Letter

Thieno[3.3]orthocyclophanes: preparations and structures†

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Rigid, layered hetareno/hetareno- and hetareno/areno-cyclophanes with closely held, non-distorted, interacting π-systems can be synthesized easily by using various building blocks.

Molecules with closely held face to face π-systems have elicited much interest in recent years, in part due to the attractiveness of such systems in the study of π–π interactions but also due to the fact that these compounds have at least partial rigidity and can exhibit cavities for catalytic activity.[1] While first examples of the former type were found in the smaller para-[2] and meta-cyclophanes,[3] other systems have been devised and synthesized[4] which do not show the effects due to the aromatic ring distortion common to para-[5] and meta-cyclophanes,[3] effects which complicate the study of the interaction of π-systems. Most of the few examples of non-distorted aromatic systems held in parallel at a close distance belong to the family of orthocyclophanes,[6] one such class of molecules being the bisareno-annelated bicyclo[4.4.1]undecanones and their derivatives.[7] Here, a simple synthesis of layered hetareno/hetareno- and hetareno/areno-orthocyclophanes of this type is presented and their physical properties are discussed.

The synthetic strategy uses bis(chloromethyl)-substituted arenes and hetarenes as building blocks in the synthesis of layered [3.3]orthothiophenophanes (Scheme 1). While we deem all combinations possible, only the syntheses of the block pairs **A**/**B**, **A**/**E**, **D**/**E** and **A**/**C** (≡**B**/**D**) have been carried out thus far. An α,β-bis(halomethyl)substituted arene or hetarene is coupled to dimethyl acetone-1,3-dicarboxylate (DMADC) to give either the symmetrically annelated dimethyl bicyclo[4.4.1]undeca-3,8-dien-11-one dicarboxylate with a ratio of the addend **A** to DMADC of 1.75 : 1.00, as in the case of **1a**,[8] or to give the known dimethyl[2,3-*d*]cyclohepten-3-one-2,4-dicarboxylate **E**.[7] Both reactions are run in two-phase systems under phase transfer catalysis [PTC, tetrabutylammonium bromide (TBABr) as catalyst]. However, in the case of double annelation leading to symmetrically annelated systems, strongly basic conditions (24 wt% NaOH) are used, while in the preparation of mono-annelated compounds less harsh conditions (5–8 wt% aq. Na_2CO_3) are employed. For the mixed annelated systems, a mono-annelated compound such as **B**, **C** or **E** is reacted in a subsequent step with either 3,4-bis(chloromethyl)-2,5-dimethylthiophene (**A**)[9] or methyl 4,5-bis(chloromethyl)thiophene-2-carboxylate (**D**)[10] to give the non-symmetrically annelated bicyclo[4.4.1]undeca3,8-dien-11-ones **A**/**E**, **D**/**E** and **B**/**D** (≡**A**/**C**), **1b**–**d**. The esters **1** are hydrolysed to the corresponding carboxylic acids with ethanolic KOH in refluxing ethanol. The carboxylic acids can be decarboxylated for the most part cleanly to **2**. For pyrolysis of the corresponding acids of **1c** and **1d**, though, the yields are moderate and especially in the reaction of the triacid of **1d** a substantial amount of polymeric material can be found. The carboxylic group at C-5′ in these substrates is more resistant towards thermolysis than the carboxylic groups at the bridgeheads, so that in the decarboxylation also the monocarboxylic acids of **2d** and **2f** can be isolated. A slight decrease in pyrolysis temperature gives the monocarboxylic acids in an appreciable amount. Subsequently these carboxylic acids have been converted with diazomethane[11] to the methyl carboxylates **2d** and **2f**. In all cases simple acetalization of the ketones with ethylene glycol furnishes the acetals **3**.§

The ketones **2** exist in a number of interconvertible conformers. At room temperature the bridge methylene protons of **2a** show a very broad signal centred at δ 2.9. Cooling leads to freezing of the molecule in one conformation. NMR measurements at −50 °C show **2a** to be solely in a chair–boat conformation as can be inferred by comparison with similar molecules. The methylene protons appear as two pairs of doublets and two signals are found for the methyl groups on the thienyl units, one singlet for each pair of methyl groups on each thiophene ring. While the ketones **2** are flexible molecules, the acetals **3** are rigid and the aromatic/heteroaromatic rings are held face to face. In the crystal, this is evidenced by an X-ray structural analysis of **3a** (Fig. 1),¶ which shows the distance between the thienyl systems to be in the range 310 (closest proximity) to 432 pm. While a small variation in distance can occur within this cyclophane series, the distance is determined by the bridging of the phane and to only a neglible degree by the electron density of the π systems themselves and the distance determined for **3a** seems to be a viable value for all thienophanes **3** studied. The angle deviation from coplanarity of the two thienyl units is 28.9°.[12] Owing to the closeness of the heteroaromatic/aromatic ring systems, a number of physical effects can be noted due to π–π interaction and electronic anisotropies of the respective underlying ring system. In solution, a significant high field shift is observed by ^{1}H NMR for the aromatic protons and for the heteroaromatic protons of the acetals as compared to the respective ketones (Fig. 2), as exemplified in **3c** *cf.* **2c** [δ_H 6.81–6.86 (**3c**) *cf.* δ 7.09 (**2c**), for the benzo protons; δ_H 6.25 and 6.48 (**3c**) *cf.* 6.95 and

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† Dedicated to Professor Armin de Meÿere on the occasion of his 60th birthday.

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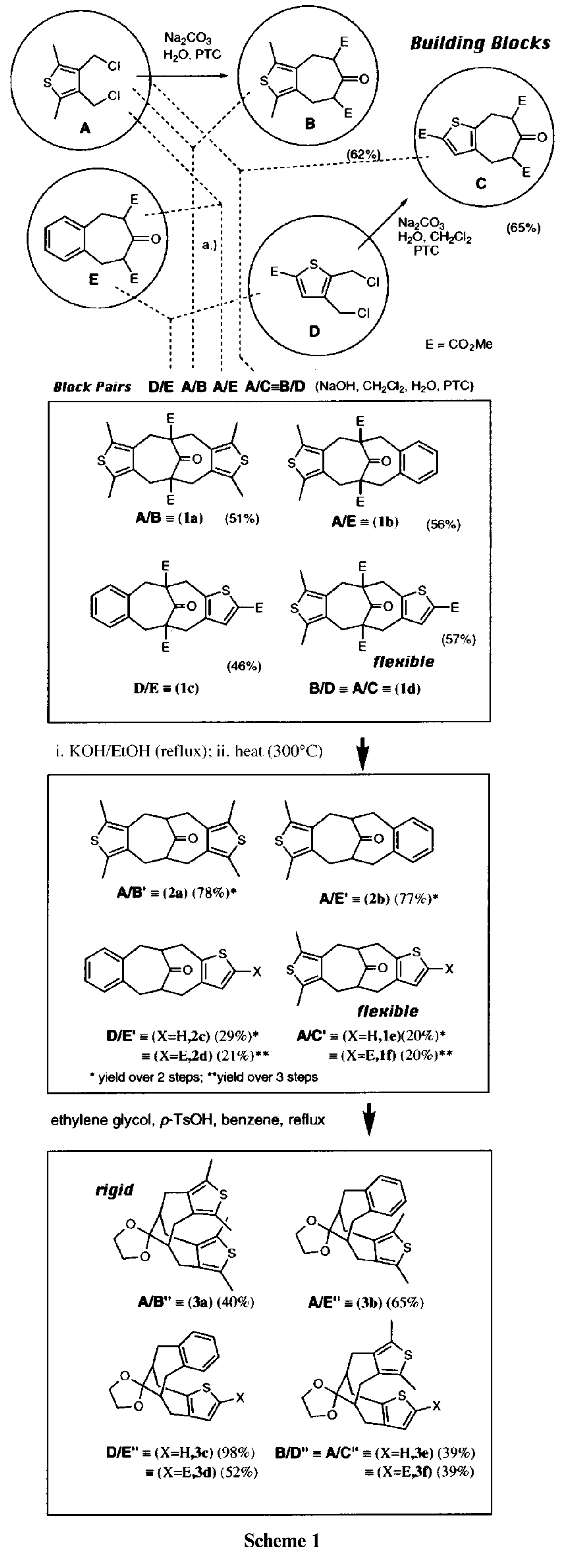

Scheme 1

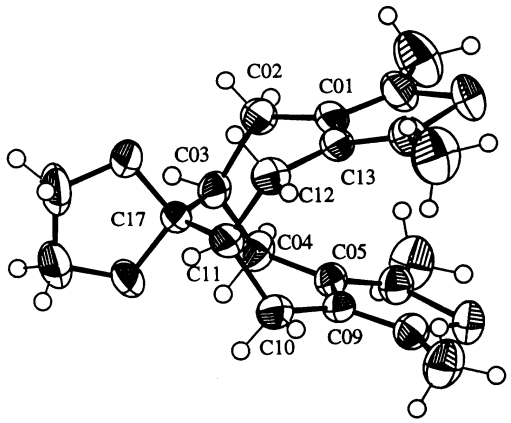

Fig. 1 X-Ray crystal structure of **3a**. Selected bond angles (°): C(11)–C(12)–C(13) 117.8(2), C(09)–C(10)–C(11) 119.3(2), C(03)–C(04)–C(05) 117.8(2), C(01)–C(02)–C(03) 118.2(2).

7.70 (**2c**, for the thieno-protons)]. This high field shift can be attributed to the magnetic anisotropy due to the facing π system, as may be found in other, similar aromatic compounds.[6,7] Another comparable series is given by methyl 4,5-dimethylthiophene-2-carboxylate **4b**[13] ($\delta_{H\text{-}3}$ 7.50), **3f** ($\delta_{H\text{-}3}$ 7.19) and **3d** ($\delta_{H\text{-}3}$ 6.91).[14] While the anisotropy of an underlying dimethylthieno group produces a shift of $\Delta\delta_{H\text{-}3} = 0.28$ ppm, an exchange for a benzo group provides a further shift of $\Delta\delta_{H\text{-}3} = 0.31$ ppm. These results seem to indicate that systems of the general type **3** can be valuable tools for evaluating the aromaticity of certain annelated ring systems as characterised by the ring current of the ring system to be analysed.

For **3a**, which has no protons as substituents on the thienyl ring systems, the assignment of the conformation in solution has to be based solely on UV spectroscopy. The UV spectra of some of the thiophenophanes **2** and **3** are shown in Fig. 3. For comparison, the UV spectra of 2,3-dimethylthiophene **4a** (λ_{max} 242 nm), methyl 4,5-dimethylthiophene-2-carboxylate **4b**, and 2,3,4,5-tetramethylthiophene **4c** have been measured. In the monomethyl carboxylates **2d** and **3f** a new absorption band appears at λ 288 nm (**2d**) and at 310 nm (**3f**), respectively. This second band has been well documented for other thiophenes with a carbonyl substituent at C-2.[15] When comparing the absorption maxima of the [3.3]orthothienophane ketone **1f** (λ_{max1} 250 nm, λ_{max2} 288 nm) with methyl 4,5-dimethylthiophene-2-carboxylate **4b** (λ_{max1} 254 nm, λ_{max2} 289 nm) and 2,3,4,5-tetramethylthiophene **4c** (λ_{max} 242 nm), it is evident that in **1f** the two thienyl units show no observable electronic interaction. In the [3.3]orthothienophane acetal **3f**, on the other hand, a significant bathochromic shift of λ_{max} is observable. This is a good indication that in **3f** the two thienyl units no longer act independently.

Notes and references

§ *Representative experimental procedures:* **1a**: to a vigorously stirred mixture of NBu$_4$Br (TBABr, 2.2 g, 6.8 mmol), aqueous 24 wt% NaOH (40 mL) and 3,4-bis(chloromethyl)-2,5-dimethylthiophene **A** (5.0 g, 24 mmol) in CH$_2$Cl$_2$ (40 mL) was added dropwise dimethyl acetone-1,3-dicarboxylate (2.5 g, 14 mmol) in CH$_2$Cl$_2$ (30 mL). The solution was stirred at room temp. for 24 h. The phases were separated, the organic phase was washed successively with a dilute aqueous HCl solution (20 mL) and with water (2 x 15 mL). The organic phase was dried over anhydrous MgSO$_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (diethyl ether–hexane, 1 : 2) to give **1a** (2.71 g, 51%) as colorless crystals; mp 215–216 °C (diethyl ether–hexane, 1 : 1); IR (KBr) *v* 2898, 2880, 2839, 1742, 1700, 1438, 1280, 1254, 1220, 1149, 1098, 1055, 998, 958, 822, 740, 696 cm^{-1}; ^{1}H NMR (270 MHz, CDCl$_3$, 293 K) δ 2.33 (s, 12H), 2.96 (br s, 8H), 3.75 (s, 6H, 2 x CO$_2$CH$_3$); ^{1}H NMR (270 MHz, CDCl$_3$, 243 K) δ 2.34 (s, 6H, 2 x CH$_3$), 2.37 (s, 6H, 2 x CH$_3$), 2.53 (d, 2H, ^2J = 14.6 Hz), 2.88 (d, 2H, ^2J = 14.6 Hz), 3.09 (d, 2H, ^2J = 12.0 Hz), 3.16 (d, 2H, ^2J = 12.0 Hz), 3.79 (s, 6H, 2 x CO$_2$CH$_3$); ^{13}C NMR (67.9 MHz, CDCl$_3$, 293 K) δ 13.05, 27–34 (broad peak), 52.58, 64.63, 131–133 (broad peak), 132.65, 173.11, 207.27; MS (70 eV) *m*/*z*(%) 446 (M$^+$, 30), 138 (100). Anal. Calc. for C$_{23}$H$_{26}$O$_5$S$_2$ (446.58): C, 61.86; H, 5.87. Found: C, 61.91; H, 5.94%.

2a: a mixture of **1a** (1.7 g, 3.8 mmol) and KOH (2.5 g, 44.6 mmol) in ethanol (50 mL) was refluxed for 2.5 h. Then water (50 mL) was added, and the solution was acidified with concentrated HCl to pH 1 and was allowed to stand overnight. The precipitate was filtered off and dried, giving **1a-CO$_2$H** (1.5 g, 95%), which was used in the next

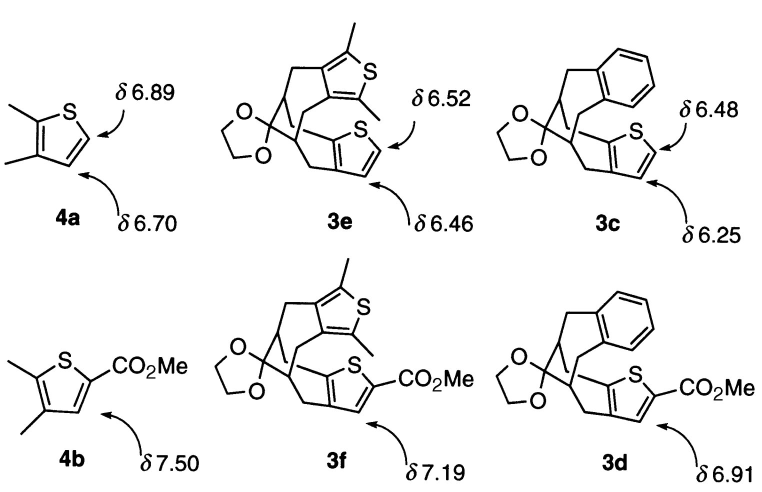

Fig. 2 ^{1}H NMR data (δ_H, 270 MHz, CDCl$_3$) of the series **4a**, **3e**, **3c** and **4b**, **3f**, **3d**.

reaction step without any further purification. **1a-CO$_2$H**: mp 322–324 °C (decomp.); IR (KBr) v 3218, 2920, 1714 (broad, multiple signal), 1443, 1384, 1318, 1265, 1216, 1150, 703, 680, 616 cm^{-1}; ^{1}H NMR (270 MHz, DMSO-d^6, 293 K) δ 2.26 (s, 12H, 4 × CH$_3$), 2.27 (d, 4H), 2.88 (d, 4H), 12.57 (s, 2H, 2 × CO$_2$H); ^{13}C NMR (67.9 MHz, DMSO-d^6, 293 K) δ 12.65, 28.5–32.5 (broad signal), 63.47, 129.0–132.0 (broad signal), 133.31, 173.28, 207.52; MS (FAB, *m*-NO$_2$C$_6$H$_4$CH$_2$OH) 575 ([M + *m*-NO$_2$C$_6$H$_4$CH$_2$OH]$^+$, 1), 418 (3), 307 (29), 289 (13), 154 (100). Anal. Calc. for $\mathrm{C_{21}H_{22}O_5S_2 \cdot 0.25\ H_2O}$ (418.52): C, 59.63; H, 5.36. Found: C, 59.86, H, 5.50%; HRMS. Found: 418.0907. Calc. for $\mathrm{C_{21}H_{22}O_5S_2}$: 418.0909. **1a-CO$_2$H** (1.0 g, 2.39 mmol) was heated *in vacuo* (0.2–0.4 Torr) at 330 °C, until the gas evolution ceased. After the reaction mixture was cooled, it was dissolved in CH$_2$Cl$_2$ (50 mL). Insoluble material was filtered off. The filtrate was concentrated *in vacuo* and submitted to column chromatography on silica gel (hexane–diethyl ether, 1 : 1) to give **2a** (645 mg, 82%) as colorless crystals; mp 252–253 °C (hexane–diethyl ether, 2 : 1); IR (KBr) v 2820, 1670, 1410, 1310, 1205, 1178, 1130, 1120, 940, 924, 870, 720 cm^{-1}; ^{1}H NMR (270 MHz, CDCl$_3$) δ 2.29 (s, 12H, 4 × CH$_3$), 2.52–2.65 (m, 8H), 3.00 (m, 2H); ^{13}C NMR (67.9 MHz, CDCl$_3$) δ 12.96, 27.44 (br), 53.35, 130.03, 134.12, 216.53; MS (70 eV) *m*/*z* (%) 330 (M$^+$, 84.4), 191 (74), 138 (100). Anal. Calc. for $\mathrm{C_{19}H_{22}OS_2}$ (330.50): C, 69.04; H, 6.71. Found: C, 69.52; H, 6.76%.

3a: a solution of **2a** (100 mg, 0.30 mmol), ethylene glycol (30 mg, 0.48 mmol) and *p*-toluenesulfonic acid monohydrate (*p*-TsOH, 5 mg, 0.026 mmol) in benzene (5 mL) were heated under reflux for 5 h. Then the solvent was evaporated directly *in vacuo* and the crude mixture was subjected to column chromatography on silica gel (hexane–diethyl ether, 2 : 1) to give **3a** (46 mg, 40%) as colorless crystals; mp 273 °C (decomp., from hexane–diethyl ether, 2 : 1); IR (KBr) v 2920, 1430, 1250, 1170, 1100, 990, 945 cm^{-1}; ^{1}H NMR (270 MHz, CDCl$_3$) δ 2.22 (m, 2H), 2.29 (s, 12H, 4 × CH$_3$), 2.70 (dd, 4H, $^3J = 5.0$, $^2J = 15.4$ Hz), 2.88 (dd, 4H, $^3J = 2.8$, $^2J = 15.4$ Hz), 4.05 (s, 4H); ^{13}C NMR (67.9 MHz, CDCl$_3$) δ 13.21, 28.03, 42.59, 64.60, 114.25, 126.95, 135.94.; MS (70 eV) *m*/*z* (%) 374 (M$^+$, 100), 312 (21), 248 (9), 235 (30). Anal. Calc. for $\mathrm{C_{21}H_{26}O_2S_2}$ (374.56): C, 67.34; H, 7.00. Found: C, 67.71; H, 7.01%.

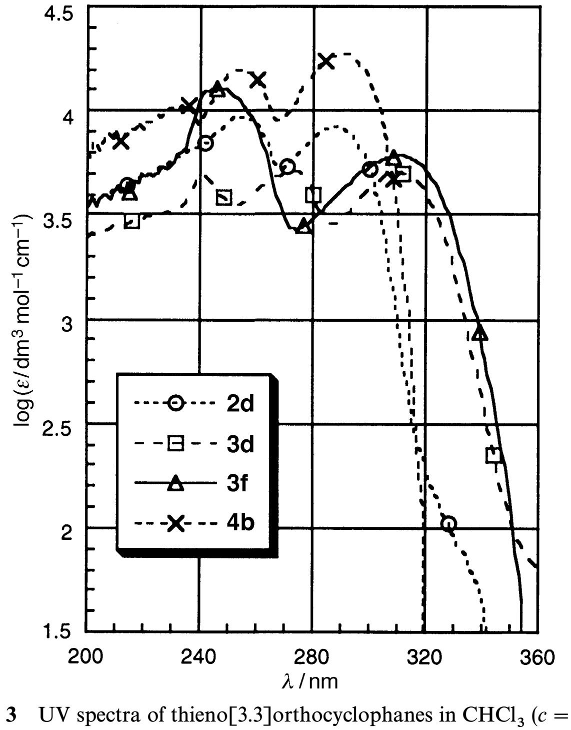

Fig. 3 UV spectra of thieno[3.3]orthocyclophanes in CHCl$_3$ ($c = 0.1$ mM).

¶ *Crystal data* for **3a**. $\mathrm{C_{21}H_{26}O_2S_2}$, $M = 374.56$, monoclinic, space group $P2_1/n$, $a = 17.520(2)$, $b = 11.007(1)$, $c = 9.900(1)$ Å, $\beta = 93.90(1)$, $V = 1904.7(3)$ Å^3, $Z = 4$, $D_c = 1.306$ g cm^{-3}, monochromated Cu-Kα radiation, $\lambda = 1.54184$ Å. A colorless prism of compound **3a**, mounted on a glass fiber in a random orientation, was used for X-ray data collection. Data were collected on an Enraf-Nonius CAD-4 diffractometer using ω–2θ scan at a temperature of 23 ± 2 °C. A total of 3348 reflections were collected of which 3348 were unique. The structure was solved by direct methods (SIR 92: M. C. Altomare, M. Burla, G. Camalli, C. Cascarano, A. Giacovazzo, G. Guagliardi and J. Polidori, *J. Appl. Crystallogr.*, 1994, **27**, 435) and refined by full-matrix least-squares calculations to give $R = 0.053$, $R_w = 0.142$ for 3241 observed independent reflections [$|F_0^2| > 3\sigma(F_0)^2$, $4.75 < \theta < 64.94°$]. All non-hydrogen atoms were located in succeeding difference Fourier syntheses and anisotropically treated. Hydrogen atoms were included in the refinement but restrained to ride on the atom to which they are bonded. All calculations were performed on an IBM RISC System/6000 380 computer using SHELX-94 (G. M. Sheldrick, SHELX-94, University of Göttingen, 1993).

CCDC, 440/113.

See http://www.rsc.org/suppdata/nj/1999/675/for crystallographic files in .cif format.

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12 Angle from planarity deviation does not exceed 2.5° within the systems studied. While the angle deviation of **3a** is at the high end of this deviation range, due to the d-orbitals of the facing sulfur atoms, a deviation which is notably less than 2.5° may be expected within the series **3e**, **3c**, **3f**, **3d**.

13 Methyl 4,5-dimethylthiophene-2-carboxylate **4b** and tetramethylthiophene **4c** have been prepared from building blocks **A** and **D** by reductive dehalogenation ($NaBH_4$–DMSO–H_2O–PTC) analogous to a reaction described by: F. Rolla, *J. Org. Chem.*, 1981, **46**, 3909. 2,3-Dimethylthiophene **4a** was synthesized from **4b** by decarboxylation catalysed by copper chromite, in the presence of BaO (9.7%).

14 While the substituent effect due to the bridge element in **3** can *de facto* not be equated to two methyl groups, changes in the chemical shift $\Delta\delta$ in the series **3f**, **3d** and **3e**, **3c** and also the comparison of **3** *vs.* **2** indicate that the predominant effect in **3** stems from the proximity of the underlying ring system.

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