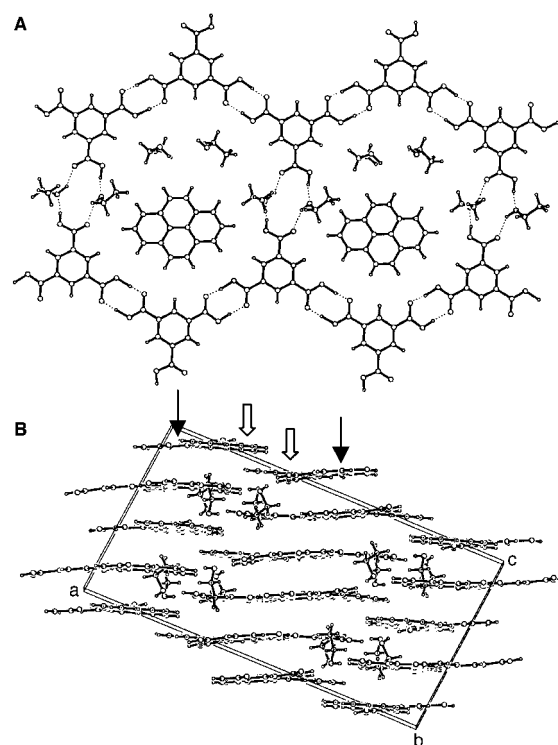

Figure 2. A) Structure of pyrene $\cdot$ **1** inclusion complex viewed down c axis showing one layer: two carboxylic acid groups on each TMA are linked by $R_2^2(8)$ dimers forming ribbons, which form sheets by inclusion of ethanol molecules in expanded carboxylic acid dimers, with the $R_4^4(12)$ graph set. B) Side view of stacking of layers shown in A: block arrows indicate two pyrene molecules and standard arrows show two TMA molecules.

The hydrogen-bonding networks comprise $R_2^2(8)$ carboxylic acid dimers and what we have termed expanded carboxylic acid dimers, [16a] which have the $R_4^4(12)$ graph set[4] (Scheme 1, **B**). The $R_2^2(8)$ dimers formed by two acid groups of each trimesic acid molecule produce an infinite zigzag ribbon along the b axis (Figure 2A), a motif similar to that found in the structure of isophthalic acid.[17] The third carboxylic acid groups link the ribbons together through 12-membered hydrogen-bonded rings that contain two ethanol molecules. The resulting expanded holes are large enough to contain a pyrene molecule and the ethyl groups of two ethanol molecules from an adjacent layer.
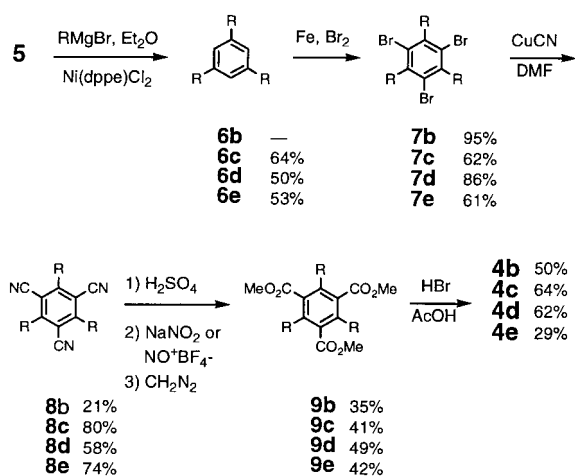
Trialkyltrimesic acids

General considerations: The second approach to break the interpenetration found in the trimesic acid lattice follows

Ermer's pioneering work on adamantane-1,3,5,7-tetracarboxylic acid (**2**).[14a, 18] As with trimesic acid, $R_2^2(8)$ carboxylic acid pairing of the four acid groups in **2** leads to a highly porous lattice. However, the tetrahedral arrangement of the acid groups in **2** means that the resulting hydrogen-bonded network will have a diamondoid architecture. Ermer showed that **2** does indeed crystallize with the formation of $R_2^2(8)$ carboxylic acid dimers.[14a] The porous diamondoid network is fivefold interpenetrated with a measured density $(1.365 \, \text{g cm}^{-1})$ in the range commonly found for close-packed structures. By substituting two of the methylene groups in **2** (see **3**), the degree of interpenetration was reduced to twofold with concomitant formation of inclusion complexes.[18]

A maximum of three sites are available for substitution in trimesic acid. Because their high symmetry suggested an easier synthesis, trialkyltrimesic acids were chosen as targets. Most appealing was the opportunity to vary the length of the alkyl substituents, and thus adjust the diameter of the holes in the putative chicken-wire network. It was anticipated that by studying a series of closely related molecules, a relationship between molecular structure and crystal structure might become apparent. Moreover, the durability of the chicken-wire network and the durability and reliability of the $R_2^2(8)$ carboxylic acid dimer as a cohesive unit for crystal engineering would be more rigorously tested.

1

2 : X = H,H
3 : X = CH₂

4a : R = CH₃
4b : R = C₂H₅
4c : R = C₃H₇
4d : R = C₄H₉
4e : R = C₅H₁₁
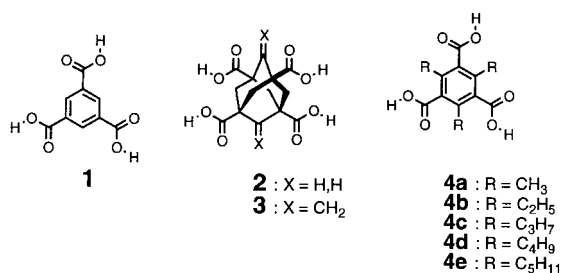
Synthesis: The synthesis of the desired trialkyltrimesic acids is outlined in Schemes 2 and 3. The synthesis of **4b–e** started with 1,3,5-trichlorobenzene (**5**) which reacted with the


	6b	—		7b	95%
	6c	64%		7c	62%
	6d	50%		7d	86%
	6e	53%		7e	61%

8b	21%	9b	35%
8c	80%	9c	41%
8d	58%	9d	49%
8e	74%	9e	42%

	4b	50%
	4c	64%
	4d	62%
	4e	29%

a = Me, **b** = Et, **c** = Pr, **d** = Bu, **e** = Pen

Scheme 2. Synthesis of building blocks **4b–e**.

corresponding alkylmagnesium bromide in diethyl ether under Kumada coupling conditions.[19] The resulting symmetrical trialkylbenzenes **6b–e** were exhaustively brominated in neat bromine in the presence of iron filings.[20] Cyanation of the tribromides **7b–e** with an excess of cuprous cyanide in *N,N*-dimethylformamide (DMF) or *N*-methylpyrrolidone afforded pure trinitriles **8b–e** in moderate yields.[21]

Hydrolysis of the very hindered nitriles in **8b–e** proved difficult, but could be achieved with a one-pot, two-step procedure wherein the trinitriles were first converted to the corresponding triamides with 80% *w/w* sulfuric acid at about 150–160 °C. Although the triamides can be isolated and characterized, they were treated directly with sodium nitrite in the same pot to afford the crude acids.[22] Hydrolysis of the less soluble **8e** gave higher yields in a mixture of sulfuric and methanesulfonic acids with the addition of nitrosyl tetrafluoroborate. The acids were purified as the trimethyl esters **9 b–e**, which were prepared by treating the crude acids with an ethereal solution of diazomethane and isolated by chromatography. Treatment of **9b–e** with hydrobromic acid in acetic acid converted the esters back to the target acids **4b–e** in pure form.

Trimethyltrimesic acid (**4a**) could not be prepared by the route outlined in Scheme 2, because the cyanation of 1,3,5-tribromo-2,4,6-trimethylbenzene proceeded in very poor yield under typical conditions for cyanation in DMF. An alternative route to **4a** is outlined in Scheme 3. Mesitylene
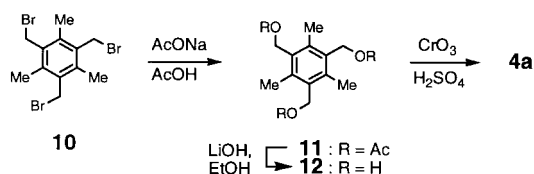
Scheme 3. Synthesis of compound **4a**.

was tribromomethylated to afford **10** in good yield.[23] Acetolysis of **10** was achieved with a mixture of acetic acid and sodium acetate, and the resulting triacetate **11** was hydrolyzed to triol **12** in 92% yield. Jones oxidation of **12** afforded trimesic acid **4a** in 46% yield. All compounds in the alternative route outlined in Scheme 3 could be conveniently purified by recrystallization.

X-ray analysis (see Table 1): Examination of CPK models suggested that the butyl or pentyl groups in **4d** and **4e**, if extended, would largely fill the 14 Å holes in the trimesic acid chicken-wire motif, although a hole as large as 2 Å might be formed in **4d**. Thus, in contrast to **4a–4c**, these compounds have the potential to fill their own voids. Although small crystals of tripentyltrimesic acid **4e** grown from acetonitrile afforded some usable diffraction data, the poor quality of the data and apparent large unit cell prevented its detailed structural refinement.

An X-ray quality crystal of tributyltrimesic acid **4d** was grown from aqueous ethanol and its structure was solved (Figure 3). As a result of the 2,4,6-trisubstitution, the carboxylic acids in **4d** are markedly twisted out of the plane of the

benzene ring with the mean deviation from perpendicularity of about 20°. Despite their very hindered environment, each carboxylic acid groups in **4d** forms an $R_2^2(8)$ dimer, which leads to the sheet-like chicken-wire motif of Figure 1 (Figure 3A). A normal from the hydrogen-bonded sheets forms an angle of about 43° with the *a* axis and the layer separations alternate between about 4 Å and about 5 Å. This latter feature, and the fact that alternating layers are offset, can be explained by partial penetration of pairs of layers (vide infra).
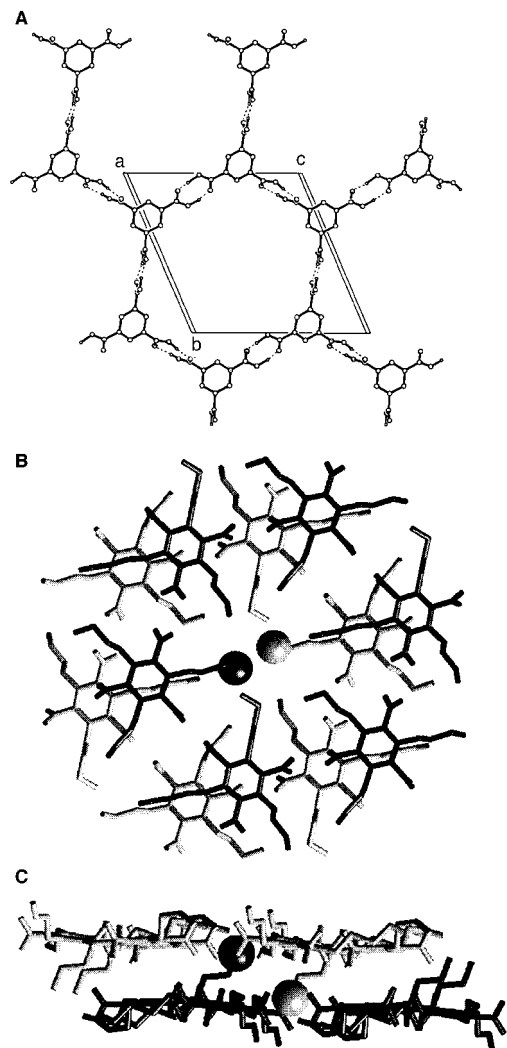

Figure 3. A) Single layer showing chicken-wire network in **4d** viewed as down *a* axis, with butyl groups removed for clarity. B), C) Side and top views of layer stacking in **4d** showing two butyl methyl groups (balls) filling holes in adjacent layers left by butyl groups.

Four methyl and adjacent methylene groups of the six butyl groups attached to the two crystallographically independent acid molecules in the asymmetric unit cell are disordered and found in a *gauche* conformation. The two ordered butyl groups are entirely in an *anti* conformation (Figure 3B). The butyl groups within a layer do not entirely fill the holes within that layer. Instead, the methyl groups of the ordered butyl chains from adjacent, closely spaced layers fill each other's holes (Figure 3B, C). This partial penetration explains both the offset arrangement of adjacent layers and the alternating

interlayer separation. Although these subtle aspects were not anticipated, the resulting network and the gross structure was the desired one and represents the first noninterpenetrated, self-filled trimesic acid chicken-wire structure.

Tripropyltrimesic acid **4c** formed X-ray quality crystals by slow evaporation of solutions of the compound in both acetone and aqueous ethanol. The corresponding X-ray structure of crystals from both samples gave identical diffraction patterns as illustrated in Figure 4. The carboxylic acid groups in **4c** are rotated even further from the plane of the benzene ring than those in **4d**. Each acid group is 3° or less from perpendicularity, yet two acid groups from each molecule form standard dimers. These contacts produce an infinite ribbon similar to that found in isophthalic acid and the
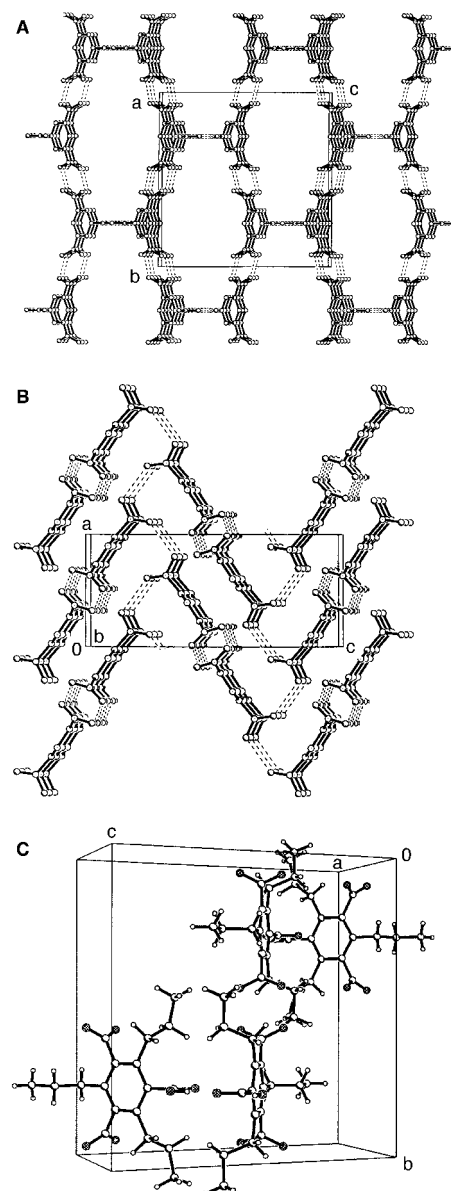

Figure 4. Three views of packing of **4c**, with propyl groups removed for clarity in A and B. A) View of the hydrogen-bonded, zigzag ribbons [$R_2^2(8)$ graph set] of **4c** running along *b* axis with catemer motif [$C(4)$ graph set] linking the ribbons along *a*. B) View emphasizing catemer hydrogen bonding. C) View of unit cell of **4c** showing packing arrangement of propyl groups.

trimesic acid inclusion complex described above. Here the structure diverges rather dramatically from that of **4d**, as a result of the third carboxylic acid groups forming hydrogen-bonded chains (**D** in Scheme 1, $C(4)$ graph set) rather than the $R_2^2(8)$ dimers that would give the chicken-wire motif (Figures 1 and 3). This hydrogen-bonding motif, known as the catemer, was described as rare in an extensive survey of carboxylic acid packing motifs published by Leiserowitz in 1976.[24] More recently, Etter and Frankenbach noted that sterically encumbered 2,6-disubstituted benzoic acids have a tendency to form this type of carboxylic acid dimer.[25] Whereas the $R_2^2(8)$ pairing of the third carboxylic acid groups without interpenetration would produce a porous structure, the $C(4)$ motif allows close packing, and linear hydrogen bonds between all carboxylic acid groups.

Triethyltrimesic acid (**4b**) was crystallized by slow evaporation of an aqueous methanol solution to give a monohydrate. Its structure, which bears little resemblance to either that of **4c** or **4d**, can be described as stacked corrugated sheets (Figure 5B). Along the b axis, polar and apolar regions are observed, resulting from segregation of the apolar alkylaromatic and polar carboxylic acid functionalities (Figure 5A).[26] Not surprisingly, the water molecule is found in
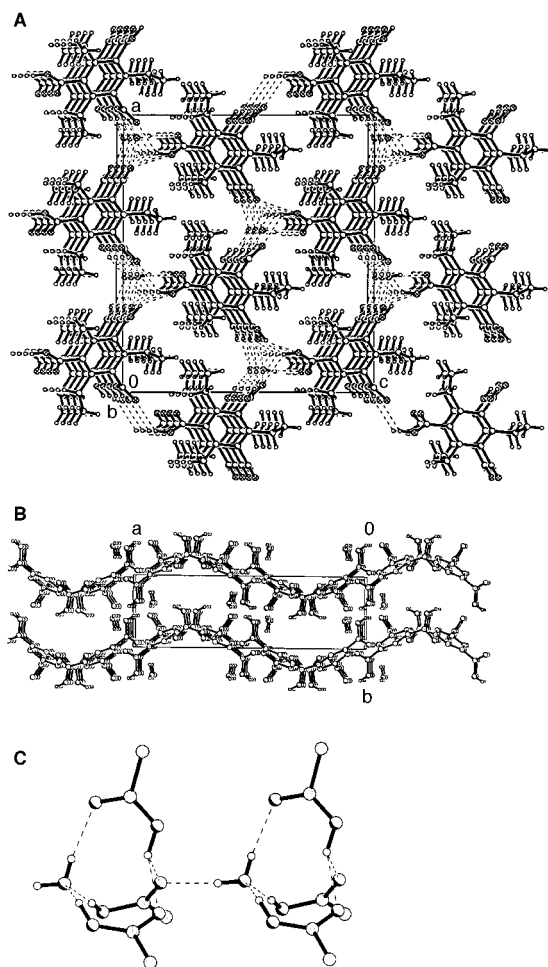
the polar region, and contributes to a hydrogen-bonded column that runs along the b axis. The hydrogen-bonding features a monoexpanded $R_2^2(8)$ carboxylic acid dimer ($R_3^3(10)$ graph set,[4] **B** in Scheme 1) and an expanded catemer ($C_2^2(6)$ graph set,[4] **E** in Scheme 1). No $R_2^2(8)$ carboxylic acid dimers are present. The water molecule is tetrahedrally coordinated and contributes both hydroxy groups and both lone pairs to hydrogen bonds (Figure 5C). Hydrate formation in the solid-state was previously studied by Desiraju; he concluded that "their proportion ..increases.. with an increase in the number of hydrogen-bond acceptor groups with respect to the donor groups".[27] In this particular crystal structure the water molecule uses its full hydrogen-bonding potential, and serves to tie the converging carboxylic acid groups together in polar columns that extend through the crystal.

A single crystal of trimethyltrimesic acid **4a** was grown from aqueous ethanol. Its X-ray analysis revealed a structure without significant voids or cavities (Figure 6). As in the case of **4b**, it forms corrugated sheets that pack one atop the other

Figure 5. Views of packing of **4b** showing A) segregation of polar and apolar functionalities as viewed along b axis, B) stacking of corrugated sheets along b axis, and C) hydrogen-bonded column containing water molecules which runs along b axis
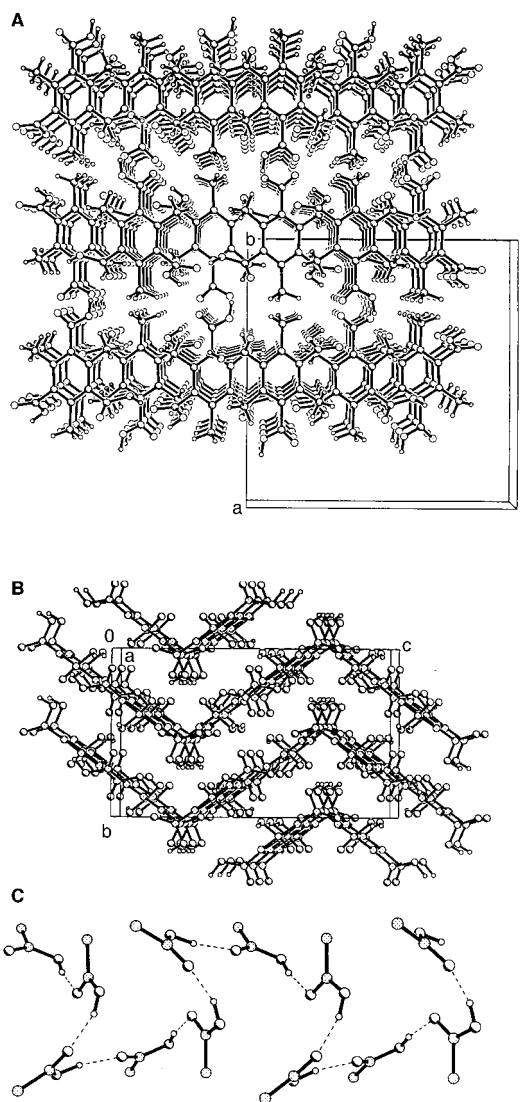

Figure 6. Views of packing of **4a** showing A) segregation of polar and apolar functionalities as viewed along b axis, B) stacking of corrugated sheets along b axis, and C) hydrogen-bonded chain [$C(4)$ graph set] which runs along b axis.

(Figure 6B) and is distinguished by the fact that no $R_2^2(8)$ carboxylic acid dimers are present. Instead, it forms what can best be described as a looping catemer of carboxylic acid groups (graph set $C(4)$,[4] Figure 6C). All the hydrogen-bonding contacts are strong and the H$\cdots$O distances are about 1.7 and 2.0 Å. $\pi-\pi$ interactions do not seem to contribute to the stabilization of the packing arrangements in **4a**, **4b**, or **4c**, perhaps because the aromatic rings are too hindered by the alkyl groups to stack.

Replacement of a putative carboxylic acid dimer with an acetylene linker: In the structure of **4c** and the pyrene $\times$ **1** inclusion complex, two of the three carboxylic acids form $R_2^2(8)$ dimers resulting in the formation of zigzag ribbons (vide supra). The third carboxylic acid group engages in non-$R_2^2(8)$ hydrogen-bonding motifs (Figure 7) that thwarted efforts to engineer the chicken-wire motif of Figure 1. This observation suggested the replacement of this putative third carboxylic acid dimer by a covalent linkage with linear geometry (Figure 7). Thus, tetraacid **13** was chosen as the target.
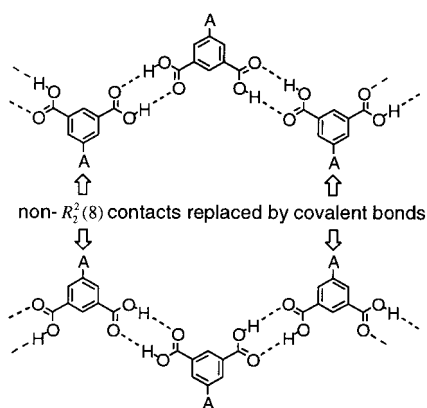
Figure 7. Schematic representation of packing seen in pyrene $\cdot$ **1** inclusion complex and **4c**, and covalent linkage between third acid groups.

The synthesis of **13** started from the known 2-butylisophthalic acid (**14**)[28] which was brominated in nitric acid to afford **15** in 80 % yield (Scheme 4). The acid groups in **15** were protected as *tert*-butyl esters by reaction of the corresponding acid chloride **15a** with lithium *tert*-butoxide, giving **16** in 71 % yield for two steps. The aryl bromide was coupled to 2-methyl-3-butyn-2-ol to afford **17** in 69 % yield, which was subsequently deprotected to **18** with base. Palladium-mediated coupling of **18** and bromide **16** followed by deprotection afforded the target tetraacid **13**. Modest yields of the coupling product were obtained, partly due to the extensive chromatography needed to remove a small amount of the **18** dimer (diyne from oxidative coupling) with an almost identical R_f value.

Crystals of tetraacid **13** were obtained by slow evaporation of a solution of the compund in THF. Gratifyingly, its structure contains the desired sheet-like hydrogen-bonded network (Figure 8). Two adjacent layers stack with a slight offset along the axis of the acetylene spacer. This generates a large elliptical hole with approximate dimensions 12 × 17 Å. The four extended butyl groups fill much of this void and
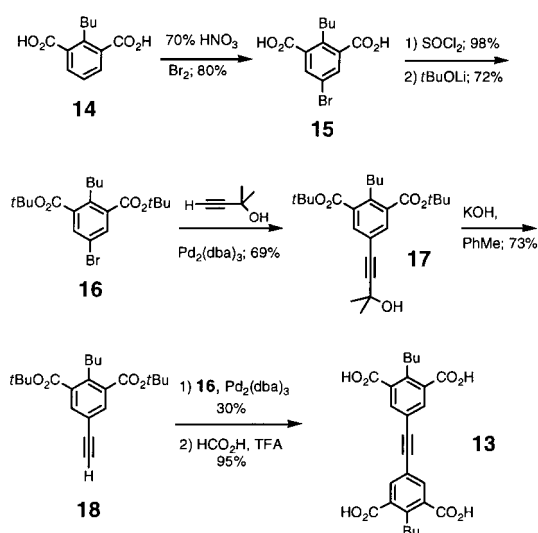
Scheme 4. Synthesis of compound **13**.
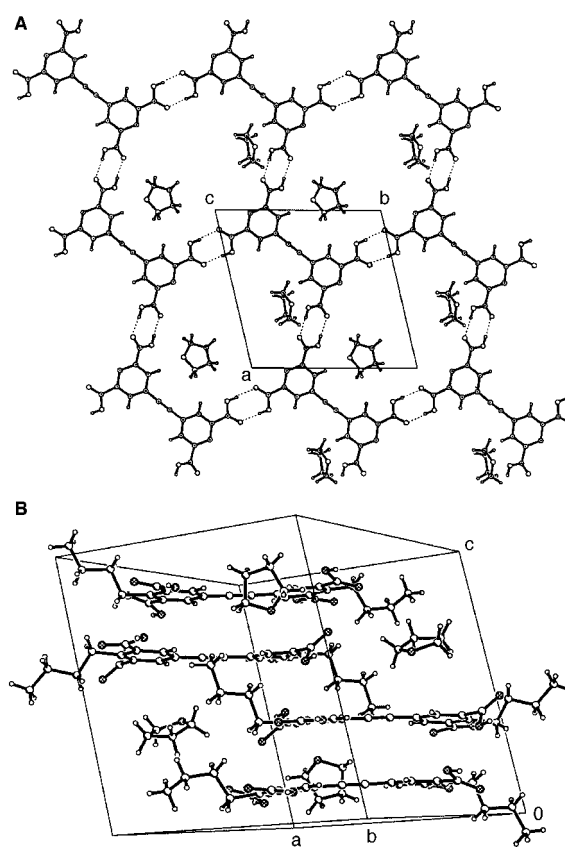
Figure 8. A) Packing view of **13** $\cdot$ 2 THF along c axis showing one layer of hydrogen-bonded network with butyl groups removed for clarity. B) Unit cell of **13** $\cdot$ 2 THF.

serve to divide the chamber into two halves, each of which contains a THF molecule. Each pair of stacked layers is significantly offset relative to each other so that the THF molecules reside in cavities, not channels. Two of the eight butyl groups in the unit cell of **13** are disordered, and both are disordered exclusively at the methyl group position. An additional feature of this crystal structure is a short (2.422 Å) C–H contact between a benzene ring hydrogen atom and the oxygen atom of the THF molecule.[29]

Conclusion

Of the six solid-state structures described in this report (i.e., $1 \times$ pyrene, **4a–d**, **13**), only two (**4d**, **13**) contained the desired sheetlike hydrogen-bonded networks analogous to that in Figure 1. In the case of **4d**, the butyl chains filled the voids of the putative, approximately 14 Å holes, while in **13** two layers stack in close alignment to create cavities filled with THF molecules. In both cases the packing of layers was left to chance. Partial interpenetration of pairs of layers occurred only in **4d**.

Neglecting the hydrate of **4b**, only two of the six structures examined produced a clathrate. The others formed close-packed structures by adopting non-$R_2^2(8)$ carboxylic acid packing motifs. Arguably, the crystal packing motifs of carboxylic acids are among the most extensively studied of all hydrogen-bonding functional groups in small molecules. Moreover, there is a strong measure of statistical significance because of the large database of carboxylic acid structures. How reliable is the $R_2^2(8)$ carboxylic acid dimer as a supramolecular organizing element in crystal engineering?

In this work, we did not grow all crystals under the same conditions, nor did we broadly examine different conditions. Thus, the structures may represent local minima in crystallographic space. Notwithstanding this possibility, the frequency of the $R_2^2(8)$ motif in the $1 \times$ pyrene, **4a–d**, and **13** structures is well below that found for carboxylic acid groups in a brief survey of the Cambridge Structural Database (CSD). Earlier we hypothesized that the likelihood of uncommon carboxylic acid packing motifs increases when $R_2^2(8)$ dimer formation would lead to a porous network. The new results described herein support this idea, although the sample size is comparatively small, and it is also true that sterically encumbered (i.e., 2,6-disubstituted) aromatic carboxylic acids favor such nonstandard motifs as suggested by Etter and Frankenbach.[25] For compounds in the CSD that adopt nonstandard packing motifs, it would be informative to see if their calculated packing coefficient are unusually low when the acids are constrained to form normal dimers. Such a finding would support our notion that so-called nanoporous crystals (i.e., clathrates) are the most difficult to engineer.[16a]

Experimental Section

General: All solvents and reagents were of reagent quality, purchased commercially, and used without further purification, except as noted below. For the synthesis of **6b**, 2,4,6-triethylbromobenzene was obtained from the Marvel chemical storeroom at the University of Illinois and used instead of commercially available 1,3,5-triethylbenzene. Diazomethane was freshly generated from Diazald® (*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide) and potassium hydroxide in a Diazald® diazomethane generator (Aldrich) as a solution in dry diethyl ether and used immediately (**Caution**: diazomethane is explosive and toxic!). Dichloromethane (CH_2Cl_2), pyridine, triethylamine, and toluene were freshly distilled from calcium hydride prior to use. Tetrahydrofuran (THF), diethyl ether, and 1,4-dioxane were freshly

Table 1. Crystal data, data collection, and refinement parameters for $1 \cdot$ pyrene, **4a–d**, **13**.[a]

Compound	$1 \cdot$ pyrene	4a	4b	4c	4d	13
chemical formula	$(C_9H_6O_6)_2(C_{16}H_{10})$ $\cdot 2(C_2H_6O)$	$C_{12}H_{12}O_6$	$C_{12}H_{18}O_6 \cdot H_2O$	$C_{18}H_{24}O_6$	$C_{21}H_{30}O_6$	$C_{26}H_{26}O_8 \cdot C_4H_8O$
formula weight	714.68	252.22	312.31	336.37	378.45	538.6
crystal system	monoclinic	orthorhombic	orthorhombic	orthorhombic	triclinic	triclinic
space group	C2/c	Pbca	Pca2$_1$	Pnma	P$\bar{1}$	P$\bar{1}$
a [Å]	28.128(5)	15.495(3)	17.897(2)	7.082(2)	10.077(3)	13.937(5)
b [Å]	16.550(3)	9.393(2)	5.6062(2)	16.381(4)	15.574(4)	13.971(5)
c [Å]	14.725(4)	15.390(7)	16.047(2)	15.853(3)	15.789(4)	14.967(6)
α [°]	90	90	90	90	64.11(2)	86.47(3)
β [°]	95.13(2)	90	90	90	75.65(2)	79.94(3)
γ [°]	90	90	90	90	77.41(2)	76.32(3)
V [Å]	6827(11)	2239.9(12)	1610.1(3)	1839.1(8)	2142.5(10)	2787(2)
Z	8	8	4	4	4	4
ρ_{calcd} [g cm^{-3}]	1.391	1.496	1.288	1.215	1.173	1.283
crystal size [mm]	$0.20 \times 0.80 \times 0.80$	$0.48 \times 0.46 \times 0.20$	$0.22 \times 0.12 \times 0.10$	$0.65 \times 0.55 \times 0.52$	$0.70 \times 0.46 \times 0.28$	$0.45 \times 0.24 \times 0.16$
μ [mm^{-1}]	0.100	0.122	0.102	0.091	0.085	0.088
temperature [K]	198	198	293	198	198	198
measured reflns	9455	2533	5703	2160	6342	8631
indep. reflns	3425	2413	2247	2050	5940	8238
θ max [°]	$2.00 < 2\theta < 50.00$	$2.65 < \theta < 26.96$	$2.28 < \theta < 23.29$	$3.58 < \theta < 26.96$	$1.46 < \theta < 22.97$	$1.52 < \theta < 23.47$
refinement on	F	F^2	F^2	F^2	F^2	F^2
final R ind (I > 2σ(I))	$R = 0.053$, $Rw = 0.063$	$R1 = 0.0453$, w$R2 = 0.1136$	$R1 = 0.0633$, w$R2 = 0.1096$	$R1 = 0.0468$, w$R2 = 0.1168$	$R1 = 0.0520$, w$R2 = 0.1332$	$R1 = 0.0883$, w$R2 = 0.1844$
R indices (all data)		$R1 = 0.1000$, w$R2 = 0.1789$	$R1 = 0.0864$, w$R2 = 0.12000$	$R1 = 0.0700$, w$R2 = 0.1313$	$R1 = 0.0725$, w$R2 = 0.1499$	$R1 = 0.2733$, w$R2 = 0.2759$
data/restraints/parameters	3425/0/497	2411/6/222	2247/1/218	2050/0/ 175	5940/82/576	8238/226/721
absorption corr.	integration	none	none	integration	integration	none
residual electron density [e Å^{-3}]	0.56/ – 0.44	0.29/ – 0.227	0.141/ – 0.139	0.259/ – 0.204	0.414/ – 0.279	0.478/ – 0.359
GoF	2.35	1.002	1.174	1.017	1.072	1.023

[a] The crystal structures for **4a–d** and **13** were solved by direct methods (SHELXS-86) and refined on F^2 (SHELXL-93); the crystal structure for $1 \cdot$ pyrene was solved by direct methods (SHELXS-86) and refined on F (I > 2.58σ(I)) (SHELX-76). Radiation (Å) Mo K$_\alpha$ ($\lambda = 0.71073$), data coll. method ω/θ. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-123664–123666, 133548–133550. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

distilled from sodium and benzophenone. Dry methanol (CH_3OH) was distilled from magnesium methoxide. All reactions except conversions of **8a–e** to **9a–e** were run under a nitrogen atmosphere. All reactions were stirred magnetically unless otherwise noted.

Flash chromatography was carried out with 40–63 µm silica gel unless otherwise noted. Thin-layer chromatography was performed on 0.2 mm silica gel coated plastic sheets (Merck) with F_{254} indicator. Preparative thin-layer chromatography was performed on silica gel coated circular plates (silica gel 60 PF_{254} containing gypsum, EM Science) with a Chromatotron (Harrison Research). Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. Kugelrohr distillation was performed under high vacuum. NMR spectra were recorded on a General Electric QE-300 (300 MHz) instrument in deuterated chloroform unless otherwise stated. When $CDCl_3$ was used as a solvent chemical shifts were measured relative to the residual chloroform peak ($\delta = 7.26$ for ^1H NMR) and the center of $CDCl_3$ multiplet ($\delta = 77$ for ^{13}C NMR); for [D_6]dimethyl sulfoxide ([D_6]DMSO), chemical shifts were measured relative to the center of residual [D_6]DMSO multiplet ($\delta = 2.49$ for ^1H NMR) and the center of [D_6]DMSO multiplet ($\delta = 39.7$ for ^{13}C NMR); for [D_6]acetone, chemical shifts were measured relative to the center of residual [D_6]acetone multiplet ($\delta = 2.04$ for ^1H NMR) and the center of [D_6]acetone multiplet ($\delta = 29.8$ for ^{13}C NMR). Coupling constants are reported in Hertz (Hz).

2,4,6-Trimethylbenzene-1,3,5-tricarboxylic acid (4a): A suspension of triol **12** (0.9 g, 4.3 mmol) in reagent grade acetone (50 mL) was treated dropwise with Jones reagent (14 mL, 38.5 mmol CrO_3) at 4 °C. The mixture was stirred for 20 min at 4 °C, 20 min at room temperature, and 5 min at 30 °C. The resulting green heterogeneous mixture was poured into cold water (150 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic fractions were extracted with water (50 mL), separated, dried with anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The resulting gray solid was recrystallized from acetonitrile to afford **4a** (0.5 g, 46 %) as short white needles: m.p. > 300 °C; ^1H NMR ([D_6]DMSO): $\delta = 13.5$ (br, 1H, CO_2H), 2.19 (s, 3H, CH_3); ^{13}C NMR ([D_4]methanol): $\delta = 172.5, 135.9, 131.6, 17.3$; anal. calcd $C_{12}H_{12}O_6$: C 57.14, H 4.79; found C 56.77, H 4.88.

2,4,6-Triethyl-1,3,5-benzenetricarboxylic acid (4b): A solution trimethyl ester **9b** (0.5 g, 1.5 mmol) in a mixture of glacial acetic acid (5 mL) and hydrobromic acid in glacial acetic acid (3.5 mL, 30 % w/w) was heated in a sealed tube at 100 °C for 24 h. The resulting homogeneous solution was cooled to room temperature, poured into cold water (100 mL), and extracted twice with diethyl ether (50 mL). The combined organic layers were washed with water (50 mL), and dried over magnesium sulfate. The solvent was removed under reduced pressure. The resulting solid was heated in a Kugelrohr apparatus at 100 °C (to remove traces of acetic acid) and recrystallized from water to afford **4b** (0.22 g, 50 %) as short, colorless needles: m.p. 253–256 °C (decomp); ^1H NMR ([D_6]acetone): $\delta = 11.5$ (br s, 1H, CO_2H), 2.70 (q, $J = 7.5$ Hz; 2H, CH_2), 1.22 (t, $J = 7.5$ Hz; 2H, CH_3); ^{13}C NMR ([D_6]acetone): $\delta = 170.3, 137.9, 134.6, 25.9, 16.2$; anal. calcd $C_{15}H_{18}O_6$: C 61.22, H 6.16; found C 61.22, H 6.17.

2,4,6-Tripropylbenzene-1,3,5-tricarboxylic acid (4c): A solution of **9c** (1.57 g, 4.1 mmol) in a mixture of glacial acetic acid (5 mL) and HBr in glacial acetic acid (5 mL, 30 % w/w) was heated overnight in a sealed tube at 100 °C. The resulting heterogeneous mixture was cooled to room temperature and poured into cold water (20 mL). A white precipitate formed, which was collected by filtration and recrystallized from 20 % v/v aqueous ethanol to afford **4c** (0.88 g, 64 %) as short, colorless needles: m.p. > 300 °C; ^1H NMR ([D_6]acetone): $\delta = 10.2$ (br s, 1H, CO_2H), 2.64 (m, 2H, CH_2-1′), 1.66 (m, 2H, CH_2-2′), 0.91 (t, $J = 7.3$ Hz, 3H, CH_3); ^{13}C NMR ([D_6]acetone): $\delta = 170.4, 136.5, 134.9, 34.9, 25.5, 14.8$; anal. calcd $C_{18}H_{24}O_6$: C 64.27, H 7.20; found C 64.08, H 7.37.

2,4,6-Tributylbenzene-1,3,5-tricarboxylic acid (4d): With a procedure analogous that for **4c**, **9d** (0.54 g) was converted into **4d** (0.3 g, 62 %; short, colorless needles): m.p. > 300 °C; ^1H NMR ([D_6]acetone): $\delta = 11.3$ (br s, 1H, CO_2H), 2.68 (m, 2H, CH_2-1′), 1.61 (m, 2H, CH_2-2′), 1.34 (m, 2H, CH_2-3′), 0.88 (t, $J = 7.3$ Hz, 3H, CH_3); ^{13}C NMR ([D_6]acetone): $\delta = 170.4, 136.7, 134.7, 34.3, 32.4, 23.7, 13.9$; anal. calcd $C_{21}H_{30}O_6$: C 66.64, H 8.00; found C 66.40, H 8.02.

2,4,6-Tripentylbenzene-1,3,5-tricarboxylic acid (4e): A solution of **9e** (1.7 g, 3.7 mmol) in a mixture of glacial acetic acid (10 mL) and HBr in

glacial acetic acid (20 mL, 30 % w/w) was heated over 48 h in a sealed tube at 130 °C. The resulting homogeneous solution was cooled to room temperature and poured into cold water (100 mL) to give a white precipitate. The solid was collected by filtration and recrystallized from 20 % v/v aqueous ethanol, followed by recrystallization from acetonitrile to afford **4e** (0.45 g, 29 %) as small, colorless crystals: m.p. 275–278 °C; ^1H NMR ([D_6]acetone): $\delta = 11.4$ (br, 1H, CO_2H), 2.64 (m, 2H, CH_2-1′), 1.66 (m, 2H, CH_2-2′), 1.31 (m, 4H, CH_2-3′, CH_2-4′), 0.86 (t, $J = 7.0$ Hz, 3H, CH_3); ^{13}C NMR ([D_6]acetone): $\delta = 170.4, 136.8, 134.8, 32.9, 32.7, 31.8, 22.8, 14.1$; anal. calcd $C_{24}H_{36}O_6$: C 68.54, H 8.63; found C 68.45, H 8.71.

1,3,5-Tripropylbenzene (6c): A solution of propylmagnesium bromide prepared from magnesium turnings (36 g, 1.5 mol) and propyl bromide (123 g, 1 mol) in diethyl ether (500 mL) was added at 4 °C with a cannula to a mechanically stirred solution of 1,3,5-trichlorobenzene (**5**) (40 g, 220 mmol) and $NiCl_2$(dppe) (0.44 mmol, 234 mg) in diethyl ether (500 mL). The resulting green reaction mixture was stirred for 2 h at 4 °C and allowed to warm to room temperature over 3 h (**Caution**: exothermic!). The green solution was refluxed overnight during which time a white precipitate formed. The heterogeneous mixture was stirred for five days at room temperature, poured into water (1 L) (**Caution**: exothermic!), acidified with a aqueous HCl (10 % w/w) to pH 1, and extracted twice with diethyl ether (200 mL). The combined organic layers were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The resulting orange liquid was dissolved in petroleum ether and passed through a plug of silica gel. The solvent was removed under reduced pressure and the resulting yellow oil was fractionally distilled at 1 mm Hg to afford **6c** (15 g) as a colorless liquid which was 90 % pure as judged by ^1H NMR spectroscopy. Fractions containing more than 10 % of 3,5-dipropylchlorobenzene (about 20 mL) were dissolved in a solution of KOH (10 g) in ethanol (100 mL). The resulting heterogeneous mixture was hydrogenated at atmospheric pressure and room temperature over palladium on calcium carbonate (5 %, 0.3 g) for 5 h, during which time it changed color from brown to black. The solvent was removed under reduced pressure. The resulting oil was acidified with aqueous HCl (100 mL, 10 % w/w) and extracted twice with CH_2Cl_2 (250 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered through a plug of celite and the solvent was removed under reduced pressure. The resulting colorless liquid was subjected to fractional distillation to afford an additional 14 g of **6b** as a colorless odorless liquid which was 95 % pure as judged by ^1H NMR (total yield: 29 g, 64 %): b.p. 80–85 °C 1 mm^{-1} Hg; ^1H NMR: $\delta = 6.82$ (s, 1H, H-1), 2.53 (m, 2H, CH_2-1′), 1.62 (m, 2H, CH_2-2′), 0.94 (t, $J = 7.4$ Hz, 3H, CH_3); ^{13}C NMR: $\delta = 142.4, 126.0, 38.1, 24.7, 14.0$.

1,3,5-Tributylbenzene (6d): With a procedure analogous to that used for **6c**, except that the reaction was worked up after the overnight reflux, **5** (36 g, 198 mmol) was converted to the crude product which was fractionally distilled (1 mm Hg) to afford **6d** (24 g, 50 %) as a colorless liquid: ^1H NMR: $\delta = 6.88$ (s, 1H, H-1), 2.66 (t, $J = 8.0$ Hz, 2H, CH_2-1′), 1.68 (m, 2H, CH_2-2′), 1.47 (m, 2H, CH_2-3′), 1.04 (t, $J = 6.7$ Hz, 3H, CH_3); ^{13}C NMR: $\delta = 142.7, 125.8, 35.7, 33.8, 22.6, 14.0$.

1,3,5-Tripentylbenzene (6e): With a procedure analogous to that used for **6c**, **5** (26 g) was converted into a colorless oil which was fractionally distilled to afford **6e** (22 g, 53 %) as a colorless oil: b.p. 140–150 °C 1 mm^{-1} Hg; ^1H NMR: $\delta = 6.88$ (s, 1H, H-2), 2.61 (m, 2H, CH_2-1′), 1.66 (m, 2H, CH_2-2′), 1.39 (m, 4H, CH_2-3′, CH_2-4′), 0.97 (t, $J = 6.8$ Hz, 3H, CH_3); ^{13}C NMR: $\delta = 142.7, 125.8, 36.0, 31.7, 31.3, 22.6, 14.1$.

1,3,5-Tribromo-2,4,6-triethylbenzene (7b): 2,4,6-Triethylbromobenzene (10 g, 41.5 mmol) was added dropwise over 15 min to a mixture of bromine (50 mL, 1 mol) and iron powder (1 g) cooled to 0 °C. The reaction mixture was allowed to warm to room temperature overnight. The excess bromine was removed by distillation. The resulting dark brown residue was dissolved in CH_2Cl_2 (150 mL) and washed successively with aqueous sodium sulfite (200 mL, 10 % w/w), water (200 mL), and brine (200 mL). The organic layer was separated, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to afford an off-white solid, which was recrystallized from 95 % ethanol to afford **6a** (15.85 g, 95 %) as long white needles: m.p. 102–103 °C (lit. m.p.[30] 104.6–104.8 °C); ^1H NMR: $\delta = 3.13$ (q, $J = 7.7$ Hz, 2H, CH_2), 1.19 (t, $J = 7.7$ Hz, 3H, CH_3); ^{13}C NMR: $\delta = 142.4, 124.2, 32.7, 12.2$.

1,3,5-Tribromo-2,4,6-tripropylbenzene (7c): With a procedure analogous to that used for **7b**, **6c** (15 g, 90 % pure by ^{1}H NMR) was converted into **7c** (22 g, 62 %) as colorless needles: m.p. 111 – 113 °C (lit. m.p.[31] 112 – 113 °C); ^{1}H NMR: $\delta = 3.03$ (m, 2 H, CH$_2$-1′), 1.58 (m, 2 H, CH$_2$-2′), 1.04 (t, $J = 7.3$ Hz, 3 H, CH$_3$); ^{13}C NMR: $\delta = 141.3$, 124.7, 41.1, 21.3, 14.2; anal. calcd C$_{15}$H$_{21}$Br$_3$: C 40.85, H 4.80, Br 54.35; found C 40.61, H 4.86, Br 54.53.

1,3,5-Tribromo-2,4,6-tributylbenzene (7d): With a procedure analogous to that used for **7b**, except that the **6d** was added by syringe pump over 1 h, **6d** (10 g) was converted into a yellow solid which was subjected to a short-path Kugelrohr distillation to afford **7d** (17 g, 86 %) as a white solid. The product was recrystallized from 2-propanol to afford long white needles: m.p. 56 – 58 °C; ^{1}H NMR: $\delta = 3.07$ (t, $J = 8.6$ Hz, 2 H, CH$_2$-1′), 1.50 (m, 4 H, CH$_2$-2′), 1.39 (m, 2 H, CH$_2$-3′), 0.99 (t, $J = 6.9$ Hz, 3 H, CH$_3$); [13]C $\delta = 141.4$, 124.6, 39.0, 30.0, 22.9, 13.9; anal. calcd C$_{18}$H$_{27}$Br$_3$: C 44.74, H 5.63, Br 49.62; found C 44.71, H 5.66, Br 49.58.

1,3,5-Tribromo-2,4,6-tripentylbenzene (7e): With a procedure analogous to that used for **7b**, **6e** (10 g) was converted into a dark oil which was distilled with a Kugelrohr apparatus. The resulting brownish oil was dissolved in a mixture of light petroleum ether (50 mL) and CH$_2$Cl$_2$ (50 mL) and passed through a short plug of silica gel. The solvent was evaporated and the resulting colorless oil was heated in a Kugelrohr apparatus to 120 – 130 °C to remove any volatiles to afford **7e** (11.3 g, 61 %) as a white waxy solid: m.p. 40 – 42 °C; ^{1}H NMR: $\delta = 3.06$ (m, 2 H, CH$_2$-1′), 1.55 (m, 2 H, CH$_2$-2′), 1.43 (m 4 H, CH$_2$-3′, CH$_2$-4′), 0.94 (t, $J = 6.9$ Hz, 3 H, CH$_3$); ^{13}C NMR: $\delta = 141.5$, 124.6, 39.2, 32.0, 27.5, 22.3, 14.1.

1,3,5-Tricyano-2,4,6-triethylbenzene (8b): A mixture of **7b** (14 g, 35 mmol) and cuprous cyanide (19 g, 210 mmol) in reagent grade DMF (140 mL) was refluxed for 50 h. The reaction mixture was cooled to room temperature, poured into a solution of ferric chloride hydrate (50 g) in aqueous HCl (400 mL, 10 % w/w) and stirred at 80 °C for 30 min. The resulting dark green mixture was extracted twice with CH$_2$Cl$_2$ (200 mL) and once with benzene (200 mL). The combined organic fractions were dried over magnesium sulfate and the solvent was removed under reduced pressure to afford a dark green solid. Kugelrohr distillation followed by flash chromatography (30 % v/v petroleum ether/CH$_2$Cl$_2$) and recrystallization from petroleum ether afforded **8b** (1.8 g, 21 %) as long white needles: m.p. 164 – 165 °C (lit. m.p.[32] 165 – 166 °C); ^{1}H NMR: $\delta = 3.13$ (q, $J = 7.6$ Hz, 2 H, CH$_2$), 1.36 (t, $J = 7.6$ Hz, 3 H, CH$_3$); ^{13}C NMR: $\delta = 156.6$, 113.8, 112.7, 28.4, 14.4.

1,3,5-Tricyano-2,4,6-tripropylbenzene (8c): With a procedure analogous to that used for **8b**, **7c** (9.66 g) was converted into a yellow solid which was recrystallized from petroleum ether to afford **8c** (2.8 g) as long white needles. The solvent from the mother liquor was removed under reduced pressure and the resulting yellowish solid was chromatographed (petroleum ether/CH$_2$Cl$_2$ 1:1). The product thus obtained was recrystallized from petroleum ether to afford **8c** (0.9 g) as long white needles. The solvent from the mother liquor was removed under reduced pressure and the resulting white solid was further purified by radial chromatography over 4 mm silica gel coated plates (9 % CH$_2$Cl$_2$/petroleum ether) to afford an additional 1.2 g of **8c** as white needles (total yield: 4.9 g, 80 %): m.p. 55 – 57 °C; ^{1}H NMR: $\delta = 3.08$ (m, 2 H, CH$_2$-1′), 1.76 (m, 2 H, CH$_2$-2′), 1.07 (t, $J = 7.3$ Hz, 3 H, CH$_3$); ^{13}C NMR: $\delta = 154.9$, 114.2, 113.5, 36.6, 23.9, 13.9; anal. calcd C$_{18}$H$_{21}$N$_3$: C 77.38, H 7.58, N 15.04; found C 77.22, H 7.55, N 15.05.

2,4,6-Tributyl-1,3,5-tricyanobenzene (8d): With a procedure analogous to that used for **8b**, **7d** (7.2 g) was converted into a crude product which was purified by flash chromatography (4 % ethyl acetate/petroleum ether). Mixed fractions were further purified by radial chromatography on a 4 mm silica gel coated plates (petroleum ether). The combined product was recrystallized from pentane to afford **8d** (2.8 g, 58 %) as long white needles: m.p. 64 – 66 °C; ^{1}H NMR: $\delta = 3.09$ (t, $J = 7.8$ Hz, 2 H, CH$_2$-1′), 1.68 (m, 2 H, CH$_2$-2′), 1.50 (m, 2 H, CH$_2$-3′), 0.98 (t, $J = 7.2$ Hz, 3 H, CH$_3$); ^{13}C NMR: $\delta = 155.3$, 114.2, 113.3, 34.7, 32.5, 22.6, 13.5; anal. calcd C$_{21}$H$_{27}$N$_3$: C 78.46, H 8.47, N 13.07; found C 78.42, H 8.45, N 13.09.

1,3,5-Tricyano-2,4,6-tripentylbenzene (8e): With a procedure analogous to that used for **8b**, **7e** (10 g) was converted into a dark oil which was chromatographed over silica gel (20 % v/v CH$_2$Cl$_2$/light petroleum ether) to afford, after Kugelrohr distillation and recrystallization from light petroleum ether (freezer), **8e** (5.1 g, 74 %) as long white needles: m.p. 41 – 43 °C; ^{1}H NMR: $\delta = 3.09$ (m, 2 H, CH$_2$-1′), 1.71 (m, 2 H, CH$_2$-2′), 1.41 (m, 4 H, CH$_2$-3′, CH$_2$-4′), 0.91 (t, $J = 7.3$ Hz, 3 H, CH$_3$); ^{13}C NMR: $\delta = 155.3$, 114.2,

113.2, 34.9, 31.5, 30.2, 22.1, 13.7; anal. calcd C$_{24}$H$_{33}$N$_3$: C 79.29, H 9.15, N 11.56; found C 79.45, H 9.04, N 11.65.

Trimethyl 2,4,6-triethylbenzene-1,3,5-tricarboxylate (9b): A mixture of **8b** (1 g, 4.2 mmol) and aqueous sulfuric acid (19 g, 80 % w/w, water (4.5 mL), and concentrated sulfuric acid (8 mL)) was heated at 150 – 160 °C for 5 h. The resulting brown homogeneous reaction mixture was cooled to 80 – 90 °C and finely ground sodium nitrite (2 g, 29 mmol) was added in portions of about 0.2 g over 2 h with vigorous stirring during which time a tan precipitate formed (**Caution**: foaming and gas evolution!). The heterogeneous mixture was allowed to stir for an additional hour, cooled to room temperature, and poured into cold water (100 mL). The resulting brownish solution was extracted with diethyl ether (150 mL). The organic layer was separated, dried over magnesium sulfate, and concentrated at reduced pressure to afford a tan solid (0.8 g). A solution of crude acid **4b** (0.8 g, ca. 2.7 mmol) in reagent grade THF (50 mL) was treated with an ethereal solution of diazomethane (60 mL) at 0 °C: diazomethane was generated from Diazald® (4.28 g, 20 mmol) and KOH (0.8 g, 14 mmol) as a solution in diethyl ether (60 mL). Excess of diazomethane was quenched with glacial acetic acid (5 mL) and the solvent was removed under reduced pressure. The resulting brown oil was dissolved in CH$_2$Cl$_2$ (160 mL) and washed with a saturated aqueous solution of sodium bicarbonate until the pH of the aqueous layer was basic and no further gas evolution occurred. The organic layer was dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Flash chromatography over silica gel (petroleum ether/CH$_2$Cl$_2$ 1:3) followed by Kugelrohr distillation afforded **9b** (0.5 g; 35 % from **8b**) as a thick colorless oil: ^{1}H NMR: $\delta = 3.82$ (s, 3 H, CO$_2$CH$_3$), 2.45 (q, $J = 7.5$ Hz, 2 H, CH$_2$), 1.09 (t, $J = 7.5$ Hz, 2 H, CH$_3$); ^{13}C NMR: $\delta = 169.2$, 138.6, 132.6, 51.8, 25.2, 15.3; anal. calcd C$_{18}$H$_{24}$O$_6$: C 64.27, H 7.19; found C 64.36, H 7.31.

Trimethyl 2,4,6-tripropylbenzene-1,3,5-tricarboxylate (9c): With a procedure analogous to that used for **9b**, **8c** (2.79 g, 10 mmol) was converted into a crude product which was dissolved in 1:1 petroleum ether/CH$_2$Cl$_2$ and passed through a short pad of silica gel, followed by a short-path Kugelrohr distillation to afford **9c** (1.57 g; 41 % from **8c**) as an oil, which later crystallized as colorless thick needles: m.p. 37 – 40 °C; ^{1}H NMR: $\delta = 3.88$ (s, 3 H, OCH$_3$), 2.43 (m, 2 H, CH$_2$-1′), 1.54 (m, 2 H, CH$_2$-2′), 0.90 (t, $J = 7.3$ Hz, 3 H, CH$_3$); ^{13}C NMR: $\delta = 169.5$, 137.6, 133.0, 52.0, 34.7, 24.6, 14.6; anal. calcd C$_{21}$H$_{30}$O$_6$: C 66.64, H 8.00; found C 66.68, H 8.04.

Trimethyl 2,4,6-tributylbenzene-1,3,5-tricarboxylate (9d): With a procedure analogous to that used for **9b**, **8d** (4.7 g) was converted into a crude product which was purified by radial chromatography on 2 mm silica gel coated plates (15 % v/v petroleum ether/CH$_2$Cl$_2$), followed by a short-path Kugelrohr distillation to afford **9d** (0.62 g; 49 % from **8d**) as a colorless viscous oil: b.p. 140 – 150 °C (Kugelrohr); ^{1}H NMR: $\delta = 3.83$ (s, 3 H, CO$_2$CH$_3$), 2.43 (t, $J = 5.7$ Hz, 2 H, CH$_2$-1′), 1.46 (m, 2 H, CH$_2$-2′), 1.26 (m, 2 H, CH$_2$-3′), 0.83 (t, $J = 7.3$ Hz, 3 H, CH$_3$); ^{13}C NMR: $\delta = 169.3$, 137.6, 132.7, 51.8, 33.2, 31.7, 22.9, 13.5; anal. calcd C$_{24}$H$_{36}$O$_6$: C 68.54, H 8.63; found C 68.52, H 8.63. (Note: In scale-up experiments filtration of the ester as a solution in 1:1 petroleum ether/CH$_2$Cl$_2$ through a pad of silica gel was successfully used instead of radial chromatography.)

Trimethyl 2,4,6-tripentylbenzene-1,3,5-tricarboxylate (9e): A mixture of **8e** (1.5 g, 4 mmol) and aqueous sulfuric acid (30 mL, 80 % w/w) was heated at 160 – 170 °C for 8 h (with reflux condensor attached!). Every 30 min water (2 mL) was added through the condensor. (**Caution!**) The resulting brown homogeneous reaction mixture was cooled to 80 – 90 °C and methanesulfonic acid (5 mL) was added followed by nitrosyl tetrafluoroborate (2.1 g, 18 mmol) in portions of about 0.3 g with vigorous stirring. The addition was complete, the reaction mixture was stirred for 30 min, cooled to room temperature and poured into cold water (100 mL). The resulting creamy solid was filtered, washed with water (200 mL), and air dried. A solution of the crude acid in reagent grade THF (100 mL) was treated with diazomethane as described for **9b**. Flash chromatography of the resulting brown residue over silica gel (30 % v/v CH$_2$Cl$_2$/petroleum ether to 50 % CH$_2$Cl$_2$/petroleum ether), followed by a short-path Kugelrohr distillation afforded **9e** (0.79 g; 42 % from **8e**) as a colorless oil: b.p. 190 – 200 °C 1 mm^{-1} Hg (Kugelrohr), ^{1}H NMR: $\delta = 3.88$ (s, 3 H, OCH$_3$), 2.45 (m, 2 H, CH$_2$-1′), 1.51 (m, 2 H, CH$_2$-2′), 1.27 (m 4 H, CH$_2$-3′, CH$_2$-4′), 0.87 (t, $J = 6.7$ Hz, 3 H, CH$_3$); ^{13}C NMR: $\delta = 169.3$, 137.6, 132.7, 51.8, 32.0, 32.0, 30.8, 22.0, 13.7.

1,3,5-Tris(acetoxymethyl)-2,4,6-trimethylbenzene (11): A mixture of **10** (1.7 g, 4.3 mmol), anhydrous sodium acetate (2 g, 24 mmol), and glacial

acetic acid (40 mL) was heated in a sealed tube at 130–140 °C overnight. The resulting heterogeneous mixture was cooled to room temperature, transferred to a flask, and the solvent was evaporated to dryness under reduced pressure. The resulting white solid was partitioned between water (100 mL) and CH₂Cl₂ (100 mL). The separated organic layer was successively washed with a saturated aqueous sodium bicarbonate (100 mL) and water (50 mL). The collected organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated to dryness. The resulting white solid was recrystallized from methanol to give **11** (1.33 g, 92 %) as long white needles: m.p. 157–159 °C (lit. m.p.[33] 158–159 °C); ¹H NMR: $\delta = 5.23$ (s, 2H, CH₂), 2.41 (s, 3H, CH₃), 2.06 (s, 3H, COCH₃); ¹³C NMR: $\delta = 170.8, 139.5, 130.8, 61.2, 20.7, 15.8$; anal. calcd C₁₈H₂₄O₆: C 64.27, H 7.20; found C 64.29, H 7.23.

1,3,5-Tris(hydroxymethyl)-2,4,6-trimethylbenzene (12): A mixture of **11** (1.33 g, 4 mmol), and lithium hydroxide hydrate (0.67 g, 16 mmol) in reagent grade ethanol (50 mL) was heated at reflux overnight. The resulting heterogeneous reaction mixture was cooled to room temperature and evaporated to dryness. The resulting white solid was suspended in cold water (100 mL), filtered, and washed with water (40 mL), dried under heating to 150 °C in vacuo to provide **12** (780 mg, 92 %) as a white solid: m.p. 271–273 °C (lit. m.p.[33] 277–279 °C); ¹H NMR ([D₆]DMSO): $\delta = 4.66$ (t, $J = 4.6$ Hz, 3H, OH), 2.41 (d, $J = 4.6$ Hz, 6H, CH₂), 2.37 (s, 3H, CH₃); ¹³C NMR ([D₆]DMSO): $\delta = 135.6, 135.5, 57.9, 15.2$; anal. calcd C₁₂H₁₈O₃: C 68.54, H 8.63; found C 68.75, H 8.74.

Bis(4-butyl-3,5-dicarboxyphenyl)acetylene (13): Trifluoroacetic acid (2 mL) was added to a solution bis(4-butyl-3,5-di(tert-butoxycarbonyl)phenyl)acetylene (**13a**) (100 mg) in 98 % formic acid (8 mL). The reaction mixture was stirred overnight at room temperature during which time a white precipitate formed. The solid was filtered and washed with water (30 mL) to afford **13** (65 mg, 95 %) as a white solid after drying at 150–160 °C under high vacuum: m.p. > 300 °C; ¹H NMR ([D₆]DMSO): $\delta = 10$ (br s, 4H, CO₂H), 8.07 (s, 4H, Ar-H), 3.29 (m, 4H, CH₂-1′), 1.58 (m, 4H, CH₂-2′), 1.39 (m, 2H, CH₂-3′), 0.91 (t, $J = 7.3$ Hz, 6H, CH₃); ¹³C NMR ([D₈]THF): $\delta = 168.5, 142.2, 134.4, 134.1, 119.6, 88.5, 33.6, 29.4, 22.5, 13.7$; an analytically pure sample was obtained by recrystallization from aqueous ethanol: anal. calcd C₂₆H₂₈O₈: C 66.94, H 5.62; found C 67.01, H 5.56.

Bis(4-butyl-3,5-di(tert-butoxycarbonyl)phenyl)acetylene (13a): A deoxygenated heterogeneous mixture of **16** (3.7 g, 9 mmol), **18** (3.1 g, 8.6 mmol), CuI (100 mg, 0.5 mmol), Pd₂(dba)₃ (20 mg, 0.02 mmol), triphenylphosphine (210 mg, 0.8 mmol), dry triethylamine (25 mL), and dry benzene (25 mL) was heated in a sealed tube at 80 °C for 48 h. The resulting brown heterogeneous mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was extracted by stirring with diethyl ether (300 mL). The solution was filtered and the solvent was evaporated under reduced pressure. The resulting brown residue was chromatographed (30 % v/v petroleum ether/CH₂Cl₂). The product was further chromatographed with radial chromatography (40 % v/v CH₂Cl₂/petroleum ether) to afford after recrystallization from ethanol **13a** (1.8 g, 30 %) as a white fluffy solid: m.p. 143–145 °C; ¹H NMR: $\delta = 7.71$ (s, 4H, Ph-H), 3.07 (m, 4H, CH₂-1′), 1.60 (s, 36H, tert-Bu), 1.59 (m, 4H, CH₂-2′), 1.39 (m, 4H, CH₂-3′), 0.93 (t, $J = 7.2$ Hz, 6H, CH₃); ¹³C NMR: $\delta = 167.1, 141.7, 135.0, 134.0, 120.2, 88.6, 82.1, 34.1, 30.1, 28.1, 23.3, 14.0$; anal. calcd C₄₂H₅₈O₈: C 73.01, H 8.46; found C 72.84, H 8.62.

5-Bromo-2-butylbenzene-1,3-dicarboxylic acid (15): A heterogeneous mixture of **14** (12 g, 27 mmol), bromine (5 mL, 97 mmol), and aqueous nitric acid (50 mL, 70 % w/w) was heated in a sealed tube for 18 h at 80–90 °C. The course of the reaction was monitored by ¹H NMR spectroscopy. The reaction mixture was cooled to room temperature and poured into cold water (200 mL). The resulting brownish solid was filtered, washed with cold water (200 mL) and dissolved in aqueous potassium carbonate (0.5 L, 10 % w/w). The traces of bromine were quenched by addition of aqueous sodium hydrosulfite (10 % w/w) until the solution changed color from slightly orange to colorless. The resulting solution was acidified with concentrated aqueous hydrochloric acid to pH 1. The white creamy precipitate formed was filtered and recrystallized from aqueous ethanol (20 % v/v) to afford acid **15** (6.5 g, 80 %) after drying in vacuo as a white solid: m.p. 245–248 °C; ¹H NMR ([D₆]DMSO): $\delta = 13.35$ (br s, 2H, CO₂H), 7.89 (s, 2H, H-4, H-6), 3.03 (m, 2H, CH₂-1′), 1.45 (m, 2H, CH₂-2′), 1.27 (m, 2H, CH₂-3′), 0.84 (t, $J = 7.2$ Hz, 3H, CH₃); ¹³C NMR ([D₆]DMSO): $\delta = 167.9, 140.9, 135.7, 134.0,$

118.3, 33.6, 29.1, 22.6, 13.7; anal. calcd C₁₂H₁₃BrO₄: C 47.86, H 4.35, Br 26.54; found C 47.87, H 4.39, Br 26.46.

5-Bromo-2-butylbenzene-1,3-dicarbonylchloride (15a): A heterogeneous mixture of **15** (6.5 g, 21 mmol), thionyl chloride (25 mL), and reagent grade DMF (two drops) was heated at reflux for 1 h to obtain a homogeneous solution. Excess thionyl chloride was removed by distillation at atmospheric pressure. Traces of thionyl chloride were removed by distillation as an azeotrope with benzene (50 mL). The resulting brownish oil was distilled at 1 mm Hg in a Kugelrohr apparatus to afford **15a** (7 g, 98 %) as a colorless thick oil: ¹H NMR: $\delta = 8.27$ (s, 2H, H-4, H-6), 2.94 (m, 2H, CH₂-1′), 1.50 (m, 4H, CH₂-2′, CH₂-3′), 0.93 (t, $J = 7.0$ Hz, 3H, CH₃); ¹³C NMR: $\delta = 166.1, 142.3, 138.0, 137.6, 119.5, 33.4, 29.6, 22.8, 13.6$; anal. calcd C₁₂H₁₁BrCl₂O₄: C 42.64, H 3.28, Br 23.64, Cl 20.98; found C 42.66, H 3.30, Br 23.60, Cl 20.97.

Di(tert-butyl) 5-bromo-2-butylbenzene-1,3-dicarboxylate (16): tert-Butyllithium (25 mL, 50 mmol, 1.5 mol L⁻¹ solution in pentane) was added dropwise at −78 °C to a solution of tert-butyl alcohol (5 mL, 52 mmol) in dry THF (80 mL). The addition was complete, and the resulting colorless solution was removed from the cooling bath, and warmed to room temperature over 1 h. The clear solution was cooled to −78 °C and a solution of **15a** (4.1 g, 12 mmol) in dry THF (6 mL) was added dropwise. The reaction mixture was removed from the cooling bath and allowed to warm to room temperature overnight. The solvent was removed under reduced pressure. The yellow slurry was diluted with water (200 mL) and extracted with diethyl ether (3 × 100 mL). The combined ethereal fractions were washed successively with water (160 mL), and brine (160 mL), and dried over magnesium sulfate. The resulting yellow oil was dissolved in CH₂Cl₂ (200 mL), and passed through a short plug of silica gel. The solvent was evaporated under reduced pressure and the pale yellow oil obtained was heated in vacuo at 120 °C in a Kugelrohr apparatus to remove the volatiles to afford **16** (3.6 g, 72 %) as a colorless viscous oil: ¹H NMR: $\delta = 7.73$ (s, 2H, H-4, H-6), 3.03 (m, 2H, CH₂-1′), 1.58 (s, 18H, tert-Bu), 1.52 (m, 2H, CH₂-2′), 1.40 (m, 2H, CH₂-3′), 0.91 (t, $J = 7.1$ Hz, 3H, CH₃); ¹³C NMR: $\delta = 166.3, 140.3, 136.2, 133.9, 118.6, 82.3, 34.0, 29.7, 28.0, 23.2, 13.9$; anal. calcd C₂₀H₂₉BrO₄: C 58.11, H 7.07, Br 19.33; found C 57.98, H 7.11, Br 19.25. (Note: heating **16** and all other di(tert-butyl)esters above 130 °C may result in decomposition.)

Di(tert-butyl) 5-(3-methyl-3-hydroxy-1-butynyl)-2-butylbenzene-1,3-dicarboxylate (17): A deoxygenated heterogeneous mixture of **16** (2.35 g, 5.7 mmol), 2-methyl-3-butyn-2-ol (4.5 mL, 46 mmol), cuprous iodide (CuI, 11 mg, 0.06 mmol), tris(dibenzylidene acetone)dipalladium ([Pd₂(dba)₃], 10 mg, 0.01 mmol), triphenylphosphine (44 mg, 0.17 mmol), and dry triethylamine (10 mL) was heated in a sealed tube at 100 °C for 24 h. The resulting brown heterogeneous mixture was cooled to room temperature, diluted with ethyl acetate (100 mL), and the solvent was evaporated under reduced pressure. The resulting brown residue was chromatographed (CH₂Cl₂) to afford **17** (1.65 g, 69 %) as a light brown oil: ¹H NMR: $\delta = 7.64$ (s, 2H, H-4, H-6), 3.03 (m, 2H, CH₂-1′), 2.20 (s, 1H, OH), 1.60 (s, 6H, CH₃), 1.58 (s, 18H, tert-Bu), 1.53 (m, 2H, CH₂-2′), 1.49 (m, 2H, CH₂-3′), 0.90 (t, $J = 7.1$ Hz, 3H, CH₃); ¹³C NMR: $\delta = 167.1, 141.3, 134.8, 134.0, 120.0, 94.5, 82.0, 80.6, 65.5, 34.1, 31.4, 30.1, 28.1, 23.2, 13.9$.

Di(tert-butyl)-5-ethynyl-2-butylbenzene-1,3-dicarboxylate (18): A heterogeneous mixture of **17** (1.65 g, 4 mmol) and powdered potassium hydroxide (2 g) in toluene (80 mL) was heated at reflux for 10 min. The resulting brown heterogeneous mixture was cooled to room temperature, poured into water (200 mL), and extracted twice with benzene (50 mL). The combined organic extracts were washed with water (100 mL), brine (100 mL), dried over magnesium sulfate, and the solvent was removed under reduced pressure. The brownish residue was flash chromatographed (CH₂Cl₂/petroleum ether 1:3) and heated in vacuo in a Kugelrohr apparatus at 80–90 °C to afford **18** (1.05 g, 73 %) as a yellowish oil: ¹H NMR: $\delta = 7.73$ (s, 2H, H-4, H-6), 3.09 (s, 1H, C≡CH), 3.05 (m, 2H, CH₂-1′), 1.57 (s, 18H, tert-Bu), 1.55 (m, 2H, CH₂-2′), 1.42 (m, 2H, CH₂-3′), 0.91 (t, $J = 7.2$ Hz, 3H, CH₃); ¹³C NMR: $\delta = 166.9, 142.0, 134.8, 134.5, 119.4, 82.0(7), 82.0(1), 78.0, 34.0, 30.0, 28.0, 23.2, 13.9$; anal. calcd C₂₂H₃₀O₄: C 73.71, H 8.43; found C 73.62, H 8.50.

Acknowledgment

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