



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 ($[\alpha]_D \sim 1000$) 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 $[\alpha]_D^{25} = +1520$ and $[\alpha]_D^{25} = -1470$. 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 predict accurately the absorption spectrum of **1**.

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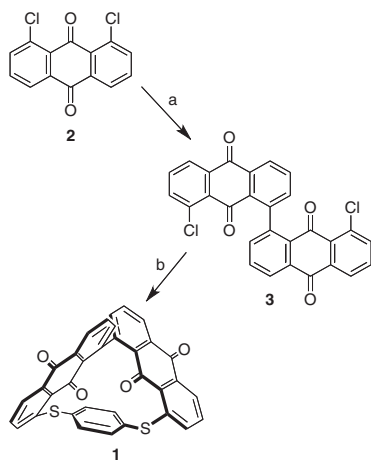
1. Introduction

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.

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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.



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

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.

Compound **1** was characterized by ¹H NMR and ¹³C 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.

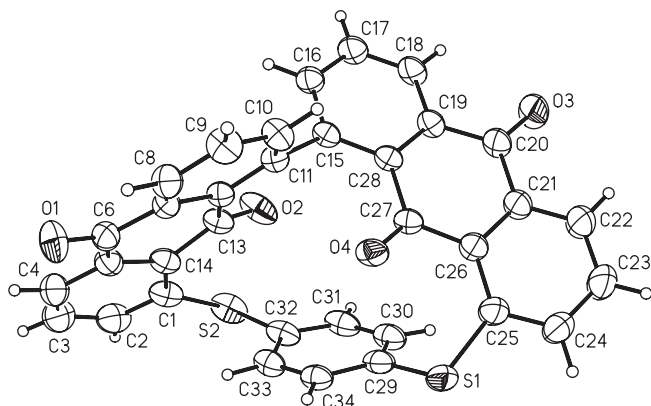


Figure 1. Molecular structure of compound **1**; thermal ellipsoids are drawn at the 50% probability level.

Single crystals of cyclophane **1** were obtained from CHCl₃-acetone solution, its X-ray structure was determined, and the molecular structure is illustrated in Figure 1. The molecule possesses approximate C₂ 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**, [α]_D²³ = +1520, and for (–)-**1**, [α]_D²³ = –1470. As a point of reference, there are only nine compounds with plausible reports of [α]_D > 7000, but at least 500 compounds with [α]_D > 1000.⁵ Circular dichroism (CD) spectroscopy gave spectra with several peaks but unexceptional intensity, with Δε₃₃₆ = +8.6, Δε₃₇₇ = –7.7, Δε₄₄₂ = +6.7, and Δε₄₇₂ = +5.9 M^{–1} cm^{–1} for (+)-**1**, and Δε₃₃₆ = –8.0, Δε₃₇₇ = +7.2, Δε₄₄₂ = –6.1, and Δε₄₇₂ = –5.5 M^{–1} cm^{–1} for (–)-**1** (Fig. 2).

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

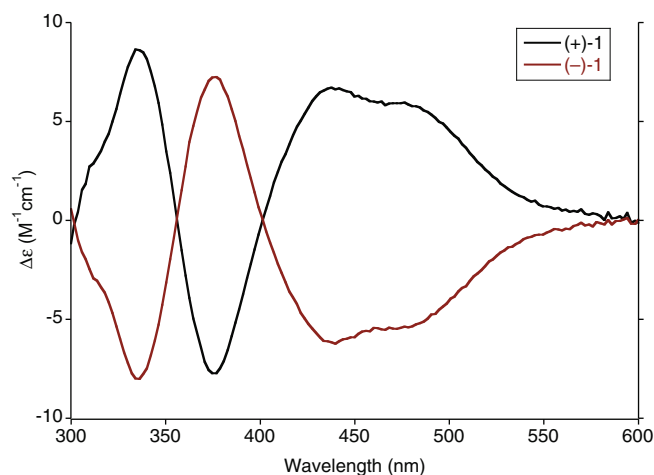


Figure 2. Circular dichroism spectra (CHCl₃) of (+)-**1** and (–)-**1**.

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