A chiral, bis-anthraquinone-bridged cyclophane with a large specific rotation

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Abstract: A wide variety of common TD-DFT methods predict that chiral cyclophane **1** should exhibit a specific rotation ranging from large ($[\alpha]_D \sim 1,000$) to unreasonably large ($[\alpha]_D > 1,000,000$) with numerous estimates between these values. Compound **1** was prepared in two steps from 1,8-dichloroanthraquinone, and its X-ray structure showed it to be, as expected, a C_2 -symmetric, roughly triangular macrocycle. Compound **1** was resolved into nearly pure enantiomers by chromatography on a chiral support, and the specific rotations of the two components were determined to be $[\alpha]_D^{23} = +1520$ and $[\alpha]_D^{23} = -1470$. These values are large, but not exceptionally so, and the wildly inaccurate TD-DFT estimates of the specific rotation of compound **1** are shown to be closely related to the failure of the same TD-DFT methods to accurately predict the absorption spectrum of **1**.

1. Introduction

Over the years we have prepared numerous complex chiral aromatic compounds, chiefly twisted polycyclic aromatic hydrocarbons¹ and *in*-cyclophanes.² In some cases, these compounds have been resolved into pure enantiomers,³ or they were prepared from enantiomerically pure starting materials,⁴ and their measured specific rotations range from $[\alpha]_D \sim 100$ to $[\alpha]_D \sim 7400$. More recently, we reviewed the many reports of compounds with extremely high specific rotations,⁵ and concluded that the largest, reliably-determined (or at least plausible) specific rotation for an organic compound in solution belongs to a helicene bisquinone prepared by Fox and Katz with a reported $[\alpha]_D = -11,560$.⁶ Therein, we determined that TD-DFT calculations at the modest B3LYP/6-31G(d) level give mostly excellent results when estimating the specific rotations of compounds with reliably-determined, high specific rotations ($[\alpha]_D \sim 1000$ - 2000), but for compounds with truly exceptional specific rotations ($[\alpha]_D > 5000$), such calculations invariably overestimate the experimental $[\alpha]_D$, sometimes grossly so.⁵ Nevertheless, it is clear that if one is to search for a compound with a "world record" $[\alpha]_D$, it will be found among those molecules for which a TD-DFT calculation gives an enormous value, even if this value is an overestimate.

For this reason, we have calculated the structures and specific rotations of hundreds of unknown molecules in the hope of identifying an easily synthesized compound with a very large specific rotation and perhaps other exceptional chiroptical properties. Compound **1** (Scheme 1) might be just such a molecule. It is an excellent candidate for two reasons: first, a B3LYP/6-31G(d) TD-DFT calculation yields $[\alpha]_D = +1,068,000$ (!) for the illustrated enantiomer of **1**, and second, a two step synthesis of **1** is easily formulated. Such a large *calculated* $[\alpha]_D$ can result only if the TD-DFT calculation yields an electronic excitation very close to the wavelength chosen for the optical rotation calculation (in this case, 589.3 nm: the sodium D line); when the two coincide, there exists a singularity in the rotation calculation.⁷ Of course, it is extremely unlikely that an experimental $[\alpha]_D$ of 1,000,000 is possible in solution, but if compound **1** does in fact have an

absorption band near to 589 nm, then it might very well have an extremely large $[\alpha]_D$. Many of the compounds with the very largest $[\alpha]_D$'s possess long-wavelength visible absorptions that in turn yield large dispersion enhancements at the sodium D line.⁵ We are thus faced with two questions: does **1** possess a long-wavelength absorption band, and if so, does it have an exceptionally large $[\alpha]_D$? No TD-DFT calculation is reliable enough to answer these questions with certainty, but the proposed synthesis of compound **1** is so simple that it demands to be performed. We report the results of this exercise herein.

2. Results and Discussion

2.1. Synthesis and Structure

Cyclophane **1** was prepared in low yield in two steps from commercially available starting materials (Scheme 1). 1,8-Dichloroanthraquinone **2** was heated with excess copper powder at 270 °C to give 1,1'-bis(8-chloroanthraquinone) **3** in 16% yield after chromatographic purification. Treatment of this material with an equimolar amount of benzene-1,4-dithiol at moderate concentration (60 mM) in refluxing DMA with excess triethylamine gave cyclophane **1** in 3% yield after two rounds of silica gel chromatography. This result is an unusual case of macrocyclization via double nucleophilic aromatic substitution.

Scheme 1^a

^aConditions: (a) Cu, 270 °C, 16%; (b) benzene-1,4-dithiol, Et₃N, DMA, 3%.

Compound **1** was characterized by ^1H NMR and ^{13}C NMR spectroscopy, as well as MALDI and high-resolution ESI mass spectrometry. However, the UV spectrum of **1** was somewhat disconcerting; its longest-wavelength absorption maximum of 484 nm is rather shorter than the 589 nm absorption predicted by TD-DFT calculation at the B3LYP/6-31G(d) level that was used to estimate the specific rotation of compound **1**. TD-DFT calculations usually, but by no means always, give reasonable predictions of the UV spectra of organic molecules,^{8,9} and the same may be said for TD-DFT predictions of specific rotation.^{5,10} With computation and experiment already in conflict, it was important to unambiguously establish the structure of **1** before any attempted resolution.

Figure 1. Molecular structure of compound **1**; thermal ellipsoids are drawn at the 50% probability level.

Single crystals of cyclophane **1** were obtained from CHCl_3 -acetone solution, its X-ray structure was determined, and the molecular structure is illustrated in Figure 1. The molecule possesses approximate C_2 symmetry, and in some sense resembles a two-bladed propeller. The mean planes of the two anthraquinones are nearly perpendicular (dihedral angle, 88.4°), and both anthraquinones have modest end-to-end twists¹ (16.5° and 18.5°). The macrocycle is rather crowded, with the internal oxygen atoms (O2 and O4) having relatively close contacts with the sulfur atoms (O2-S2, 2.97 Å; O4-S1, 2.98 Å), basal ring carbon atoms (O2-C32, 2.89 Å; O4-

C29, 2.86 Å), and carbon atoms on opposing anthraquinones (O2-C15, 2.72 Å; O4-C11, 2.76 Å). The experimental geometry very closely resembles the DFT-calculated structures, and thus it only remained to resolve the cyclophane and measure its specific rotation.

2.2. Resolution and Chiroptical Properties

A sample of cyclophane **1** was resolved by preparative supercritical fluid chromatography (SFC) on a chiral support. The resolved enantiomers possessed a high degree of chemical and optical purity: for (+)-**1**, chemical purity > 96%, ee > 95%; for (–)-**1**, chemical purity > 99%, ee > 94%. The experimental specific rotations proved to be large, but not extremely large: for (+)-**1**, $[\alpha]_{\text{D}}^{23} = +1520$, and for (–)-**1**, $[\alpha]_{\text{D}}^{23} = -1470$. As a point of reference, there are only nine compounds with plausible reports of $[\alpha]_{\text{D}} > 7000$, but at least 500 compounds with $[\alpha]_{\text{D}} > 1000$.⁵ Circular dichroism (CD) spectroscopy gave spectra with several peaks but unexceptional intensity, with $\Delta\epsilon_{336} = +8.6$, $\Delta\epsilon_{377} = -7.7$, $\Delta\epsilon_{442} = +6.7$, and $\Delta\epsilon_{472} = +5.9 \text{ M}^{-1}\text{cm}^{-1}$ for (+)-**1**, and $\Delta\epsilon_{336} = -8.0$, $\Delta\epsilon_{377} = +7.2$, $\Delta\epsilon_{442} = -6.1$, and $\Delta\epsilon_{472} = -5.5 \text{ M}^{-1}\text{cm}^{-1}$ for (–)-**1** (Figure 2).

Figure 2. Circular dichroism spectra (CHCl₃) of (+)-**1** and (–)-**1**.

2.3. TD-DFT Calculations of UV Absorption Spectra and Specific Rotation

In view of the failure of B3LYP/6-31G(d) calculations to give reasonable predictions of the UV spectrum and specific rotation of cyclophane **1**, we wondered whether the use of larger basis sets or other functionals would have improved the results. Extensive benchmarking of TD-DFT methods for the prediction of UV spectra has been performed,^{8,9} but these studies have failed to yield a clear preference for any particular method. Most relevant to the work herein is a study of anthraquinone derivatives by Jacquemin et al.,^{11a} which was succinctly summarized by Muniz-Miranda et al.^{11b} as follows: "In a recent benchmark on anthraquinone derivatives, Jacquemin et al. found that global hybrids like B3LYP and PBE0 provide very good wavelengths but incorrect relative intensities; global hybrids with a larger amount of HF exchange like M06-2X blue shift the peak positions, but they give correct band shapes, whereas long-range-corrected functionals like CAM-B3LYP and ω B97XD gave satisfactory results." Our own calculations of the spectra of compound **1** with these and other functionals find even the measured assessment of Muniz-Miranda et al. to be overly optimistic.

The UV spectra of compound **1** were calculated with a wide variety of TD-DFT methods and basis sets, and the salient results from these calculations are shown in Table 1. The results fall into three distinct classes: (a) the B3LYP,^{12,13} B3PW91,^{12,14} and X3LYP¹⁵ functionals give spectra whose longest wavelength absorption is near to the sodium D line (589 nm); (b) the BLYP,^{13,16} B97D,¹⁷ and PBEPBE¹⁸ functionals give spectra with extremely long wavelength absorptions (~ 900 nm); and (c) the M062X,¹⁹ CAM-B3LYP,²⁰ and ω B97XD²¹ functionals give spectra with longest wavelength absorptions below 450 nm. Basis set size has little effect on the general appearance of the spectra, though the spectral lines are invariably shifted to slightly longer wavelengths as the basis set size increases. Figure 3 shows stick spectra of compound **1**, including the spectral lines and oscillator strengths, calculated at the B3LYP/6-31G(d), BLYP/6-

31G(d), and M062X/6-31G(d) levels (which are representative of the three computational classes), as well as the experimental spectrum of compound **1**.

Figure 3. Comparison of the experimental UV spectrum (CHCl_3) of compound **1** with plots of the wavelengths and oscillator strengths calculated at the M062X/6-31G(d) (**A**), BLYP/6-31G(d) (**B**), and B3LYP/6-31G(d) (**C**) levels of theory.

Table 1. Calculated UV absorption and specific rotation data for compound **1**.

Method	max $\lambda_{\max}$ (nm)	$\lambda_{\max}$ nearest to 589 nm		$[\alpha]_D^a$
Experiment	485	485		+1520
<i>Calculated maximum $\lambda_{\max} \sim 589$ nm</i>				
B3LYP/6-31G(d)	589	589		+1068431
B3LYP/cc-pVDZ	592	558	592	+81746
B3LYP/6-311G(d,p)	592	556	592	+110655
B3LYP/cc-pVTZ	600	563	600	+34947
B3LYP/6-311+G(2d,p)	609	572	609	+32315
X3LYP/6-31G(d)	574	574		−5306
X3LYP/cc-pVDZ	576	576		−8023
X3LYP/6-311G(d,p)	576	576		−8169
X3LYP/cc-pVTZ	584	584		−32612
X3LYP/6-311+G(2d,p)	593	557	593	+73339
B3PW91/6-31G(d)	597	560	597	+40544
B3PW91/6-311+G(2d,p)	614	575	614	+34386
<i>Calculated maximum $\lambda_{\max} >> 589$ nm</i>				
BLYP/6-31G(d)	876	585	606	−6016
BLYP/6-311+G(2d,p)	914	575	597	−39801
B97D/6-31G(d)	877	570	593	−94561
B97D/6-311+G(2d,p)	905	585	640	+89324
PBEPBE/6-31G(d)	887	535	600	−19296
PBEPBE/6-311+G(2d,p)	923	556	590	−65325
<i>Calculated maximum $\lambda_{\max} << 589$ nm</i>				
M062X/6-31G(d)	439	439		+1067
M062X/6-311+G(2d,p)	445	445		+866
CAM-B3LYP/6-31G(d)	423	423		+962
CAM-B3LYP/6-311+G(2d,p)	432	432		+777
ω B97XD/6-31G(d)	422	422		+1086
ω B97XD/6-311+G(2d,p)	430	430		+883

^aCalculated at 589.3 nm. The actual sodium D line is a doublet with lines at 589.0 and 589.6 nm.

None of the methods listed in Table 1 (and others not listed) give a satisfactory reproduction of the experimental spectrum. The M062X functional gives the best match, but even with the larger 6-311+G(2d,p) basis set, the calculated longest-wavelength absorption is blue shifted by 40 nm from the experimental value of 485 nm (although it is conceivable that the longer wavelength absorptions in the experimental spectrum are due to vibronic bands not accounted for in the TD-DFT calculations). The CAM-B3LYP and ω B97XD methods, which were recommended by Jacquemin et al.,^{11a} give similar but slightly poorer results than M062X. All of the other computational methods examined yield absorption lines much longer (by 100-450 nm) than any in the experimental spectrum, and whenever a calculated absorption is near to the sodium D line (589 nm), the calculated $[\alpha]_D$ is very large.

As mentioned briefly in the introduction, the extraordinarily large $[\alpha]_D$ calculated at the B3LYP/6-31G(d) level (which happened to be the level at which we screened compounds) is easily understood. Near to absorption lines, there is a very large dispersion enhancement, which can lead to very large specific rotations. If one examines ORD spectra, it is observed that the sign of optical rotation often inverts near to absorption maxima. In solution, where absorption lines are broad, there are contributions to the absorption on both sides of the inversion point, and there is a gradual decline and inversion of the observed rotation at this point. For a calculated stick spectrum, consisting of infinitely sharp lines, there are actually singularities in the rotation calculations at the calculated absorption lines;⁷ very near to the singularities, and the calculated rotations become extremely large.⁷ All of our calculations of $[\alpha]_D$ were performed using a value of 589.3 nm for the sodium D line; the actual sodium D line is a doublet with lines at 589.0 and 589.6 nm, and the average of the two is commonly employed in such calculations. The B3LYP/6-31G(d)-calculated longest wavelength absorption for **1** falls at 589.47 nm, only 0.2 nm from this nominal D line value, and thus the calculated rotation is exceptionally high.

It is important to understand that when a compound has an absorption band near to the sodium D line, the dispersion enhancement does in fact give rise to a much larger than expected $[\alpha]_D$. Indeed, four of the 12 highest reported $[\alpha]_D$'s (including the two highest) were measured for compounds that have $\lambda_{\text{max}} > 530 \text{ nm}$,⁵ but the experimental effect is not nearly so great as the calculated effect.

Unfortunately, benchmarking studies of optical rotation calculations largely fail to address this problem. It has long been recognized that the $[\alpha]_D$'s of the hydrocarbon helicenes are overestimated by TD-DFT calculations,^{22,23} and the reason for the problem, the underestimation of valence excitation energies, has been correctly identified.²² However, even the "OR45 Benchmark" set of chiral molecules of Autschbach et al.¹⁰ contains no organic compound with an absorption maximum greater than 370 nm (heptahelicene²⁴), and thus it is relatively easy to obtain good calculated $[\alpha]_D$'s provided that the TD-DFT calculations yield reasonable electronic excitation energies. This is certainly not the case for molecules with long-wavelength visible absorption bands. It is our recommendation that, for the present, it is best to treat TD-DFT calculated $[\alpha]_D$'s for compounds with significant experimental *or* calculated absorption bands above 500 nm with the greatest caution.

3. Experimental

3.1 General

All solvents and reagents were commercial, reagent grade materials, and were used without further purification. ^1H NMR spectra and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, on a Bruker AVANCE 300 spectrometer. Spin-spin coupling constants are reported to the nearest 0.5 Hz. MALDI-TOF mass spectra were recorded on a Bruker Autoflex III spectrometer; high-resolution ESI-TOF mass spectra were obtained on an Agilent 6220 spectrometer. UV spectra were recorded on a Hewlett-Packard 8452A spectrophotometer; specific rotations were determined on an Atago AP-300 automatic polarimeter.

3.2 Data for compounds

3.2.1. 1,1'-Bis(8-chloroanthraquinone) 3. A thoroughly mixed combination of 1,8-dichloroanthraquinone (0.838 g, 3.49 mmol) and copper powder (2.4 g, 38 mmol) was placed in a screw-capped tube and heated in a metal bath at 270 °C for 25 min. Immediately after removal from the metal bath, the mixture was extracted with toluene while mixing the material in the tube with a glass stirring rod. The copper powder was filtered away, and the filtrate was concentrated to dryness. Purification of the yellow residue by silica gel column chromatography (solvent, 1:4 hexanes- CH_2Cl_2) gave bisquinone **3** (0.133 g, 0.276 mmol, 16%) as a yellow powder. ^1H NMR (300 MHz, CDCl_3) δ 7.56 (dd, J = 7.5 Hz, 1.5 Hz, 2 H), 7.63 (t, J = 8.0 Hz, 2 H), 7.69 (dd, J = 8.0 Hz, 1.5 Hz, 2 H), 7.84 (t, J = 7.5 Hz, 2 H), 8.27 (dd, J = 7.5 Hz, 1.5 Hz, 2 H), 8.39 (dd, J = 8.0 Hz, 1.5 Hz, 2 H); ^{13}C NMR (75 MHz, CDCl_3) δ 126.2, 126.7, 131.1, 132.8, 133.1, 133.2, 133.3, 134.5, 135.5, 136.0, 137.3, 142.8, 182.7, 182.9 (14 of 14 expected resonances); MS (MALDI-TOF, DCTB + $\text{CF}_3\text{CO}_2\text{Na}$ matrix) m/z 482 (M^+ , 100), 483 ($\text{M} + \text{H}$, 38), 505 ($\text{M} + \text{Na}$, 17); HRMS (ESI-TOF) m/z 483.0182 ($\text{M} + \text{H}$), calcd for $\text{C}_{28}\text{H}_{13}\text{Cl}_2\text{O}_4$ 483.0185.

3.2.2. Cyclophane 1. Triethylamine (0.25 mL) was added to an argon-saturated solution of compound **3** (0.436 g, 0.902 mmol) and benzene-1,4-dithiol (0.128 g, 0.902 mmol) in DMA (15 mL) in a screw-capped tube. The solution was flushed with argon once again, and it was heated with stirring at 160 °C for 17 h. After cooling to room temperature, the precipitate that formed during the reaction was filtered away. EtOAc was added to the filtrate, and the resulting solution was washed several times with water, dried, and concentrated. This material was fractionated by silica gel column chromatography (solvent, 3:7 hexanes-CH₂Cl₂) to give 90% pure cyclophane **1**. This crude product was further purified by silica gel preparative TLC (solvent, 3:7 hexanes-CH₂Cl₂) to give pure cyclophane **1** (0.014 g, 25 μmol, 3%) as an orange solid. ¹H NMR (300 MHz, CDCl₃) δ 6.59 and 7.05 (AA'BB' system, 4 H), 7.17 (dd, *J* = 7.5 Hz, 1.5 Hz, 2 H), 7.63 (t, *J* = 7.5 Hz, 2 H), 7.72 (t, *J* = 7.5 Hz, 2 H), 8.00 (dd, *J* = 7.5 Hz, 1.5 Hz, 2 H), 8.31 (dd, *J* = 7.5 Hz, 1.5 Hz, 2 H), 8.39 (dd, *J* = 7.5 Hz, 1.5 Hz, 2 H), ¹³C NMR (75 MHz, CDCl₃) δ 126.0, 126.6, 127.3, 128.6, 131.5, 132.3, 132.7, 133.0, 133.8, 136.4, 137.0, 138.0, 139.3, 141.0, 144.0, 181.1, 182.8 (17 of 17 expected resonances); UV (CHCl₃) λ_{max} (ε) 362 (8600), 424 (sh, 1400), 484 (1200); MS (MALDI-TOF, DCTB + CF₃CO₂Na matrix) *m/z* 552 (M⁺, 95), 553 (M + H, 100), 575 (M + Na, 15); HRMS (ESI-TOF) *m/z* 553.0564 (M + H), calcd for C₃₄H₁₇O₄S₂ 553.0563. Single crystals suitable for X-ray analysis were obtained from solutions in CHCl₃-acetone.

3.2.3. Resolution of cyclophane 1. A sample of compound **1** (14 mg) was resolved by preparative SFC on a 2 cm x 25 cm Whelk-O1 (*R,R*) column eluted with 35% methanol and 5% CH₂Cl₂ in CO₂ at 100 bar with a flow rate of 60 mL/min. (+)-**1** eluted first (5 mg, chemical purity > 96%, ee > 95%; analytical method, 0.46 cm x 25 cm Whelk-O1 (*R,R*) column eluted with 40% methanol in CO₂ at 100 bar with a flow rate of 3 mL/min), [α]_D²³ +1520 ± 80 (*c* 0.081, CHCl₃), and it was followed by (–)-**1** (6 mg, chemical purity > 99%, ee > 94%), [α]_D²³ –1470 ± 110 (*c* 0.086, CHCl₃).

3.3. Computational methodology

All density functional calculations were performed with GAUSSIAN 09;²⁵ the built-in default thresholds for wave function and gradient convergence were employed. A variety of different functionals and basis sets were employed (see Table 1) for geometry optimization and TD-DFT calculations of optical rotation and UV spectra. All TD-DFT calculations were performed on molecular geometries optimized at the same level of theory. For calculations using the 6-31G(d) basis set, all potential minima were characterized by analytical frequency calculations, but such calculations were generally not performed with larger basis sets. Specific rotations were calculated by using the keywords POLAR=OPTROT CPHF=RDFREQ with 0.07732 au as the desired “frequency” (this energy corresponds to a frequency of 589.3 nm). Electronic absorption spectra for the compounds were calculated by using the keyword TD=(NSTATES=*N*), where *N* ranged from 10 to 50, depending on the calculation. The atomic coordinates and absolute energies for all calculated structures can be found in the Supplementary Data.

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