Synthesis, resolution and racemization study of helically twisted *o*-terphenyls

Jian Ping Gao, Xian Sheng Meng, Timothy P. Bender, Sean MacKinnon, Valerie Grand and Zhi Yuan Wang*

Department of Chemistry, Carleton University, 1125 Colonel By Drive, Ottawa, Ontario, Canada K1S 5B6.
E-mail: wangw@ccs.carleton.ca

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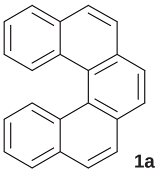
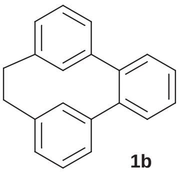
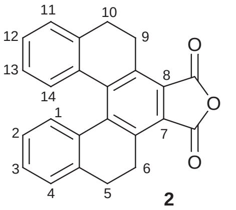
The synthesis, resolution and racemization studies of helical *o*-terphenyls, useful chiral building blocks are reported.

Understanding of the structure–chiroptics relationships of helical molecules is of theoretical and synthetic importance. Systematic distortion of helical aromatic systems by disturbance of the conjugated π-electron array,[1] from conformationally rigid helicences[2] (*e.g.* **1a**) to less rigid helically twisted *o*-terphenyl (*e.g.* **1b**),[3] provides a useful way to gain knowledge about chiroptics of organic molecules. In order to gain further insight into the chiroptical properties of the helical *o*-terphenyl system, *o*-terphenyls **2**, **3** and **4**, which are structurally related to *o*-terphenyl **1b,** were chosen for study. Compounds **2**[4] and **3**[5] contain the same *o*-terphenyl moiety as **1b** but it is bridged by two ethylene or propylene units, respectively. Little is known about the resolution and chiroptical properties of bridged helical *o*-terphenyls such as **2** and **3**. Considering the similarity in π-conjugation, it occurred to us that, if resolvable and stable, optically pure bridged *o*-terphenyl derivatives would have a high optical activity as [5]helicene does. Moreover, these *o*-terphenyl derivatives are advantageously more soluble than fully aromatized helicenes and can be made on a large scale from readily available starting materials through a non-photocyclization route.[4] We recently introduced the nitro, amino and isocyanato groups into *o*-terphenyl **2** at the C-1 (*e.g.* **4**[7a]) and C-3 positions[6,7] and obtained several polymers using functionalized **2**.[7a,d,e] Therefore, resolved *o*-terphenyls **2**–**4** would be valuable building blocks for making optically active compounds and polymers. To resolve these *o*-terphenyl derivatives, chemical and chromatographic resolutions and recrystallization were attempted. Chemical resolution of **4** was achieved using brucine.[8] Since dextrorotatory [5]helicene has *P* helicity,[9] this resolved laevorotatory helical *o*-terphenyl **4** should have *M* helicity. Attempted on chemical resolution of **2** using the same route was unsuccessful, as the corresponding acid ethyl ester had no optical activity. Chromatographic separation using a chiral column was attempted for compounds **2**, **3** and **4**.[10] Racemic **4** could be readily resolved by this means. However, anhydride **2** came out as a single peak under the same chromatographic conditions using different solvent systems. Surprisingly, compound **3** gave two well-resolved peaks and the *M* enantiomer was obtained in high optical purity.


1a


1b



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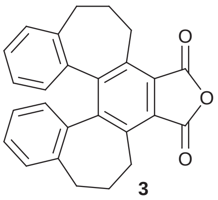

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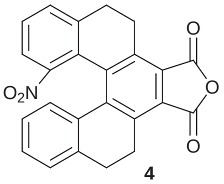

4

The resolved (*M*)-**4** showed very large specific optical rotations (*e.g.* −1518 at 589 nm and −7100 at 436 nm), comparable to that of (*M*)-[5]helicene (−1670 at 589 nm and −4950 at 436 nm, Table 1). Its CD spectrum [Fig. 1(*a*)] shows a strong negative band near 370 nm and a positive peak around 290 nm. In comparison with (*M*)-**4**, the resolved **3** displayed a rather low optical rotation (−55 at 589 nm). The striking difference in optical rotation between **3** and **4** is believed to be mainly due to variation in the degree of π-electron delocalization within the terphenyl moiety. Calculations have shown that optical rotations of helically twisted aromatic systems depend largely on the extended π-electron conjugation.[11] There is only a slight change in the geometry of the terphenyl moiety going from ethylene linkages in **4** to propylene linkages in **3**, as indicated by the X-ray structure analyses. The terphenyl unit in **4** is quite planar, the nitrobiphenyl unit being twisted by 37.4° and the other biphenyl being twisted by 29.1° (Fig. 2).[12] However, the biphenyl moiety in **3** has a large twist of 58°, indicating that the π-electrons of the terphenyl unit in **3** are less delocalized than those in **4**. Similarly, resolved **1b** was reported to have an optical rotation of 3210 at 365 nm and a smaller twist angle of about 47.8°. The UV-VIS spectra [Fig. 1(*b*)] of **2** and **4** display two strong peaks near 365 and 285 nm, whereas **3** had two bands centered at 330 and 270 nm. These absorption data further confirm a decrease in π-electron conjugation from **4** to **3**. Thus, the π-electron conjugation in the helically twisted *o*-terphenyl system directly relates to the strength of the optical rotation at a given wavelength. The greater the conjugation, or the smaller the twist angle is, the higher the optical rotation.

Thermal racemization studies were carried out at 49.8 °C (±0.1 °C) for (*M*)-**4**, and at 22.0 °C (±0.1 °C) for resolved **3**. The results are listed in Table 1, together with those of **1a** and **1b** for comparison. The half-life ($t_{1/2}$) of racemization at 49.8 °C was determined to be 2340 min for (*M*)-**4**, longer than that (62.7 min at 57 °C) of (*M*)-[5]helicene (**1a**).[2] Accordingly, the racemization barrier for compound (*M*)-**4** (27.7 kcal mol^{-1}) is higher than that (23.5 kcal mol^{-1}) of [5]helicene. As the lower helicenes racemize faster than higher ones,[2d,13,14] helical *o*-terphenyls having a substituent larger than hydrogen at the inner C$_1$-position are expected to have an increased barrier for

Table 1 Specific optical rotations and racemization half-life times ($t_{1/2}$) of resolved helical *o*-terphenyls and [5]helicene

Compound	Helicity	$[\alpha]_{589}$	$[\alpha]_{546}$	$[\alpha]_{436}$	$t_{1/2}$/min
3	*M*	−55	−94	−349	1100 (22.0 °C)
4	*M*	−1518	−1998	−7100	2340 (49.8 °C)
1a	*M*	−1670	−2025	−4950	62.7 (57.0 °C)
1b	*M*	−3210[a]			243.4 (100 °C)

[a] At 365 nm, 20 °C.

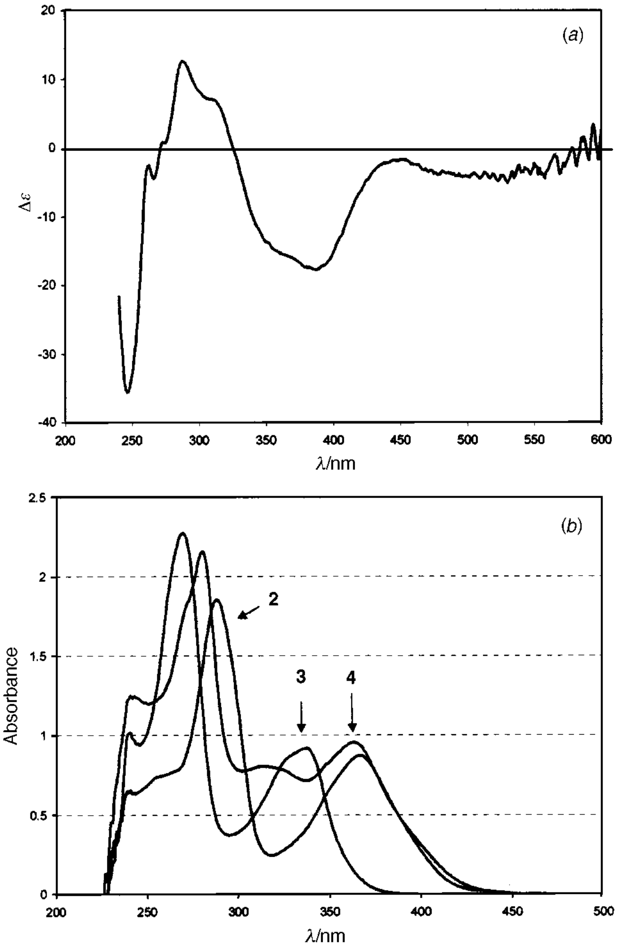

Fig. 1 (*a*) CD spectrum of (*M*)-**4** and (*b*) UV-VIS spectra of **2**–**4**.

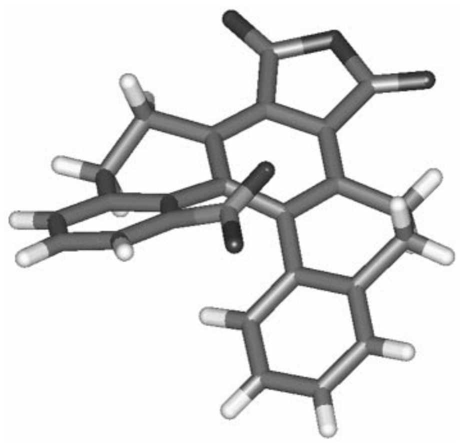

Fig. 2 Molecular geometry of **4** determined by X-ray analysis (ref. 12).

thermal racemization, which allows for effective resolution.[14] The X-ray structure of **4** shows a substantial overlapping between the nitro group and the opposite benzene ring. For compound **2**, although the terphenyl unit adopts a helical conformation and has a higher degree of π-conjugation (smaller twist angle of 32.4°) than compound **3**, the degree of overlapping between the two terminal benzene rings is probably too small to allow for resolution at ambient temperatures. Comparing compounds **2** and **3**, the former is conformationally unstable and racemizes rapidly at ambient temperatures. Owing to two extra CH_2 units, **3** has the two terminal rings overlapped to a great enough extent to allow for resolution but still easily racemizes with a half-life time of 1100 min at 22 °C. In comparison, **1b** was successfully resolved and had a racemization activation energy of about 30 kcal mol^{-1}, which is close to that (27.7 kcal mol^{-1}) of **4** and higher than that (23.5 kcal mol^{-1}) of **1a**.

In conclusion, chemical resolution of the bridged C_1-substituted helical *o*-terphenyls can be achieved. The racemization barrier depends on the degree of overlapping of the two terminal rings and optical activity relates to the degree of π-conjugation of the *o*-terphenyl moiety.

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8 The mixture of racemic **4** (2.96 g, 7.46 mmol) and brucine (3.30 g, 8.38 mmol) in 380 ml of absolute ethanol was heated to reflux until TLC showed no more anhydride. The reaction solution was then cooled to room temperature. On standing overnight, a crop of yellow crystals separated, which was filtered off, washed with ethanol and dried under vacuum to give 2.20 g of **4**·brucine salt: $[\alpha]_D^{22}$ = +640. Recrystallization twice of the first crop from CH_2Cl_2–EtOH raised the optical rotation to +665, which on decomposition with HCl afforded the corresponding acid esters: 1.08 g, $[\alpha]_D^{22}$ +1406 (c = 0.098, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1728, 1697(C=O); δ_H(400 MHz, $CDCl_3$) 1.43 (t, 3H), 2.66 (m, 1H), 2.81 (m, 5H), 3.01 (m, 1H), 3.19 (m, 1H), 4.44 (q, 2H), 6.69 (d, 1H), 6.90 (t, 1H), 7.21 (t, 1H), 7.30 (d, 1H), 7.33 (t, 1H), 7.47 (d, 1H), 7.59 (d, 1H); δ_C(50 MHz, $CDCl_3$) 169.4 and 169.2 (C=O, ester), 174.7 and 174.4 (C=O, acid). The mother liquor of the first crop was left open to air at room temperature for several days and the second crop precipitated out. The yellow solid was then filtered off, washed with ethanol and dried under vacuum to give 1.18 g of **4**·brucine salt ($[\alpha]_D^{22}$ −739), which upon treatment with HCl produced the acid ester: $[\alpha]_D^{22}$ −1243 (c 0.093, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1727, 1698 (C=O). Heating the acid ester ($[\alpha]_D^{22}$ −1243, *e.g.*, 150 mg) at 50 °C under vacuum (5 mmHg) for 6 h, followed by recrystallization once from hexane–CH_2Cl_2 afforded optically pure (*M*)-**4:** $[\alpha]_D^{22}$ −1518 (c 0.050, $CHCl_3$).

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12 Single crystals of racemic **4** suitable for X-ray analysis were obtained on slow evaporation of a CH_2Cl_2 solution. *Crystal data* for **4**: $C_{24}H_{15}NO_5$, M = 397.38, triclinic, space group $P\bar{1}$, μ = 0.10 mm^{-1}. a = 8.1376(6), b = 11.0822(8), c = 11.2149(8) Å, α = 103.642(8), β = 98.747(7), γ = 108.001(8)°, V = 906.64(11) $Å^3$, T = −100 °C, Z = 2, measured reflections = 5254, unique reflections = 4159, R(int) = 0.016. CCDC 182/1271.

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