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Control of functional group proximity and direction by conformational networks: synthesis and stereodynamics of persubstituted arenes

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Abstract—The cooperative nonbonded interactions present in hexaethylbenzene result in an arrangement of alkyl groups such that the 1,3,5 and 2,4,6 substituents point to opposite faces of the benzene ring. Correspondingly, derivatives of hexaethylbenzene have their functional groups convergent (*meta* as in 1,3,5-trisubstituted-2,4,6-triethylbenzene) or divergent (*ortho*, *para* as in 1,2-disubstituted-3,4,5,6-tetraethylbenzenes or 1,4-disubstituted-2,3,5,6-tetraethylbenzenes) due to this cooperative conformational network. To illustrate this structural feature and probe its dynamics, 1,4-di-X-2,3,5,6-tetraethylbenzenes have been synthesized. The dynamic stereochemistry of the disubstituted compounds has been studied by variable temperature ^{1}H NMR spectroscopy. Using the same strategy, the 1,3,5-tris(CH_2Y)-2,4,6-triethylbenzenes have also been prepared. The steric bulk of the substituent in the disubstituted compounds has been found to influence the barrier height. The trends found are applicable for the use of these compounds as angular building blocks for the design of ligands, polymers, and supramolecular architectures.

1. Introduction

Molecular-assembly research for the design of nanomaterials and crystal engineering uses simple building blocks and connectivity principles to construct such diverse materials as zeolites[1] and nonlinear optical materials.[2,3] Aggregation,[4] hydrogen bonding,[5] and dative bonding[6] have been used for the spontaneous assembly of nanomaterials.[7] The ability to control the proximity and direction of functional groups allows one to tailor physical properties such as chelation, amphiphilicity, and polymer dynamics.[8] Several different approaches have been used to attempt to preselect nanostructures by varying the number of coordination sites and metal geometries.[9,10] The basis of this simple approach as visualized by Stang is the construction of nanomaterials by using two types of building blocks: linear (**L**) and angular (**A**) units, both of which contain chelation sites.[11] The addition of two linear units leads to monolayer materials. Depending on the coordination angle of the angular units, they can combine with bidentate linear units (**L**) or other angular units to form various geometrical lattices (Fig. 1).[12–17]

For example, squares ($\mathbf{A}_4\mathbf{L}_4$ where the subscript is the number of units, and a superscript is the molecule designation; see Fig. 2) have been formed at room temperature from linear 4,4′-bipyridine units ($\mathbf{L}^1$=bipy) and angular units of square planar *cis*-tetracoordinated group 10 metals ($\mathbf{A}^1$ where M=Pd, Pt; Y=weakly coordinated ligand, e.g. triflate; and X=strongly coordinated ligand, e.g. ethylenediamine).[13,14] Angle–angle building block combinations lead to other squares, hexagons, and octahedrons. Two examples of octahedrons ($\mathbf{A}_4\mathbf{A}'_6$) were synthesized by Fujita[15] with four $\mathbf{A}^2$ and six $\mathbf{A}^1$ (M=Pd) units and Stang[14] with four $\mathbf{A}^3$ and six $\mathbf{A}^1$ (M=Pd, Pt) units resulting metal–metal distances across the octahedron on the order of 1.5 nm.

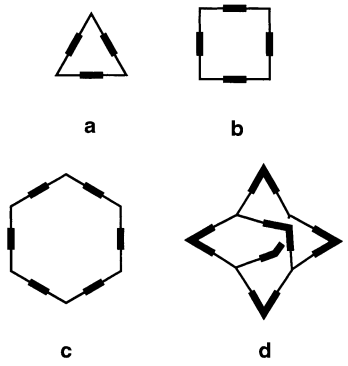

Figure 1. Structure of triangle (**a**, $\mathbf{A}_3\mathbf{L}_3$), square (**b**, $\mathbf{A}_4\mathbf{L}_4$), hexagon (**c**, $\mathbf{A}_6\mathbf{L}_6$), and octahedron (**d**, $\mathbf{A}_4\mathbf{A}'_6$).

Keywords: 1,3,5-trisubstituted-2,4,6-triethylbenzene; 1,2-disubstituted-3,4,5,6-tetraethylbenzenes; 1,4-di-X-2,3,5,6-tetraethylbenzenes.

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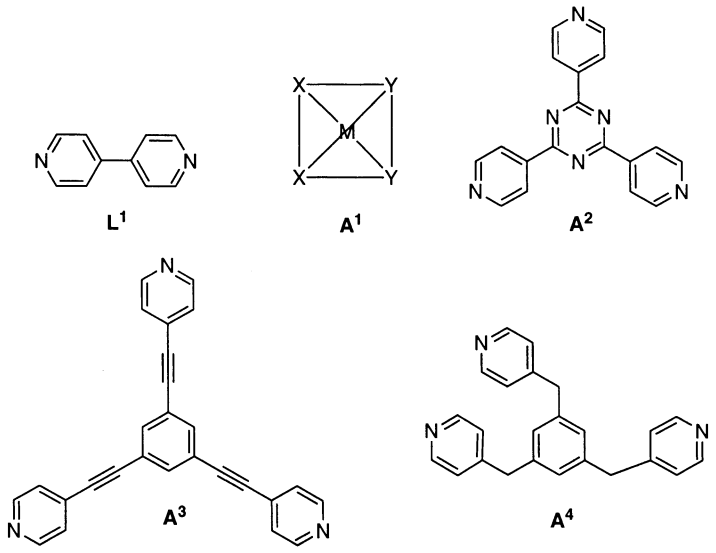


Figure 2. Examples of linear (**L**) and angular (**A**) units.

A 1,3,5-trialkyl benzene ring has frequently been used as a convenient, albeit conformationally ambiguous, center plate for the assembly of polyfunctional molecules.[18] Extension of the previously described building block approach to include **A** tridentate units with a more flexible backbone leads to cages ($\mathbf{A}_2\mathbf{A}'_3$), which are formed in water from the self-assembly of two 2,4,6-(4-pyridylmethyl)benzene molecules ($\mathbf{A}^4$) and three Pd(II) units ($\mathbf{A}^1$).[19] But what about other polyalkylarenes?

The alkyl groups of hexaethylbenzene (**1**, HEB) are a novel conformational network in which cooperative nonbonded interactions direct the vicinal alkyl groups to point to opposite sides of the benzene ring resulting in a 1,3,5 vs. 2,4,6 facial segregation.[20] This alternating structure is also the dominant structure as determined by variable-temperature NMR studies of HEB chromium tricarbonyl complex (**1**Cr).[20] Although mobile on the NMR timescale ($\Delta G^{\neq} \sim 11.5$ kcal/mol for **1**Cr), this arrangement is stable enough to insure that in any instant >99% of the molecules in solution adopt this conformation.[20] Thus, it is not surprising to find this conformational networking used in the design of ligands, polymers, and supramolecular architectures.[21]

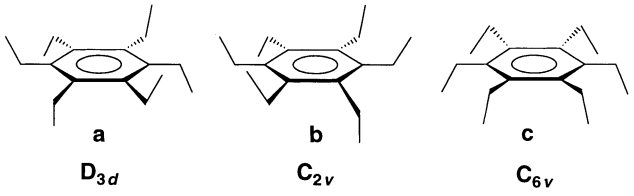


Figure 3. Lowest energy and highest energy conformations of hexaethylbenzene (HEB, **1**) as by determined by EFF-HMO calculations.

From Empirical Force Field-Extended Hückel Molecular Orbital (EFF-HMO) calculations, Mislow and Iverson determined the energy of the conformations of **1** with respect to the different orientation of the ethyl groups (Fig. 3).[20] In general, this type of static gearing persists for a number of cognates of **1**.[22] The lowest energy conformation, the alternating up–down conformation having D_{3d} symmetry (**a**), lies several kcal/mol below the next accessible conformation (**b**) and more than 10 kcal/mol below conformation **c** (C_{6v}). The interconversion of one to the other by holding all ethyls in the plane would cost over 30 kcal/mol.[20] It is not surprising that conformation **a** was dominant in the crystal structure.[20]

Replacement of ethyl groups in HEB by additional CH_2X groups has explicit stereochemical consequences. *ortho* (1,2) or *para* (1,4) Substitution points the new substituents

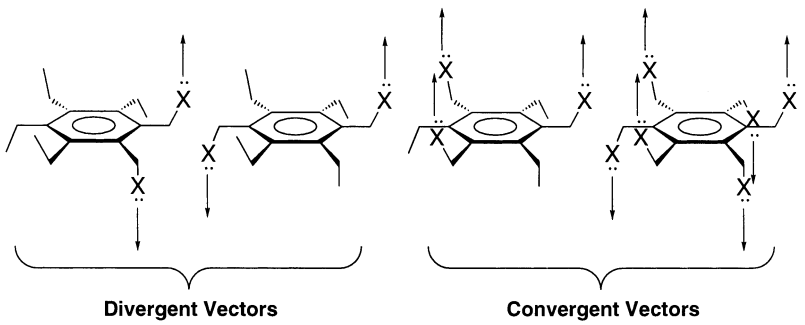


Figure 4. Possible substitution patterns for the HEB mimics. Left: *ortho* and *para* substitution gives divergent functionality; Right: all *meta* substitution gives convergent functionality.

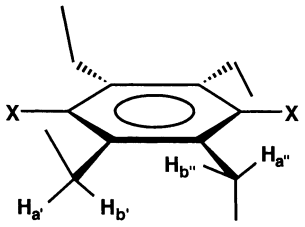
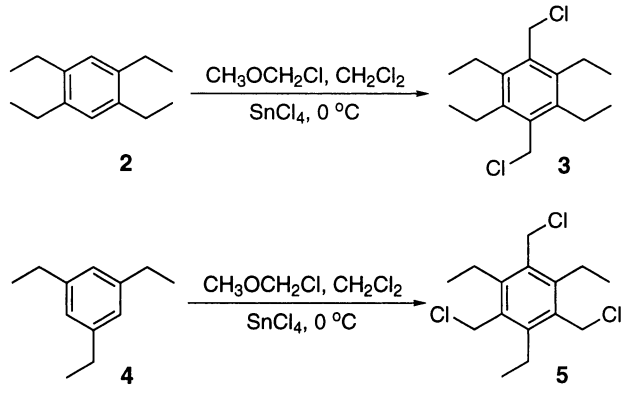


Figure 5. Diastereotopic protons in 1,4-disubstituted-2,3,5,6-tetraethylbenzene.

in divergent directions, which may be utilized as linear (**L**) units, whereas *meta* (1,3) substitution makes them convergent (Fig. 4). All-*meta*-related trisubstitution makes the substituents convergent and can strongly differentiate one face from the other as in an amphiphile. This substitution pattern would lead to novel angular (**A**) units for molecular assembly. Indeed, hexa-substitution cleanly leads to the possibility of ditopic molecules with like or unlike facial-topic character.

The utility of HEB derivatives as preorganized templates depends not only on the static-gearing effects but also on the stereodynamics of the alkyl groups, of which less is known. The dynamic behavior of the *ortho*- or *para*-substituted derivatives is directly measurable by ^{1}H NMR spectroscopy due to the symmetry of the molecule, and provides a gauge of the effective steric bulk of a substituent in this kind of molecule. The trends seen in these dynamics can be transferred faithfully to the *meta* and 1,3,5-trisubstituted derivatives, where direct measurement is more difficult.[23] Even though the 1,3,5-trisubstituted and 1,4-disubstituted compounds have been synthesized and should have similar dynamic behavior, the 1,4-disubstituted isomers provide the ideal spectroscopic handle for our purposes. The static 1,4-



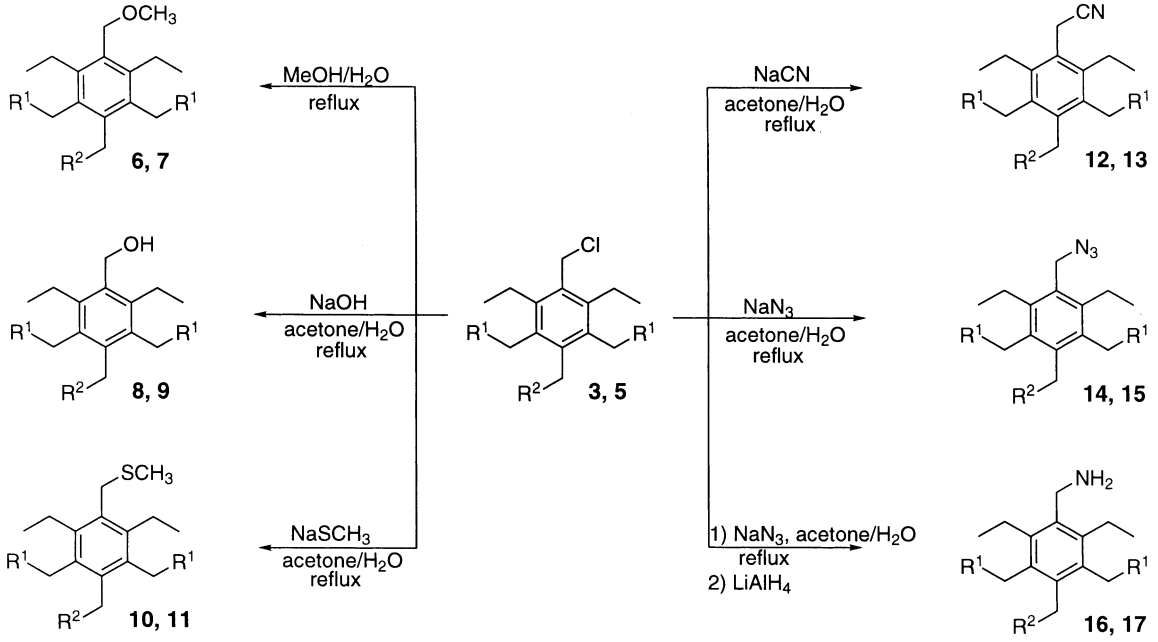
Scheme 1.

disubstituted systems have one very simple AB pattern when the methyl group protons are decoupled and coalescence to a singlet is easily monitored when alkyl motion becomes rapid on the NMR time scale (Fig. 5).[24,25]

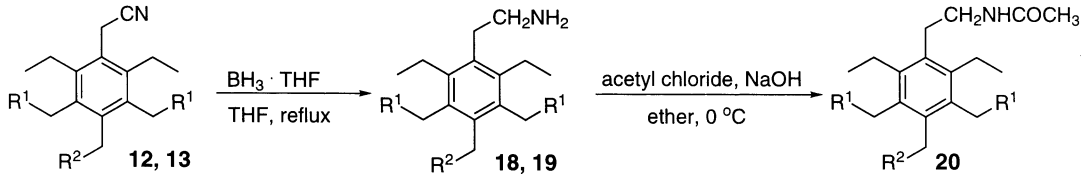
2. Results and discussion

2.1. Synthesis

Three approaches were used to prepare these compounds: (a) derivatization of an alkylated benzene; (b) alkylation of a substituted benzene; and (c) construction of the benzene nucleus with the pendant alkyls and substitutions falling into place. Following the first approach, 1,4-bis(chloromethyl)-2,3,5,6-tetraethylbenzene (**3**) was synthesized from 1,2,4,5-tetraethylbenzene (**2**) as previously described.[25] In a similar manner, the synthesis 1,3,5-tris(chloromethyl)-2,4,6-triethylbenzene (**5**) was achieved starting from commercially available 1,3,5-triethylbenzene (**4**) (Scheme 1).[26]



Scheme 2. **3**: $R^1 = CH_3$, $R^2 = Cl$; **5**: $R^1 = Cl$, $R^2 = CH_3$; **6**: $R^1 = CH_3$, $R^2 = OCH_3$; **7**: $R^1 = OCH_3$, $R^2 = CH_3$; **8**: $R^1 = CH_3$, $R^2 = OH$; **9**: $R^1 = OH$, $R^2 = CH_3$; **10**: $R^1 = CH_3$, $R^2 = SCH_3$; **11**: $R^1 = SCH_3$, $R^2 = CH_3$; **12**: $R^1 = CH_3$, $R^2 = CN$; **13**: $R^1 = CN$, $R^2 = CH_3$; **14**: $R^1 = CH_3$, $R^2 = N_3$; **15**: $R^1 = N_3$, $R^2 = CH_3$; **16**: $R^1 = CH_3$, $R^2 = NH_2$; **17**: $R^1 = NH_2$, $R^2 = CH_3$.



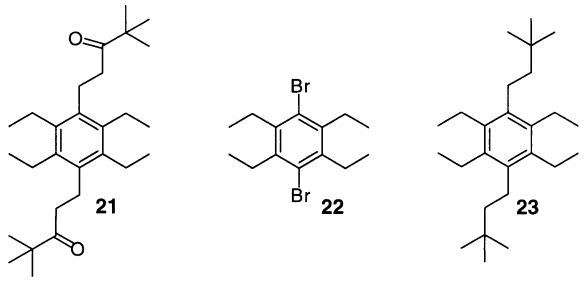
Scheme 3. 12: R^1=CH_3, R^2=CN; **13**: R^1=CN, R^2=CH_3; **18**: R^1=CH_3, R^2=CH_2NH_2; **19**: R^1=CH_2NH_2, R^2=CH_3; **20**: R^1=CH_3, R^2=$CH_2NHCOCH_3$.

Displacement reactions on these benzyl chlorides by standard S_N2 conditions were unsuccessful. Indeed, the chlorides did not react even with strong nucleophiles after 24 h in refluxing acetone or in aqueous sodium hydroxide. Evidently, the conformational preference places the flanking alkyl group in a position to block backside attack on the CH_2X fragment. However, reactions with a 1:1 solution of methanol/aqueous sodium hydroxide led to 1,4-bis(methoxymethyl)-2,3,5,6-tetraethylbenzene (**6**) or 1,3,5-tris(methoxymethyl)-2,4,6-triethylbenzene (**7**) as the isolated products from **3** and **5**, respectively (Scheme 2). The hydroxy derivatives **8** and **9** were finally synthesized by refluxing the appropriate chloromethyl compound in 1:1 acetone/water. We believe these reactions to take place by S_N1-like mechanisms.

On the basis of the water/acetone results, S_N1 conditions were used to synthesize a series of compounds by simply changing the nucleophile: the thioethers, 1,4-bis(methylthiomethyl)-2,3,5,6-tetraethylbenzene (**10**) and 1,3,5-tris-(methylthiomethyl)-2,4,6-triethylbenzene (**11**), were obtained in 85 and 81% yield using sodium thiomethoxide; the cyanides, 1,4-bis(cyanomethyl)-2,3,5,6-tetraethylbenzene (**12**) and 1,3,5-tris(cyanomethyl)-2,4,6-triethylbenzene (**13**),[21f] in 89 and 88% yield using sodium cyanide; and the azides, 1,4-bis(azidomethyl)-2,3,5,6-tetraethylbenzene (**14**) and the 1,3,5-tris(azidomethyl)-2,4,6-triethylbenzene (**15**),[21d] in 74 and 70% yield using sodium azide, respectively (Scheme 2). The methyl ethers were also synthesized using the corresponding alcohol in water to yield **6** and **7** with 91 and 10% yields.

The amines, 1,4-bis(aminomethyl)-2,3,5,6-tetraethylbenzene (**16**) and 1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene (**17**), were synthesized in 37 and 44% yield by treating the corresponding azidomethyl benzene with lithium aluminum hydride.[27] Compound **17** has been synthesized previously using two different synthetic methods: reduction of **15** with triphenylphosphine in THF/water[21d] and hydrogenation of 1,3,5-tricyano-2,4,6-triethylbenzene.[21g] The cyanides were reduced to give 1,4-bis(2′-aminoethyl)-2,3,5,6-tetraethylbenzene (**18**) and 1,3,5-tris(2′-aminoethyl)-2,4,6-triethylbenzene (**19**)[21f] using borane tetrahydrofuran complex in 57 and 63% yield (Scheme 3).[28–30] Compounds **13** and **19** were prepared by the method of Walsdorff et al.[21f] Nucleophilic displacement of bromide in 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene with tetraethylammonium cyanide gave **13**, and reduction of the nitriles with lithium aluminum hydride–aluminum chloride gave **19**. Other standard conditions that used different diborane complexes or lithium aluminum hydride were unsuccessful. The bis(aminoethyl) compound was acylated to form 1,4-bis(acetamidoethyl)-2,3,5,6-tetraethylbenzene (**20**) in 74% yield. A Reetz reaction between **3** and the TMS enolate of pinacolone yielded 1,4-bis(4,4-dimethyl-3-oxopentyl)-2,3,5,6-tetraethylbenzene (**21**) in 85% yield.[24,25]

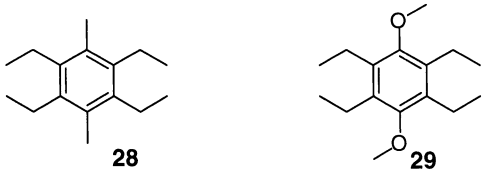
Durene as well as 1,2,4,5-tetraethylbenzene have been nitrated to yield the corresponding 1,4-dinitroarenes. Bromination of the ring yielded 1,4-dibromo-2,3,5,6-tetraethylbenzene (**22**) (40% yield).



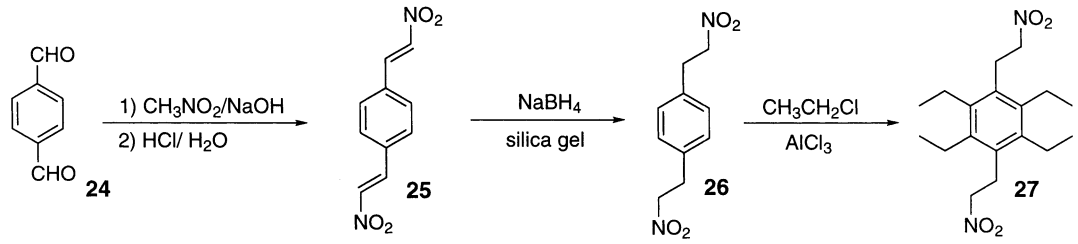
The second approach to the synthesis of the 1,4-disubstituted compounds was to introduce the 1,4 substituents first, then ethylate the remaining positions. 1,4-Dineohexyl-2,3,5,6-tetraethylbenzene (**23**) was synthesized by successive acetylation of benzene with 3,3-dimethylbutyryl chloride followed by Wolff–Kishner reduction and exhaustive ethylation of the resulting 1,4-dineohexylbenzene as described previously.[25]

Knoevenagel reaction of terephthalaldehyde (**24**) with nitromethane gives the 1,4-bis(nitrovinyl)benzene (**25**).[31] The vinyl groups were selectively reduced with sodium borohydride and silica gel in isopropanol[32] to give 1,4-bis(nitroethyl)benzene (**26**), which was exhaustively ethylated to give the final product, 1,4-bis(nitroethyl)-2,3,5,6-tetraethylbenzene (**27**) (Scheme 4).

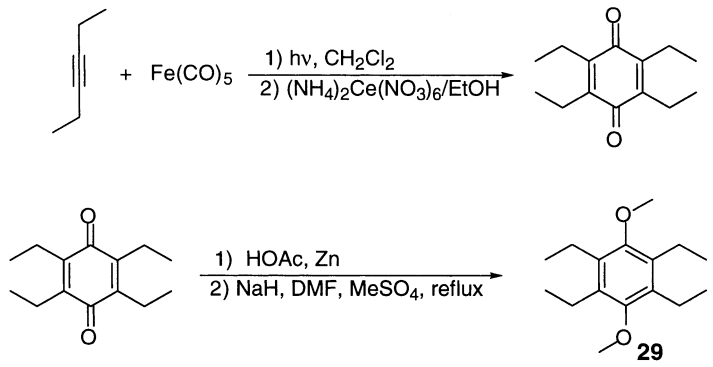
This strategy was also used to synthesize 1,4-dimethyl-2,3,5,6-tetraethylbenzene (**28**). Ethylation of *para*-xylene with aluminum chloride as the catalyst in neat bromoethane at reflux gave the desired product in 18% yield. Attempts to substitute the methyl groups by benzylic bromination were unsuccessful.



The third approach to the synthesis of 1,4-disubstituted tetraethylbenzenes involved the construction of the benzene ring. This is accomplished using a method of Reppe for the synthesis of quinones.[33,34] Here the tetraethylquinone is



Scheme 4.



Scheme 5.

produced from 3-hexyne and iron pentacarbonyl under UV light with or without the addition of solvent. The important step is the oxidative removal of the transition metal from the quinone using the iron nitrate or more conveniently ceric ammonium nitrate.[35,36] The resulting quinone was reduced to the dihydroquinone and methylated to yield 1,4-dimethoxy-2,3,5,6-tetraethylbenzene (**29**, Scheme 5).

2.2. The structure of 23

The molecular structure of **23** was determined by X-ray analysis. The crystals are monoclinic, space group $P2_1/c$, with two molecules per unit cell. The average value of the ring–carbon bond distances (C_{ar}–C_{ar}) is 1.407 Å, the average value of the C_{ar}–C_{ar}–C_{ar} bond angles is 120.0°, and the average value of C_{ar}–CH_2–CH_3 bond angles is 113.4°. The CH_2–C_{ar}–C_{ar}–CH_2 torsion angles reveal a slight puckering of the methylene carbons out of the plane in the direction opposite to their methyl groups by an average of 0.7°. The average of the C_{ar}–C_{ar}–CH_2–CH_3 torsion angle is 89.9°, i.e. the plane defined by two adjacent ipso-carbons is perpendicular to the plane defined by the corresponding ethyl group carbons (Table 1). Comparison of the crystal structures of **23** and **1** show that **23** has essentially the same ring geometry and arm conformation as **1**.[20]

2.3. Dynamic stereochemistry

Variable temperature NMR studies were performed on compounds **3**, **6**, **10**, **12**, **14**, **16**, **18**, **20**, **21**, **22**, **23**, **27**, and **29** in deuteriofreon.[37] All of the compounds with the exception of **14** and **20** exhibited an AB pattern due to the diastereotopic geminal methylene protons on the ethyl groups at low temperatures. In each case, the AB pattern of the methylene protons observed under the conditions where the methyl protons were decoupled. The barriers to rotation, T_c, $\Delta\nu$, J_{AB}, and k_c for compounds **3**, **6**, **10**, **12**, **16**, **20**, **21**, **22**, **23**, **27**, and **29** are collected in Table 2. The compounds are listed with respect to the type of substituent (X, CH_2X, and CH_2CH_2X groupings). The free energies of activation were calculated using the Gutowsky–Holm approximation.[38,39]

From the low temperature NMR experiments, it is evident that the surrogates adopt either the **a** conformation (as in the crystal) or the **c** conformation. As discussed previously, the **c** conformation is highly unlikely due to the unfavorable interactions of the alkyl groups. Therefore, the disubstituted surrogates adopt conformation **a** both in solution and solid states. By analogy, it is presumed that the 1,3,5-trisubstituted systems also adopt the **a** conformation.[40]

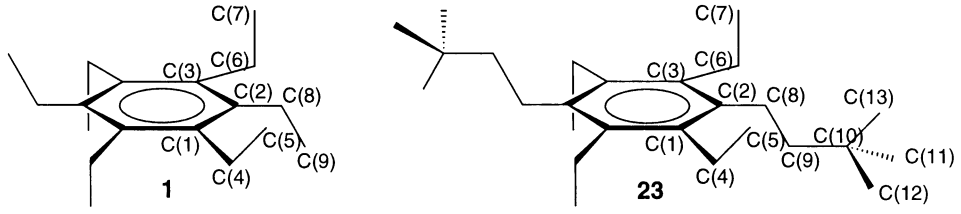


Table 1. Experimental structural parameters (bond lengths in Angstroms (Å), angles in degrees (°)) for **23** and **1**

Bond lengths	**23**	**1**	Bond angles	**23**	**1**
C(1)–C(2)	1.404 (4)	1.402 (3)	C(2)–C(1)–C(3a)	120.1 (2)	120.0 (2)
C(1)–C(3a)	1.405 (4)	1.403 (3)	C(1)–C(2)–C(3)	119.9 (2)	120.1 (2)
C(2)–C(3)	1.411 (4)	1.400 (3)	C(2)–C(3)–C(1a)	119.9 (2)	119.9 (2)
Torsion angles			C(3)–C(6)–C(7)	113.4 (2)	113.1 (2)
C(4)–C(1)–C(2)–C(8)	−0.7		C(2)–C(8)–C(9)	113.0 (2)	112.6 (2)
C(8)–C(2)–C(3)–C(6)	1.8		C(1)–C(4)–C(5)	113.7 (2)	112.7 (2)
C(2)–C(1)–C(4)–C(5)	−89.8				
C(2)–C(3)–C(6)–C(7)	90.1	89.7 (2)			
C(1)–C(2)–C(8)–C(9)	−88.9	−90.0 (2)			
C(3)–C(2)–C(8)–C(9)	90.1	89.0 (2)			

Table 2. Data for estimation of the barriers to rotation about the sp^2–sp^3 bond by the Gutowsky–Holm approximation. [$k_c=\pi/2(\Delta\nu_{ab}^2+6J_{ab}^2)^{1/2}$; $\Delta G^{\neq}_c=4.576T_c(10.319+\log T_c/k_c)$ cal/mol]

Compound # substituent	T_c (K)	$\Delta\nu$ (Hz)	J_{ab} (Hz)	k_c (s^{-1})	$\Delta G^{\neq}_c$
22-Br	204±5	125±2	13±1	286±12	9.5±0.3
29-OCH_3	166±5	120±2	14±1	278±12	7.7±0.3
3-CH_2Cl	210±5	42±2	14±1	20±12	11.5±0.3
6-CH_2OCH_3	193±5	23±2	14±1	92±12	9.4±0.3
10-CH_2SCH_3	235±5	94±2	14±1	221±12	11.1±0.3
12-CH_2CN	198±5	83±2	14±1	200±12	9.3±0.3
16-CH_2NH_2	193±5	22±2	14±1	93±12	10.4±0.3
20-$(CH_2)_2NHCOCH_3$	228±5	50±2	14±1	134±12	11.0±0.3
21-$(CH_2)_2COC(CH_3)_3$	241±5	128±2	14±1	295±12	11.3±0.3
23-$(CH_2)_2C(CH_3)_3$	229±5	24±2	14±1	94±12	11.2±0.3
27-$(CH_2)_2NO_2$	236±5	97±2	14±1	229±12	11.2±0.3
1-CH_2CH_3	–	–	–	–	11.8[a]
1Cr-CH_2CH_3	–	–	–	–	11.5±0.6[b]

[a] Ref. 20, EFF calculations.
[b] Ref. 20, signals observed through coalescence of the chromium tricarbonyl complex of HEB.

The barriers to rotation of the ethyl groups can be divided into three different categories characterized by the nature of the substituent. The relative interaction of each position (α, β, γ) with relationship to the arene carbon can be evaluated by the variability of the barrier height with the change of steric bulk at that given position (Fig. 6). For the α position, there are three different atoms or groups: bromine in **22**, oxygen in **29**, and methylene in the remaining compounds. There is a correlation between the energy of activation and the van der Waals radius of the α position.[41,42] The van der Waals radius of oxygen is 0.55 Å smaller than those of a bromine atom and a methylene group, and the barrier for **29** is 1.6 kcal/mol lower in energy those of the other substituents. As the size of the α group increases, the barrier increases. Therefore, a group the size of a methylene unit is required to mimic **1**.

The barriers to rotation ($\Delta G^{\neq}$) were plotted against the van der Waals radii at position β (Fig. 7). The data show a direct correlation between the barrier height and van der Waals radii. The plot shows a steep rise until 1.7 Å, and then there is a grouping of compounds with similar barrier heights. The chlorine, sulfur and methylene groups have the same group to within 0.5 kcal/mol. An exception is 1,4-bis(cyanomethyl)-2,3,5,6-tetraethylbenzene (**12**) which may reflect the manner in which the van der Waals radius of the cyano group has been estimated.

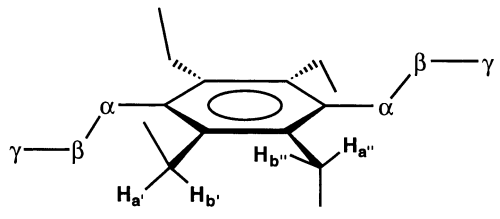


Figure 6. α, β, and γ positions of 1,4-disubstituted-2,3,5,6-tetraethylbenzenes.

A cyano group is best approximated as a cone, smaller at the carbon than at the nitrogen. The value for the carbon end of the cyano group may be overestimated because of the omnipresent nitrogen. A better estimate of steric bulk for the cyano group comes from the Taft scale, E_s.[43,44] For Cl, OMe and CN, the E_s values are −0.97, −0.55, and −0.51, respectively. Methoxy and cyano groups have essentially the same Taft parameter and barrier to rotation; the methoxy and cyano groups have the same effective steric size even though the v dW radius of the cyano group overestimates its size. This result may also explain why the 1,3,5-tris (cyanomethyl)-2,4,6-triethylbenzene exhibits a 1-up-5-down conformation in the solid state.[40]

The last position considered is the γ position. The average $\Delta G^{\neq}$ for the compounds in this grouping is 11.2±0.1 kcal/mol with a range of 0.3 kcal/mol. Because the γ group can rotate out of the way of the methyl groups, the γ group is not 'involved' in altering the energetics of the ethyl group rotation. The γ group does not affect the energetics of the ethyl group rotation but it acts as a magnetic perturbation to

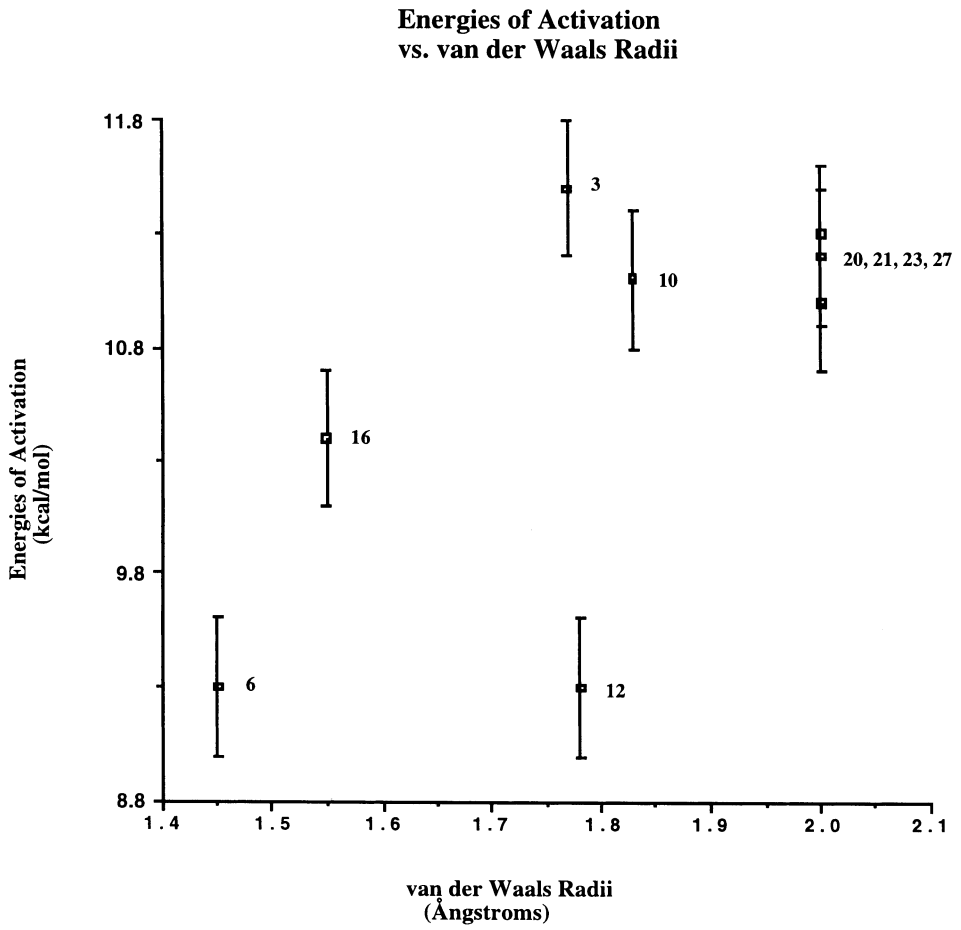


Figure 7. Plot of the free energies of activation of compounds with $-CH_2X$ substituents vs. van der Waals radii.

desymmetrize the system, except in compound **19**. With the amino group in the γ position no decoalescence is observed as the temperature is lowered. Examination of the $\Delta\nu$ values for 1,4-dimethoxy-2,3,5,6-tetraethylbenzene (**29**) vs. 1,4-bis(methoxymethyl)-2,3,5,6-tetraethylbenzene (**6**) lends an explanation for this observation. In **29**, $\Delta\nu$ is 100 Hz larger than in **6**. The value of $\Delta\nu$ is very sensitive to substituent. Since an oxygen and nitrogen have similar $\Delta\nu$ values in the β position and similar electronegativities, it is evident that the $\Delta\nu$ for **19** would be very small.

3. Conclusions

The purpose of this paper is to demonstrate how cooperative conformational networks can control the proximity of functional groups. This goal was accomplished by the design and study of the stereodynamics of sp^2–sp^3 rotations in 'surrogates' for hexaethylbenzene. From variable-temperature ^1H NMR studies of 1,4-disubstituted-2,3,5,6-tetraethylbenzenes, it was found these compounds exhibit the **a** (C_{2h}) conformation as their minimum and that the size of the group at the 1 and 4 positions greatly influences the height of the rotational energy barrier. By analogy, it is presumed that the *meta* as well as the 1,3,5-trisubstituted-2,4,6-triethylbenzene systems also adopt conformation **a** in solution. Furthermore, in the crystal, 1,4-dineohexyl-2,3,5,6-tetraethylbenzene (DNHTEB, 23) exhibits an alternating up–down configuration similar hexaethylbenzene. With the control of functional group direction and synthetic methodology in hand, these compounds can be utilized as either linear (1,4-disubstituted compounds) or angular (1,3,5-trisubstituted compounds) building blocks in supramolecular assembly.

4. Experimental

4.1. General

Proton NMR spectra were recorded on the following instruments: a Varian Unity 500, a Nicolet 1180E computer interfaced with an Oxford magnet operating at 360 MHz, a GE/Nicolet QE300, a Bruker AC 250 spectrometer. Carbon NMR spectra were recorded on a Varian Unity 500 spectrometer operating at 125.7 MHz, a QE300 spectrometer operating at 75 MHz, a Bruker AC 250 spectrometer operating at 62.9 MHz, and a Nicolet NT200 spectrometer operating at 50 MHz. Infrared spectra were recorded on a Perkin–Elmer 1420 IR spectrometer. Unless otherwise stated, commercial chemicals were used as supplied. Starting materials can be obtained from the following sources: 1,2,4-triethylbenzene (Fluka); 3-hexyne (Albany/Farchan/Wiley); iron pentacarbonyl, chromium hexacarbonyl (Strem); chloromethyl methyl ether, 3,3-dimethylbutyryl chloride, and terephthaldehyde (Aldrich). Dioxane was distilled from calcium

hydride then sodium. Benzene was distilled and then sodium. Tetrahydrofuran was distilled either from sodium or lithium aluminum hydride.

1,4-Dimethoxytetraethylbenzene (**29**) was synthesized according to the previously described procedure from 2,3,5,6-tetraethylquinone, which was reduced to the corresponding 1,4-dihydroxy-2,3,5,6-tetraethylbenzene, and then methylated to produce **29**.[25] 1,4-Bis(chloromethyl)-2,3,5,6-tetraethylbenzene (**3**) was synthesized by Friedel–Crafts acylation of 1,2,4-triethylbenzene, Wolff–Kishner reduction to produce 1,2,4,5-tetraethylbenzene and chloromethylation to yield **3**. 1,4-Bis(methoxymethyl)-2,3,5,6-tetraethylbenzene (**6**) was produced by the methanolysis of **3**. 1,4-Dineohexyl-2,3,5,6-tetraethylbenzene (**23**) was synthesized by successive alkylation of benzene with 3,3-dimethylbutyryl chloride followed by Wolff–Kishner reduction and exhaustive ethylation of the resulting 1,4-dineohexylbenzene. 1,4-Bis(4,4-dimethyl-3-oxopentyl)-2,3,5,6-tetraethylbenzene (**21**) was synthesized by reacting the trimethylsilyl-protected enolate of pinacolone with **3** using titanium tetrachloride as the catalyst. Compounds **13**,[21f] **15**,[21d] **17**,[21d,21g] and **19**[21f] were synthesized using previously reported methodologies.

4.1.1. 1,3,5-Tris(chloromethyl)-2,4,6-triethylbenzene (5). Compound **5** was synthesized according to an adapted procedure of Gambarova for chloromethylation of alkylbenzenes.[45–49] 1,3,5-Triethylbenzene (1.50 g, 9.2 mmol) was dissolved in dry dichloromethane (35 mL) at 0°C. To the swirling solution, chloromethyl methyl ether (6.79 g, 9 mL, 84.3 mmol) was added. Then, stannic chloride (21.6 g, 9.71 mL, 83 mmol) was added slowly to the precooled, swirling solution. After three h at 0–5°C, the reaction was quenched with ice water and stirred until the color changed from brown to white oil. This was then extracted with chloroform, dried with anhydrous sodium sulfate, and evaporated yielding a cream solid, which was recrystallized from ethanol. (2.12 g, 6.85 mmol, 77%) mp 144°C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.31 (9H, t, ^3J=7.6 Hz), 2.92 (6H, q, ^3J=7.6 Hz), 4.69 (s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ 16.0, 22.6, 40.6, 132.6, 144.9; Exact Mass (EI) 306.0716; calcd for $C_{15}H_{21}Cl_3$ (M^+) 306.0709.

4.1.2. 1,3,5-Tris(methoxymethyl)-2,4,6-triethylbenzene (7). 1,3,5-Tris(chloromethyl)-2,4,6-triethylbenzene (0.51 g, 1.7 mmol) was dissolved in 45 mL of methanol and heated to reflux. A solution of sodium hydroxide (0.30 g, 7.5 mmol) in water (~35 mL) was added. The reaction mixture was refluxed for 15 h. After which, the reaction was cooled and poured onto water/ice. The resulting white solid was filtered and washed with water yielding **7** (0.05 g, 0.17 mmol, 10%): mp 83–84°C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.19 (9H, t, ^3J=7.5 Hz), 2.93 (6H, q, ^3J=7.5 Hz), 3.42 (9H, s), 4.45 (6H, s); ^{13}C{^{1}H} NMR ($CDCl_3$ 62.9 MHz) δ 16.7, 23.0, 58.5, 66.9, 132.2, 145.2; Exact Mass (EI) 294.2195; calcd for $C_{18}H_{30}O_3$ (M^+) 294.2195.

4.1.3. 1,3,5-Tris(hydroxymethyl)-2,4,6-triethylbenzene (9). 1,3,5-Tris(chloromethyl-2,4,6-triethylbenzene (0.51 g, 1.7 mmol) was dissolved in acetone (50 mL) and heated to reflux. Water (25 mL) was added to the solution. The pH was tested of the solution periodically. When the solution was found to be acidic, sodium hydroxide was added (total amount: 0.36 g, 9.0 mmol). The reaction progress was also monitored via thin layer chromatography (1:9 chloroform/hexanes) until the spot for the starting material disappeared. The reaction mixture was cooled, neutralized with HCl, and poured onto ice. The product was isolated after normal aqueous workup to yield a white solid (0.20 g, 0.8 mmol, 47%) mp 158–159°C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.26 (9H, t, ^3J=7.5 Hz), 2.95 (6H, q, ^3J=7.5 Hz), 4.78 (6H, s); ^{13}C {^{1}H} NMR (acetone-d_6, 62.9 MHz) δ 17.3, 23.05, 58.7, 135.9, 144.2; IR (KBr) 3500–3050 (bs) cm^{-1}; Exact Mass (EI) 252.1732; calcd for $C_{15}H_{24}O_3$ (M^+) 252.1725.

4.1.4. 1,4-Bis(methylthiomethyl)-2,3,5,6-tetraethylbenzene (10). Compound **3** (0.50 g, 1.8 mmol) was dissolved in acetone (20 mL) and heated to reflux. A solution of sodium thiomethoxide (0.37 g, 5.2 mmol) in water (10 mL) was added. The solution was refluxed overnight. After 15 h, the reaction was cooled and poured onto water/ice and the resulting white solid was filtered and washed with water yielding **10** (0.461 g, 1.5 mmol, 85%): mp 135–136°C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.22 (12H, t, ^3J=7.6 Hz), 2.19 (6H, s), 2.77 (8H, q, ^3J=7.6 Hz), 3.74 (4H, s); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ 15.9, 16.8, 22.4, 33.5, 132.6, 139.3; Exact Mass (EI) 310.1789; calcd for $C_{18}H_{30}S_2$ (M^+) 310.1779.

4.1.5. 1,3,5-Tris(methylthiomethyl)-2,4,6-triethylbenzene (11). Compound **5** (0.51 g, 1.7 mmol) was dissolved in acetone (45 mL) and heated to reflux. A solution of sodium thiomethoxide (0.52 g, 7.4 mmol) in water (5 mL) was added. The solution was refluxed overnight. After 15 h, the reaction was cooled and poured onto water/ice. The resulting white solid was filtered and washed with water yielding **11** (0.47 g, 1.4, 81%) mp 128–129°C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.27 (9H, t, ^3J=7.5 Hz), 2.14 (9H, s), 2.81 (6H, q, ^3J=7.5 Hz), 3.75 (6H, s); ^{13}C{^{1}H} NMR ($CDCl_3$ 62.9 MHz) δ 16.1, 16.6, 22.9, 33.0, 131.6, 142.2; Exact Mass (EI) 342.1515; calcd for $C_{18}H_{30}S_3$ (M^+) 342.1510.

4.1.6. 1,4-Bis(cyanomethyl)-2,3,5,6-tetraethylbenzene (12). 1,4-Bis(chloromethyl)-2,3,5,6-tetraethylbenzene (1.0 g, 3.5 mmol) was dissolved in acetone (40 mL) and heated to reflux. Potassium cyanide (0.68 g, 10.5 mmol) was added. Then, water (~15 mL) was slowly added until the solution became turbid. Acetone (2 mL) was added, and the reaction was left to reflux overnight. After 15 h, the solution was poured onto ice water (100 mL) and the product precipitated out as a white powder. This solution was filtered yielding **12** (0.84 g, 3.1 mmol, 89%): mp 197–199°C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.22 (12H, t, ^3J=7.6 Hz), 2.73 (8H, q, ^3J=7.6 Hz), 3.69 (4H, s); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ 14.9, 17.7, 22.9, 118.3, 127.7, 139.4; IR (KBr) 2238 cm^{-1}; Exact Mass (EI) 268.1940; calcd for $C_{18}H_{24}N_2$ (M^+) 268.1944.

4.1.7. 1,3,5-Tris(cyanomethyl)-2,4,6-triethylbenzene (13). Compound **5** (0.70 g, 2.3 mmol) was dissolved in acetone (60 mL) and heated to reflux. Sodium cyanide (0.50 g, 10.2 mmol) was added. Then, 25 mL of water was added

slowly until the solution became turbid. Acetone (2 mL) was added, and the reaction was left to reflux overnight. After 15 h, the solution was poured onto ice water (100 mL), and the product precipitated out as a white powder which was filtered and recrystallized from absolute ethanol yielding 1,3,5-tris(cyanomethyl)-2,4,6-triethylbenzene (0.60 g, 2.0 mmol, 88% yield): mp 220–222°C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.24 (9H, t, ^3J=7.6 Hz), 2.83 (6H, q, ^3J=7.6 Hz), 3.88 (6H, s); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ 14.3, 17.8, 24.0, 117.1, 126.8, 142.6; IR (KBr) 2248 cm^{-1}; Exact Mass (CI) 297.2065; calcd for $C_{18}H_{28}N_4$ $(M+NH_4)^+$ 297.2079.

4.1.8. 1,4-Bis(azidomethyl)-2,3,5,6-tetraethylbenzene (14). A 100 mL round-bottom flask was charged with 1,4-bis (chloromethyl)-2,3,5,6-tetraethylbenzene (0.5 g, 1.8 mmol) and acetone (35 mL), and the mixture was heated to reflux. Sodium azide (0.34 g, 5.2 mmol) was then added to the swirling solution. Water (~10 mL) was added slowly to dissolve the azide until the solution turned turbid. Acetone (3 mL) was added, and the reaction was refluxed overnight. After 16 h, the reaction mixture was quenched with ice water (100 mL). After normal aqueous workup, the reaction yielded 1,4-bis(azidomethyl)-2,3,5,6-tetraethylbenzene (0.393 g, 1.3 mmol, 74% yield): mp 94–96°C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.24 (12H, t, ^3J=7.6 Hz), 2.78 (8H, q, ^3J=7.6 Hz), 4.68 (4H, s); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 62.9 MHz) δ 15.7, 22.5, 48.4, 131.7, 140.2; IR (KBr) 2080 cm^{-1}; Exact Mass (CI) 300.2062; calcd for $C_{16}H_{24}N_6$ (M^+) 300.2062.

4.1.9. 1,3,5-Tris(azidomethyl)-2,4,6-triethylbenzene (15). Compound **5** (0.70 g, 2.3 mmol) was dissolved in acetone (35 mL) and heated to reflux in order to dissolve **5**. Afterwards, sodium azide (0.65 g, 10 mmol) was added. Water (approximately 10 mL) was added until the solution turned turbid. The reaction was heated to reflux overnight. After 16 h, the reaction mixture was quenched with ice water (50 mL). A white solid precipitated from this solution. The solid was recrystallized using absolute ethanol which resulted in long clear needles of **15** (0.24 g, 0.7 mmol, 70% yield): mp 65–66°C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.24 (9H, t, ^3J=7.6 Hz), 2.85 (6H, q, ^3J=7.6 Hz), 4.49 (6H, s); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 62.9 MHz) δ 15.7, 23.1, 47.9, 130.0, 145.0; IR (KBr) 2080 cm^{-1}; Exact Mass (CI) 345.2276; calcd for $C_{15}H_{25}N_{10}$ $(M+NH_4)^+$ 345.2264.

4.1.10. 1,4-Bis(aminomethyl)-2,3,5,6-tetraethylbenzene (16). To a swirling solution containing 1,4-bis(azidomethyl)-2,3,5,6-tetraethylbenzene (0.39 g, 3.1 mmol) dissolved in 20 mL of dry tetrahydrofuran and cooled to 0°C, lithium aluminum hydride (0.30 g, 7.9 mmol) was slowly added. The reaction mixture was heated at reflux overnight. After 17 h, the reaction was neutralized with dilute hydrochloric acid (10%). The resulting solution was evaporated in vacuo yielding a white solid, which consisted of lithium salts, and product. The solid was triturated with ether and filtered. The ether layer was dried over anhydrous magnesium sulfate and evaporated yielding **16** (0.12 g, 0.48 mmol, 37%): mp 132–135°C; ^{1}H NMR (freon-d_1, 500 MHz) δ 1.58 (12H, t, ^3J=7.6 Hz) 2.25 (8H, q, ^3J=7.6 Hz), 3.78 (4H, s); $^{13}C\{^1H\}$ NMR (CD_3OD, 125 MHz) δ 16.6, 23.2, 39.7, 138.4, 140.1; IR (KBr) 3440, 3340, 3290 cm^{-1}.

4.1.11. 1,3,5-Tris(aminomethyl)-2,4,6-triethylbenzene (17). Compound **15** (2.0 g, 1.0 mmol) dissolved in dry tetrahydrofuran (100 mL). Lithium aluminum hydride (0.50 g, 13.2 mmol) was slowly added to the swirling mixture, and the reaction mixture was heated at reflux overnight. After 17 h, the reaction was cooled and quenched with dilute hydrochloric acid (until gas evolution ceased). The resulting solution was evaporated in vacuo resulting in a white solid, which consisted of the lithium salts, and the product. The solid was triturated with ether and filtered. The ether was dried with anhydrous magnesium sulfate and evaporated yielding **17** (0.11 g, 0.44 mmol, 44% yield): mp 127–128°C; ^{1}H NMR (CD_3OD, 250 MHz) δ 1.19 (9H, t, ^3J=7.5 Hz), 2.83 (6H, q, ^3J=7.5 Hz), 3.84 (6H, s), 4.76 (s); $^{13}C\{^1H\}$ NMR (CD_3OD, 62.9 MHz) δ 17.2, 23.7, 33.9, 137.8, 142.4; Exact Mass (CI) 250.2296; calcd for $C_{15}H_{27}N_3$ $[M+H]^+$ 250.2283.

4.1.12. 1,4-Bis(2′-aminoethyl)-2,3,5,6-tetraethylbenzene (18). Tetrahydrofuran was predried over calcium hydride, dried over sodium, and finally distilled from lithium aluminum hydride. A two-necked 50 mL round bottom flask was fitted with a reflux condenser and a septum then placed in an ice bath. Borane–tetrahydrofuran complex (1.0 M, 28 mL, 28.5 mmol) was added to the flask.[28–30] After the solution was cooled to 0°C, a solution containing 1,4-bis(cyanomethyl)-2,3,5,6-tetraethylbenzene (0.50 g, 1.9 mmol) in tetrahydrofuran (15 mL) was added slowly to the swirling solution. The reaction mixture was allowed to warm to room temperature. The flask was then fitted with a heating mantle, and the solution was refluxed. As the temperature increased, hydrogen evolved. The temperature was regulated so that the hydrogen evolution was constant but not too vigorous. After 40 h, the reaction was cooled to room temperature, and 6 M HCl (10 mL) was added to the flask. The mixture was heated until gas evolution subsided. The tetrahydrofuran was removed in vacuo. Aqueous sodium hydroxide solution was added and the aqueous layer was washed with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate and removed yielding a white solid, **18** (0.30 g, 1.1 mmol, 57%): mp 121–123°C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.18 (12H, t, ^3J=7.2 Hz), 2.63 (8H, q, ^3J=7.2 Hz), 2.75 (4H, m) 2.88 (4H, m); $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz) δ 16.0, 21.7, 33.5, 43.6, 133.5, 137.6; IR (KBr) 3346, 3266, 3172 cm^{-1}; Exact Mass (CI) 277.2644; calcd for $C_{18}H_{34}N_2$ $[M+H]^+$ 277.2643.

4.1.13. 1,3,5-Tris(2′-aminoethyl)-2,4,6-triethylbenzene (19). Tetrahydrofuran was predried over calcium hydride, dried over sodium, and finally distilled from lithium aluminum hydride. A two-necked 50 mL round bottom flask was fitted with a reflux condenser and a septum then placed in an ice bath. Borane–tetrahydrofuran complex (1.0 M, 28 mL, 28.5 mmol) was added to the flask.[28–30] After the solution was cooled to 0°C, a solution containing 1,3,5-tris (cyanomethyl)-2,4,6-tetraethylbenzene (0.40 g, 1.35 mmol) in tetrahydrofuran (15 mL) was added slowly to the swirling solution. The reaction mixture was allowed to warm to room temperature. The flask was then fitted with a heating mantle, and the solution was refluxed. As the temperature increased, hydrogen evolved. The temperature was regulated so that the hydrogen evolution was constant but not too vigorous.

After 40 h, the reaction was cooled to room temperature, and 6 M HCl (10 mL) was added to the flask. The mixture was heated until gas evolution subsided. The tetrahydrofuran was removed in vacuo. Aqueous sodium hydroxide solution was added and the aqueous layer was washed with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate and removed yielding a white solid (0.25 g, 0.84 mmol, 63%): 220°C (dec); ^{1}H NMR (CD_3OD, 250 MHz) δ 1.19 (9H, t, ^3J=7.1 Hz), 2.68 (6H, q, ^3J=7.1 Hz), 2.89 (4H, m), 3.58 (4H, m); $^{13}C\{^1H\}$ NMR (CD_3OD, 62.9 MHz) δ 16.5, 23.5, 32.6, 43.5, 133.8, 141.2; IR (KBr) 3340, 3260 cm^{-1}; Exact Mass (CI) 292.2758; calcd for $C_{18}H_{34}N_3$ $[M+H]^+$ 292.2753.

4.1.14. 1,4-Bis(acetamidoethyl)-2,3,5,6-tetraethylbenzene (20). 1,4-Bis(aminoethyl)-2,3,5,6-tetraethyl-benzene (0.40 g, 1.4 mmol) was dissolved in dry tetrahydrofuran (30 mL) in a 3-necked 100 mL round bottom flask. The flask was fitted with an 25 mL addition funnel which contained acetyl chloride (0.20 mL, 2.93 mmol) dissolved in dry tetrahydrofuran (20 mL). To the swirling solution, triethylamine (0.205 mL, 1.5 mmol) was added, and the flask was cooled to 0°C. Half of the acetyl chloride–THF solution was added slowly to the reaction. Then, another equivalent of triethylamine (0.205 mL, 1.46 mmol) was added. The rest of the acetyl chloride–THF solution was added. The solution was slowly warmed to room temperature and left to react for 16 h. The reaction solution was washed with water, ether, chloroform, dried with sodium sulfate and evaporated yielding a white tartar-like solid. This was recrystallized with absolute ethanol yielding **20** (0.39 g, 1.1 mmol, 74%); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.16 (12H, t, ^3J=7.2 Hz), 2.0 (6H, s), 2.68 (8H, q, ^3J=7.2 Hz), 2.83 (4H, m), 3.38 (4H, m); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 15.8, 22.3, 23.3, 29.5, 40.7, 138.8, 170.1; IR (KBr) 3260, 3072, 1639 cm^{-1}; Exact Mass (EI) found 361.2848; calcd for $C_{22}H_{36}O_2N_2$ $[M+H]^+$ 361.2855.

4.1.15. 1,4-Dibromo-2,3,5,6-tetraethylbenzene (22). 1,2,4,5-Tetraethylbenzene (0.95 g, 5.0 mmol) was dissolved in carbon tetrachloride (15 mL). The solution was cooled to 0°C in an NaCl ice–salt bath. Bromine (1.07 g, 0.34 mL, 6.7 mmol) and aluminum chloride (0.73 g, 5.5 mmol) were added to the swirling solution. The ice bath was removed, and the reaction mixture warmed to room temperature. After 16 h, the solution was quenched with ice water. The organic layer was extracted with methylene chloride, washed with water, dried over anhydrous sodium sulfate, and evaporated yielding a white oily solid (0.70 g, 2.0 mmol, 40%). Compound **22** was recrystallized from ethanol: mp 106–107°C; ^{1}H NMR (freon–d_1, 500 MHz) δ 1.13 (12H, t, ^3J=7.5 Hz), 2.88 (8H, q, ^3J=7.5 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ 13.9, 28.0, 127.8, 140.6; Exact Mass (DEI) 345.9933; calcd for $C_{14}H_{20}Br_2$ (M^+) 345.9932.

4.1.16. 1,4-Bis(nitrostyryl)benzene (25). Terephthalaldehyde (6.71 g, 0.05 m), nitromethane (6.1 g, 100 mmol), and methanol (20 mL) were added to a 250 mL Erlenmeyer flask which was placed in an ice bath.[31] The mixture was stirred and the temperature was kept below 15°C. A solution of (4.2 g, 105 mmol) sodium hydroxide dissolved in water (20 mL) was diluted by ice water (10 mL). The sodium hydroxide solution was added to the stirred reaction mixture while keeping the reaction between 10 and 15°C. The compound dissolved upon addition. The white solid/solution turned clear and yellow. Methanol (2 mL) was added to the solution. After 15 min of standing, ice water (50 mL) was added to the reaction mixture. A solution of dilute hydrochloric acid (20 mL in 30 mL of distilled water) was placed in a 500 mL Erlenmeyer flask. The nitrostyrene precursor was added to the swirling solution with stirring. It was added slowly so that the solid would form and not oil out. A yellow solid precipitated upon addition. The solid was filtered and triturated with absolute ethanol yielding a yellow solid, **25** (5.2 g, 24 mmol, 47%): mp 232–235°C [Lit. 50 mp 200–230°C]; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 7.79 (4H, s), 8.34 (2H, d, J=14 Hz), 8.16 (2H, d, J=14 Hz); $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz) δ 130.3, 133.5, 137.9, 139.3; Exact Mass (DEI) 221.0566; calcd for $C_{10}H_8N_2O_4$ (M^+) 221.0562.

4.1.17. 1,4-Bis(nitroethyl)benzene (26). 1,4-Dinitrostyrene (3.0 g, 13.6 m), isopropanol (82 mL), chloroform (435 mL) and silica gel (52 g) were placed in a 1000 mL Erlenmeyer flask.[51] To the swirling suspension, sodium borohydride (4.24 g, 110 mmol) slowly was added in spatula's portions over a period of 20 min. The mixture was then stirred for another 20 min. Dilute hydrochloric acid (1%) was added to decompose the excess sodium borohydride. The mixture was filtered. The filtrate was extracted with methylene chloride, washed with brine, dried with sodium sulfate and evaporated yielding a white solid, **26** (2.8 g, 120 mmol, 92%): mp 78–80°C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 3.30 (4H, t, ^3J=7.2 Hz), 4.60 (4H, t, ^3J=7.2 Hz), 7.18 (4H, s); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 62.9 MHz) δ 32.9, 76.1, 129.2, 135.0; Exact Mass (CI) 224.0788; calcd for $C_{10}H_{12}N_2O_4$ (M^+) 224.0797.

4.1.18. 1,4-Bis(nitroethyl)-2,3,5,6-tetraethylbenzene (27). Compound **27** was synthesized by exhaustive ethylation of **26**.[52] A mixture of **26** (0.2 g, 0.9 mmol), ethyl chloride (1.72 g, 27.0 mmol, 2 mL), and aluminum chloride (0.71 g, 5.3 mmol) was stirred in a 5 mL-screwtop vial at 5°C for 18 h. The reaction was quenched with ice water. The resulting organic later was extracted with methylene chloride, dried with anhydrous sodium sulfate, and evaporated yielding and white solid, which was a mixture of starting material and product. The compound was purified on a silica gel 2000 micron prep plate with 20% ethyl acetate/80% hexanes as the eluent (0.05 g, 0.015 mmol, 1.7%): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 2.0 (12H, t, ^3J=7.2 Hz), 2.64 (8H, q, ^3J=7.2 Hz), 3.97 (4H, m), 4.49 (4H, m); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 15.8, 22.4, 27.7, 75.1, 130.7, 138.9; Exact Mass (CI) 336.2049; calcd for $C_{18}H_{28}N_2O_4$ (M^+) 336.2049.

4.1.19. 1,4-Dimethyl-2,3,5,6-tetraethylbenzene (28). *para*-Xylene (2.0 g, 19 mmol) was dissolved in ethyl bromide (20 mL, 29.2 g, 268 mmol) in a two-neck 50 mL round bottom flask fitted with a condenser and drying tube. Anhydrous aluminum chloride (1.32 g, 9.9 mmol) was added slowly while the solution bubbled and turned from clear to yellow to orange. After two hours at reflux, the solution was poured onto ice/water, extracted with methylene chloride, dried with anhydrous sodium sulfate, and evaporated yielding a white solid, **28**, which was recrystallized from absolute ethanol (0.72 g, 3.3 mmol, 17.5%): mp

114–117 °C; ^{13}H NMR ($CDCl_3$, 360 MHz) δ 1.15 (12H, t, ^3J=7.6 Hz), 2.28 (6H, s), 2.67 (8H, q, ^3J=7.6 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 14.7, 15.1, 23.0, 131.5, 138.0; Exact Mass (DEI) 218.2029; calcd for $C_{16}H_{26}$ (M^+) 218.2034.

4.2. Variable-temperature NMR measurements

All variable-temperature experiments were performed on a 500 MHz spectrometer. A chilled stream of nitrogen gas regulated the temperature. Temperatures were corrected using a calibration graph. A copper-constantan thermocouple was inserted into an NMR tube with solvent at a similar height to that of a normal sample. Thermocouple readings from inside the tube were then correlated to readings from the thermocouple mounted in the probe. This calibration was repeated from time to time. Temperatures during a given experimental run were then extrapolated from the calibration curve and the reading from the probe and the reading from the probe thermocouple. Temperature readings were accurate within 5°C. Samples were dissolved in dichlorofluoromethane-d_1,[37] transferred cold, and inserted into the probe at −35°C.

4.3. Error analysis

Following a standard propagation of error analysis on the equation, $k_c=\pi/2(\Delta\nu_{ab}{}^2+6J_{ab}{}^2)^{1/2}$, one arrives at the error in k_c. The free energy of activation is calculated from the Gutowsky–Holm approximation, $\Delta G^{\neq}{}_c=4.576T_c(10.319+\log T_c/k_c)$ cal/mol. The contribution of k to the error in $\Delta G^{\neq}{}_c$ comes through a small log term added to a large constant and is relatively small compared to the contribution from T_c. For simplicity, we have treated the term within the parentheses as being without error as compared to T_c and calculated the error in $\Delta G^{\neq}{}_c$ as directly proportional to the error in T_c.

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Appendix A. Supporting information

A.1. X-ray crystallography. Study of 1,4-dineohexyl-2,3,5,6-tetraethylbenzene 23

Crystals of 1,4-dineohexyl-2,3,5,6-tetraethylbenzene **23** were grown by dissolving **23** is ethyl acetate and diffusing hexanes into the solution. A colorless crystal of approxi-

Table A1. Summary of crystal data, intensity collection and refinement for $C_{26}H_{46}$

Formula	$C_{26}H_{46}$
Formula weight	358.6
Crystal color	Colorless
Crystal size, mm	0.18×0.21×0.32
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a=12.776 (5) Å b=10.230 (6) Å c=9.636 (5) Å β=92.50 (4)°
Volume	1258.3 (11) Å^3
Z	2
d_{calc}	0.947 g cm^{-3}
μ	3.52 cm^{-1}
Scan type	$2\theta-\theta$
Scan speed	Variable; 2.00–5.00°/min in ω
Scan range	$2°<2\theta<110°$
No. of unique reflections	1590
No. of reflections ($I>4\sigma$ (I))	1280
No. of parameters	119
R	0.0627
R_w	0.0743
Largest residual peak	0.14 eÅ^{-3}
GOF	4.56

Table A2. Atomic coordinates (×10^4) and isotropic temperature factors (Å^2×10^3) for $C_{26}H_{46}$

	X	Y	Z	$U_{(eq)}$
C(1)	4094 (2)	5699 (3)	−427 (3)	51 (1)
C(2)	4014 (2)	4601 (3)	438 (3)	51 (1)
C(3)	4924 (2)	3906 (3)	876 (2)	51 (1)
C(4)	3118 (2)	6457 (3)	−898 (3)	63 (1)
C(5)	2606 (3)	5958 (4)	−2249 (3)	83 (1)
C(6)	4837 (2)	2707 (3)	1796 (3)	61 (1)
C(7)	4699 (3)	1439 (3)	983 (3)	78 (1)
C(8)	2949 (2)	4173 (3)	923 (3)	57 (1)
C(9)	2656 (2)	4830 (3)	2271 (3)	61 (1)
C(10)	1576 (2)	4523 (3)	2797 (3)	71 (1)
C(11)	727 (3)	4992 (5)	1808 (4)	129 (2)
C(12)	1478 (3)	5164 (5)	4200 (4)	137 (2)
C(13)	1443 (4)	3061 (4)	2994 (5)	127 (2)
H(4A)	3295	7361	−1018	80
H(4B)	2618	6405	−186	80
H(5A)	1992	6459	−2505	80
H(5B)	3099	6024	−2969	80
H(5C)	2415	5058	−2129	80
H(6A)	4253	2817	2380	80
H(6B)	5461	2646	2384	80
H(7A)	4652	714	1609	80
H(7B)	4068	1491	407	80
H(7C)	5287	1319	411	80
H(8A)	2937	3242	1046	80
H(8B)	2424	4399	220	80
H(9A)	2708	5759	2151	80
H(9B)	3172	4575	2974	80
H(11A)	802	5919	1696	80
H(11B)	795	4569	927	80
H(11C)	50	4803	2153	80
H(12A)	1540	6090	4072	80
H(12B)	816	4970	4587	80
H(12C)	2034	4863	4821	80
H(13A)	1486	2631	2112	80
H(13B)	2000	2758	3614	80
H(13C)	781	2866	3380	80

Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

mately 0.18×0.21×0.32 mm^3 was chosen for X-ray structure determination. Crystal data: $C_{26}H_{46}$, M=358.6 g/mol; Monoclinic (space group $P2_1/c$); a=12.776 (5) Å, b=10.230 (6) Å, c=9.636 (5) Å, b=92.50 (4)° and V=1258.3 (11) $Å^3$. d_{calc}=0.947 mg/m^3, Z=2. X-Ray intensities were collected at 294 K on a Nicolet R3m/V diffractometer applying CuKα radiation (s=1.54184 Å). A total of 1590 independent reflections were collected with $15°<2\theta<40°$ of which 1280 with $I>4\sigma$ (I) were considered unique and observed. The structure was solved by direct methods with the SHELXTL PLUS software.† [Sheldrick, 1989 #3281] All nonhydrogens were refined anisotropically. Hydrogen atoms were included at ideal positions with U fixed isotropically at 0.08 $Å^2$. R and R_w factors after refinement were 0.627 and 0.743%, respectively. The largest peak in the final Fourier difference map was 0.14 $eÅ^{-3}$ (Tables A1–A5).

Table A3. Bond lengths (Å) for $C_{26}H_{46}$

C(1)–C(2)	1.404 (4)	C(1)–C(4)	1.521 (4)
C(1)–C(3A)	1.405 (4)	C(2)–C(3)	1.411 (4)
C(2)–C(8)	1.522 (4)	C(3)–C(6)	1.521 (4)
C(3)–C(1A)	1.405 (4)	C(4)–C(5)	1.520 (4)
C(6)–C(7)	1.521 (4)	C(8)–C(9)	1.524 (4)
C(9)–C(10)	1.524 (4)	C(10)–C(11)	1.491 (5)
C(10)–C(12)	1.513 (4)	C(10)–C(13)	1.518 (6)

Table A4. Bond angles (°) for $C_{26}H_{46}$

C(2)–C(1)–C(4)	120.3 (2)	C(2)–C(1)–C(3A)	120.1 (2)
C(4)–C(1)–C(3A)	119.5 (2)	C(1)–C(2)–C(3)	119.9 (2)
C(1)–C(2)–C(8)	120.1 (2)	C(3)–C(2)–C(8)	119.9 (2)
C(2)–C(3)–C(6)	120.0 (2)	C(2)–C(3)–C(1A)	119.9 (2)
C(6)–C(3)–C(1A)	120.0 (2)	C(1)–C(4)–C(5)	113.7 (2)
C(3)–C(6)–C(7)	113.4 (2)	C(2)–C(8)–C(9)	113.0 (2)
C(8)–C(9)–C(10)	116.8 (2)	C(9)–C(10)–C(11)	111.4 (3)
C(9)–C(10)–C(12)	108.6 (3)	C(11)–C(10)–C(12)	110.2 (3)
C(9)–C(10)–C(13)	110.7 (3)	C(11)–C(10)–C(13)	108.4 (3)
C(12)–C(10)–C(13)	107.5 (3)		

Table A5. Anisotropic displacement coefficients ($Å^2$×10^3) for $C_{26}H_{46}$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	52 (2)	52 (2)	49 (2)	−7 (1)	3 (1)	3 (1)
C(2)	52 (2)	55 (2)	46 (1)	−7 (1)	6 (1)	−2 (1)
C(3)	56 (2)	51 (2)	45 (2)	−3 (1)	7 (1)	1 (1)
C(4)	58 (2)	68 (2)	62 (2)	3 (1)	4 (1)	7 (1)
C(5)	73 (2)	100 (3)	76 (2)	9 (2)	−12 (2)	7 (2)
C(6)	64 (2)	62 (2)	57 (2)	8 (1)	8 (1)	3 (1)
C(7)	87 (2)	59 (2)	87 (2)	10 (2)	5 (2)	−2 (2)
C(8)	57 (2)	60 (2)	55 (2)	−4 (1)	4 (1)	−5 (1)
C(9)	53 (2)	73 (2)	56 (2)	−2 (1)	8 (1)	−6 (1)
C(10)	49 (2)	92 (2)	72 (2)	−2 (2)	10 (1)	−10 (2)
C(11)	61 (2)	195 (5)	130 (4)	4 (4)	10 (2)	16 (3)
C(12)	91 (3)	214 (6)	111 (3)	−43 (4)	56 (3)	−37 (3)
C(13)	120 (3)	131 (4)	135 (4)	18 (3)	47 (3)	−37 (3)

The anisotropic displacement exponent takes the form: $\exp[-2\pi^2(U_{11}h^2a*^2+U_{22}k^2b*^2+U_{33}l^2c*^2+2U_{12}hka*b*+2U_{13}hla*c*+2U_{23}klb*c*)]$.

† Sheldrick, G. M. In University of Göttingen: Göttingen 1989.

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