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# Synthesis, thermal reactivity and structure of 1,2-bis(4-hydroxy-3-methoxyphenylethynyl)benzene

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The crystal structure of the new enediyne **3** was determined by X-ray diffraction. **3** crystallizes in the orthorhombic space group P*bca* (No. 61) with $a = 12.7148(9)$ Å, $b = 7.4872(8)$ Å, $c = 38.890(4)$ Å, $\alpha = \beta = \gamma = 90^\circ$ and $Z = 8$. The three-dimensional structure is characterized by an 8-membered cyclic array linking four molecules of **3** by hydrogen bonding between phenolic and methoxy groups. Furthermore, stabilization by $\pi$–$\pi$-stacking and CH $\cdots$ $\pi$ interactions is present. The important *cd* distance (between the two terminal acetylene carbons of the enediyne) which is relevant for the Bergman cyclization, was determined to 401 pm, being in good agreement with the high cyclization barrier ($\Delta G^{\ddagger} = 147.9$ kJ mol$^{-1}$ at 220°C) that was determined by differential scanning calorimetry (DSC).

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**KEY WORDS:** Enediyne; V-shaped molecule; Bergman cyclization; Hydrogen bond; $\pi$–$\pi$-Stacking, CH $\cdots$ $\pi$ Interactions.

## Introduction

The antibacterial and antitumor properties of naturally occurring enediynes have aroused great interest.[1a] Their ability to effect highly specific DNA cleavage *via* the formation of $\sigma$-biradicals[2] is thought to be responsible for their potent activity.[1] At present, considerable research is focused on the synthesis of simple enediyne model compounds[1b–d,3] that mimic the above property under physiological conditions. While simple acyclic enediynes can cleave DNA photochemically, [4] their thermal Bergman cyclization with ensuing DNA cleavage will require substantial heating. *En route* to investigate the influence of the substitution at enediynes we decided to prepare enediyne **3**. Herein, we describe the preparation, thermal reactivity and interesting solid state structure of the hitherto unknown compound.

## Synthesis

4-Bromo-2-methoxyphenol was converted into the trimethylsilylalkynyl-substituted compound **1** using Sonogashira coupling conditions.[5] After the removal of the trimethylsilyl group by potassium hydroxide, the resulting 4-ethynyl-2-methoxyphenol (**2**) was coupled with half an equivalent of 1,2-diiodobenzene to form the enediyne **3** (Scheme 1).

## Experimental

4-Bromo-2-methoxyphenol was purchased from Lancaster and trimethylsilylacetylene from

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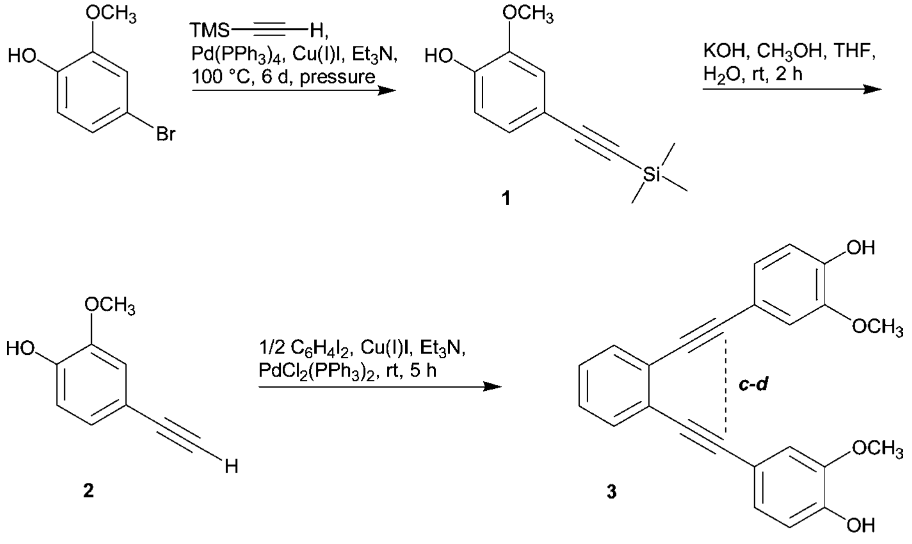

**Scheme 1.** Synthesis of the enediyne **3**.

Aldrich. DSC measurements were done on a DSC7 of Perkin Elmer at heating rates of 10°C min$^{-1}$.

### *Synthesis of* 1

Under nitrogen atmosphere 4-bromo-2-methoxyphenol (2.40 g, 11.8 mmol), copper(I) iodide (462 mg, 2.43 mmol) and tetrakis(triphenylphosphine)palladium(0) (1.40 g, 1.21 mmol) were suspended in anhydrous triethylamine (40 mL) and placed in a sealing tube. Then trimethylsilylacetylene (4.84 g, 49.3 mmol, 6.34 mL) was added and the reaction mixture was allowed to stir at 100°C for a total of 6 d. The mixture was concentrated, the remaining residue dissolved in dichloromethane (150 mL), washed twice with a 2.5% aq. potassium cyanide solution (70 mL) and three times with water (70 mL). Evaporation of the solvent and chromatographic purification on silica gel furnished a slightly brown solid that was purified by sublimation at 100°C under reduced pressure. The 2-methoxy-4-trimethylsilylethynylphenol (**1**) (2.04 g, 9.26 mmol, 78%) was received as colorless crystals. TLC ($CH_2Cl_2$/petrolether(30/50), 1:1): $R_f = 0.2$. M.p: 93°C. IR(NaCl, $\tilde{\nu}$/cm$^{-1}$): 3384 (m, O—H), 2958 (m, C—H), 2152 (m, C≡C), 1594 (m, O—$H_{\text{deform.}}$), 1511 (s), 1454 (m), 1248 (s, C—O), 1157 (m), 1118 (m), 1031 (m), 939 (w), 848 (s). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.23 (s, 9H), 3.88 (s, 3H), 5.72 (s, 1H), 6.82 (d, $^3J = 8.1$ Hz, 1H), 6.95 (d, 1H, $^4J = 1.8$ Hz), 7.02 (dd, $^3J = 8.1$ Hz, $^4J = 1.8$ Hz, 1H). $^{13}$C NMR (63 MHz, $CDCl_3$): $\delta$ 0.02, 55.9, 91.9, 105.4, 114.1, 114.4, 114.7, 126.0, 145.8, 146.4. Anal. for $C_{12}H_{16}O_2Si$ (220.3): Calcd. C 65.43, H 7.33. Found C 65.12, H 7.30.

### *Synthesis of* 2

2-Methoxy-4-trimethylsilylethynylphenol (**1**) (188 mg, 853 $\mu$mol) was dissolved in a mixture of methanol (2 mL) and tetrahydrofuran (2 mL). A solution of potassium hydroxide (500 mg) in water (2 mL) was added and the mixture was stirred at ambient temperature for 2 h. The solution was neutralized with 1 M hydrochloric acid, treated with diethyl ether (20 mL), and the aqueous layer was extracted three times with ether (15 mL). The combined organic layers were dried over magnesium sulfate and the solvent was removed under reduced pressure at ambient temperature. 4-Ethynyl-2-methoxyphenol (**2**) (126 mg, 852 $\mu$mol, >99%) was received as an orange-brown oil and was used for the next step without further purification. TLC ($CHCl_3$/*n*-hexane): $R_f = 0.3$. IR (NaCl, $\tilde{\nu}/cm^{-1}$): 3389 (s, O—H), 3286 (s, C≡CH), 2919 (s, C—H), 2097 (w, C≡C), 1593 (s, $O{-}H_{deform.}$), 1511 (s), 1455 (m), 1419 (m), 1373 (m), 1274 (s), 1237 (m, C—O), 1202 (m), 1143 (m), 1121 (s), 1032 (s), 855 (w), 820 (w), 791 (w). $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.97 (s, 1H), 3.88 (s, 3H), 6.84 (d, $^3J = 8.1$ Hz, 1H), 6.97 (d, $^4J = 1.7$ Hz, 1H), 7.04 (dd, $^3J = 8.1$ Hz, $^4J = 1.7$ Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 63 MHz): $\delta$ 56.0, 75.3, 76.5, 113.6, 114.3, 114.5, 126.2, 146.1, 146.6. Anal. for $C_9H_8O_2$ (148.2): Calcd. 148.0524. Found 148.0520 (HRMS).

### *Synthesis of* **3**

1,2-Diiodobenzene (125 mg, 379 $\mu$mol, 50.0 $\mu$l) was added under nitrogen to a suspension of copper(I) iodide (7.40 mg, 38.9 $\mu$mol) and bis(triphenylphosphine)palladium(II) chloride (13.3 mg, 18.9 $\mu$mol) in anhydrous triethylamine (1.5 mL). After the addition of 2-methoxy-4-ethynylphenol (126 mg, 850 $\mu$mol) in anhydrous triethylamine (2 mL) the reaction mixture was allowed to stir for 5 h at ambient temperature. The solvent was evaporated under reduced pressure, the remaining residue was dissolved in dichloromethane (25 mL) and the organic layer was washed twice with an 1% aq. potassium cyanide solution (20 mL) and three times with water (20 mL). After drying over magnesium sulfate and evaporation of the solvent, the crude product was purified by column chromatography on silica gel. The fraction (TLC [$CH_2Cl_2$]: $R_f = 0.1$) causing a fluorescent spot on the TLC was isolated and purified by recrystallization from chloroform. 1, 2-Bis(4-hydroxy-3-methoxyphenylethynyl)benzene (**3**) was received (60.0 mg, 162 $\mu$mol, 43%) as colorless crystals. M.p. 123°C. IR (NaCl, $\tilde{\nu}/cm^{-1}$): 3510 (m, O—H), 2938 (w, C—H), 2204 (w, C≡C), 1590 (m, C—H), 1514 (s, CH), 1451 (m), 1418 (m), 1317 (m), 1255 (s, C—O), 1206 (m), 1118 (m), 1031 (m). $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 3.79 (s, 6H), 5.76 (s, 2H), 6.86 (d, $^3J = 8.1$ Hz, 2H), 7.03 (d, $^4J = 1.8$ Hz, 2H), 7.13 (dd, $^3J = 8.1$ Hz, $^4J = 1.8$ Hz, 2H), 7.27 (m, 2H), 7.51 (dd, 2H). $^{13}C$ NMR ($CDCl_3$, 63 MHz): $\delta$ 55.9, 86.8, 93.8, 113.9, 114.5, 115.0, 125.6, 126.0, 127.7, 131.3, 146.2, 146.4. Anal. for $C_{24}H_{18}O_4$ (370.4): Calcd. 370.1205. Found 370.1200 (correct HRMS).

### *X-ray crystallography*

X-ray diffraction intensity collection was carried out with graphite-monochromatized MoK$\alpha$ radiation on an Enraf-Nonius-CAD4 diffractometer (filter factor 15.41, $\lambda = 0.71073$ Å). Crystal data and details of measurement and refinement are summarized in Table 1. According to the $\mu \times r < 0.05$ criterion, no absorption correction had to be applied. The crystal structure was solved by direct methods (Program SHELXS 97) in the space group P*bca* (Nr. 61).[6] The hydrogen atoms were included in idealized positions coupled to their respective carbon atoms. Least-squares cycles for the structure refinement (Program SHELXL 97)[6] with 258 parameters and 3253 used reflections resulted in a reflex/parameter ratio of 13/1. The refinement converged at $R_1(\mathbf{3}) = 0.0450$, $wR_2 = 0.0975$.

## Discussion

Enediyne **3** (Pearson symbol *o*P368) crystallizes in the orthorhombic system in the space group P*bca* with eight molecules in the unit cell. All atoms of **3** (Fig. 1) are placed on general positions 8*c* (1). Along [100] the crystal displays a layer structure (Fig. 2), which is stabilized by hydrogen bonds (Fig. 3) and by aromatic $\pi$–$\pi$-interactions (Fig. 4).

**Table 1.** Crystal Data and Structure Refinement Details for **3**[a,b]

| Parameter | **3** |
|---|---|
| Empirical formula | $C_{24}H_{18}O_4$ |
| Crystal dimension/mm$^3$ | $0.4 \times 0.2 \times 0.2$ |
| $M$ | 370.38 |
| Crystal system | Orthorhombic |
| Space group | P*bca* |
| $a$(Å) | 12.7148(9) |
| $b$(Å) | 7.4872(8) |
| $c$(Å) | 38.890(4) |
| $V$/nm$^3$ | 3.7022(6) |
| $Z$ | 8 |
| $T$/K | 293(2) |
| $D_c$/Mg m$^{-3}$ | 1.329 |
| λ(Å) | 0.71073 |
| $\mu$(mm$^{-1}$) | 0.090 |
| $F$(000) | 1552 |
| $\theta$ Range for data collection/° | 2.09–24.98 |
| Limiting indices | $0 \le h \le 15, 0 \le k \le 8,$ $-46 \le l \le 46$ |
| Reflections collected | 6440 |
| Independent reflections | 3253 |
| Completeness to $\theta = 24.98$ | 99.9 |
| Max., min. transmission | 0.9822, 0.9648 |
| Data, restraints, parameters | 3253, 0, 258 |
| Goodness-of-fit on $F^2$ | 1.038 |
| Final R indices [$I > 2\sigma(I)$] | $R_1 = 0.0450, wR_2 = 0.0975$ |
| R indices (all data) | $R_1 = 0.0925, wR_2 = 0.1222$ |
| Extinction coefficient | 0.0043(5) |
| Largest diff. peak and hole/e Å$^{-3}$ | 0.183 and −0.159 |

[a] Full-matrix, least squares refinement on $F^2$.
[b] See here for full crystallographic data (CCDC 236788).

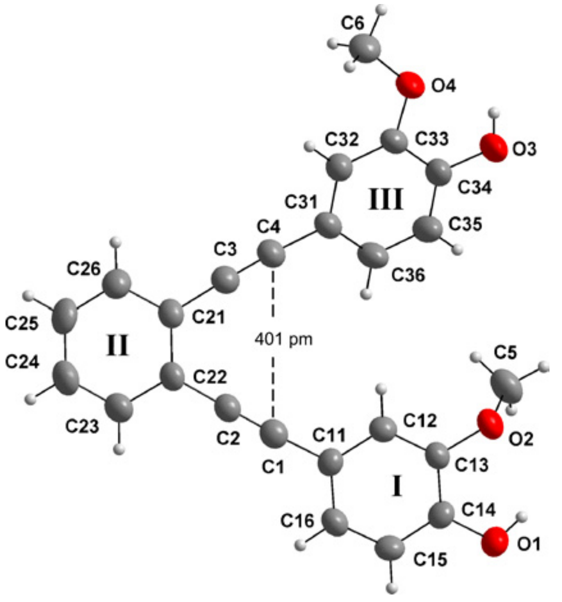

**Fig. 1.** Structure of enediyne **3**. Distance provided in pm. Thermal ellipsoids are drawn at the 50% probability level.

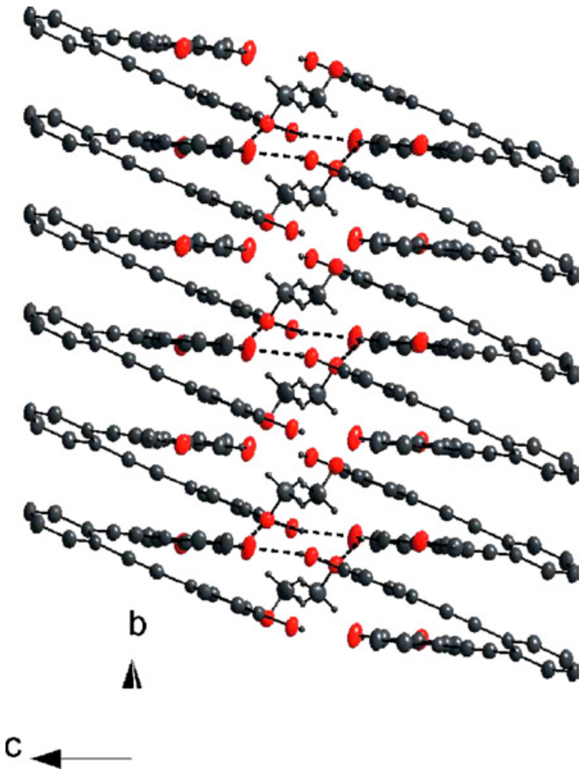

**Fig. 2.** Crystal system along [100].

The solid state structure of enediyne **3** exhibits a remarkable inter- as well as intramolecularly hydrogen bonded 8-membered array (Fig. 3) in which phenolic and methoxy groups are engaged. The pivotal hydrogen bonding pattern is formed by four molecules of **3**, each of which participates with only one of its two 2-hydroxyanisole units. Two molecules of **3** use the methoxy and hydroxy groups in the hydrogen bonding, while the two remaining molecules participate only with their hydroxy group. For the former molecules, the methoxy group acts as an acceptor and the hydroxy group as a donor giving rise to a bifurcated hydrogen bonding. For the latter molecules the hydroxy group acts as both donor and acceptor. Based on Etter[7] classification the OH···O hydrogen bonded ring structure

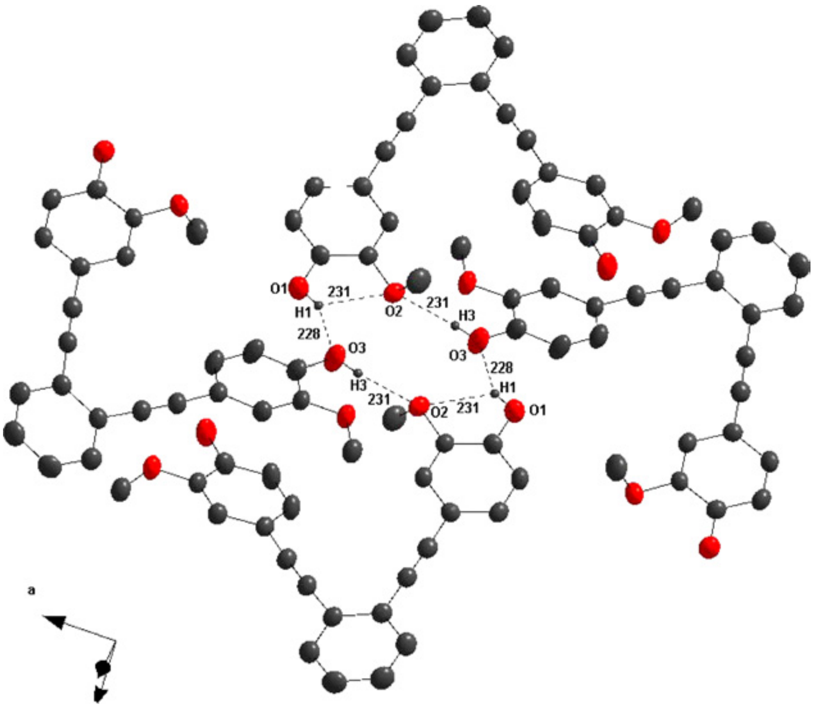

**Fig. 3.** Picture depicting the tetramer formed by bifurcated hydrogen bonding leading to an 8-membered cyclic array. Distances are provided in pm. Further distances and angles are furnished in Table 2.

could be assigned to the graph set designation $R_4^4$ (8).

Hydrogen bonding involving the methoxy groups results in intermolecular MeO···HO (231.3(2) pm) and intramolecular MeO···HO (231.4(2) pm) interactions of similar strength. In contrast, the ···HO···HO hydrogen bonding interaction between hydroxy groups was slightly stronger (227.6(2) pm).

Interestingly, the two molecules that are only involved with their hydroxy groups in the central hydrogen bonding pattern have their

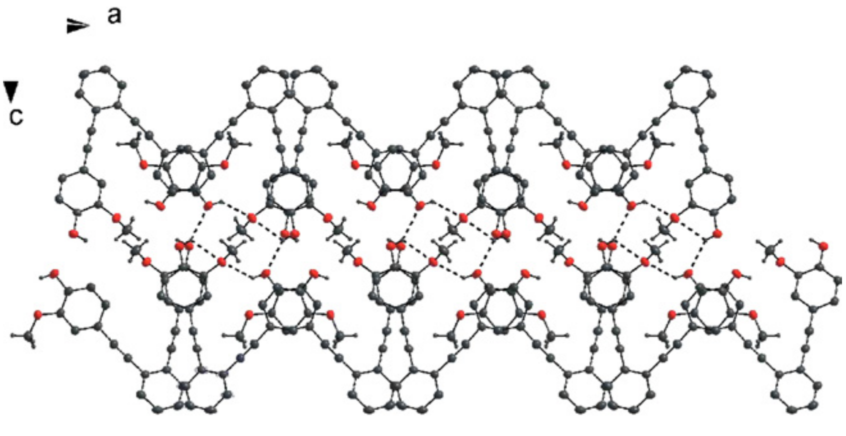

**Fig. 4.** Crystal system along [010] with a look at the hydrogen bonded 8-membered array.

*ortho*-methoxy group participating in moderate to weak intramolecular $\mathrm{CH}\cdots\pi$ interactions with their two phenylalkyne units (310.8, 322.8, 304.2, 324.0(3) pm).

Moreover, the aromatic subunits are arranged in a coplanar $\pi$–$\pi$-stacking fashion with an average inter-planar distance of 3.7 Å. To realize this arrangement the aromatic systems are twisted by about 20° (Fig. 4).

Because of nonlinear acetylene groups the V-shaped molecule differs from the ideal geometry ($\angle$C2−C1−C11 = 177.35(25)°, $\angle$C22−C2−C1 = 179.07(25)°, $\angle$C4−C3−C21 = 178.06(25)° and $\angle$C31−C4−C3 = 176.3(26)°) (Table 2). The phenyl rings within **3** are not coplanar ($\angle$C(36)−C(31)−C(21)−C(22) = 24.06(25)° and $\angle$C(21)−C(22)−C(11)−C(12) = 12.64(21)°) but nevertheless furnish a distinct delocalized $\pi$-system. The distance between the two terminal acetylenic carbon atoms C1 and C4 (Fig. 1: called *cd* distance in enediynes) was determined to 401 pm. It is much longer than the *cd* distance (344 and 350 pm) of analogous benzoenediynes that are incorporated into 11-membered ring systems,[8] while it is comparable to that of other acyclic diphenylsubstituted enediynes (*cd* distances 377–423 pm).[9]

Like other diaryl substituted benzoenediynes **3** is expected to undergo Bergman cyclization at elevated temperature.[8–10] Indeed, differential scanning calorimetry (DSC) measurements indicated a cyclization onset temperature of 189°C,

**Table 2.** Selected Bond Distances (pm) and Angles (°) of **3**

| | | | |
|---|---|---|---|
| Phenyl-I | | Phenyl-II | |
| O(1)−C(14) | 136.5(2) | O(3)−C(34) | 137.1(3) |
| O(2)−C(13) | 139.5(2) | O(4)−C(33) | 136.6(3) |
| O(2)−C(5) | 142.8(3) | O(4)−C(6) | 142.5(3) |
| C(11)−C(16) | 139.2(3) | C(21)−C(26) | 139.5(3) |
| C(11)−C(12) | 139.4(3) | C(21)−C(22) | 140.5(3) |
| C(12)−C(13) | 137.2(3) | C(22)−C(23) | 139.5(3) |
| C(13)−C(14) | 137.9(3) | C(23)−C(24) | 137.2(3) |
| C(14)−C(15) | 138.0(3) | C(24)−C(25) | 137.9(4) |
| C(15)−C(16) | 137.8(3) | C(25)−C(26) | 137.7(3) |
| Phenyl-III | | Acetylene-bridge | |
| C(31)−C(36) | 138.4(3) | C(1)−C(2) | 119.7(3) |
| C(31)−C(32) | 139.9(3) | C(3)−C(4) | 119.0(3) |
| C(32)−C(33) | 137.6(3) | C(4)−C(31) | 143.7(3) |
| C(33)−C(34) | 139.0(3) | C(1)−C(11) | 143.2(3) |
| C(34)−C(35) | 137.3(3) | C(2)−C(22) | 143.5(3) |
| C(35)−C(36) | 137.5(3) | C(3)−C(21) | 143.5(3) |
| | | C(1)−C(4) | 401.1(3) |
| Angles | | | |
| C(2)−C(1)−C(11) | 177.35(25) | C(4)−C(3)−C(21) | 178.06(25) |
| C(22)−C(2)−C(1) | 179.07(25) | C(31)−C(4)−C(3) | 176.3(26) |
| C(22)−C(21)−C(3) | 120.3(2) | C(21)−C(22)−C(2) | 120.6(2) |
| ∠(I, II) | 12.64(21) | ∠(II, III) | 24.06(25) |
| ∠(I, III) | 38.61(20) | | |
| Angles of bifurcated hydrogen bonds | | O···O distances | *d*(O···O) |
| O(2)···H(1)···O(3) | 99.07(6) | O2···O3 | 291.7(2) |
| H(1)···O(2)···H(3) | 143.80(7) | O1···O2 | 275.4(2) |
| | | O1···O3 | 298.8(2) |
| H-bonds[a] | *d*(O−H) | | |
| O2···H1 | 231.4(2) | | |
| O2···H3 | 231.3(2) | | |
| O3···H1 | 227.6(2) | | |

[a] Symmetry operators: 1) $x + \frac{1}{2}, y - \frac{1}{2}, z$; 2) $-x + 1, y - 1, -z + \frac{1}{2}$; 3) $-x + \frac{1}{2}, y + \frac{1}{2}, -z + \frac{1}{2}$.

being in good agreement with thermal cyclization conditions for related systems. Closer inspection of the DSC[11] data allowed to derive an activation barrier $\Delta G^{\ddagger} = 147.9$ kJ mol$^{-1}$ at 220°C.

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