



## The Determination of the Absolute Configuration of a Chiral Molecular Tweezer Using CD Spectroscopy

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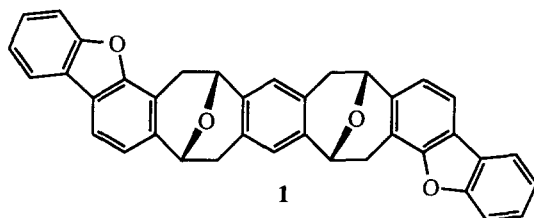
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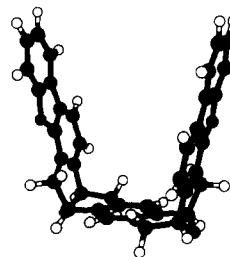
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**Summary:** Calculation of the CD spectrum of **1** and comparison to an experimentally determined CD spectrum is used to establish the absolute stereochemistry of **1**. © 1997 Elsevier Science Ltd.

Recently, one of us (MH) reported the synthesis of the chiral molecular tweezer **1** along with a crystal structure of its trinitrobenzene inclusion complex.<sup>1</sup> In an effort to begin to examine and understand the ability of such a molecular tweezer to discriminate between enantiomeric guests, studies of the behavior of **1** and related compounds on chiral stationary phases have been performed.<sup>2</sup> As part of that effort, a preparative separation of **1** was carried out on an (*R,R*) Whelk-O chiral column.<sup>3</sup> Studies of molecular models mindful of the proposed mechanism of chiral discrimination of the Whelk-O chiral stationary phase led to the conclusion that on the aforementioned column, the *RRRR* enantiomer of **1** should elute more quickly than its mirror image.<sup>4</sup> To establish the absolute stereochemistry of the enantiomers, the CD spectrum of each was recorded.<sup>5</sup> This paper describes the calculation of the CD spectra of the *RRRR* enantiomer of **1**. This work establishes the absolute stereochemistry of each enantiomer of **1** and lends support to the mechanistic model previously invoked for chiral discrimination by the (*R,R*) Whelk-O CSP.

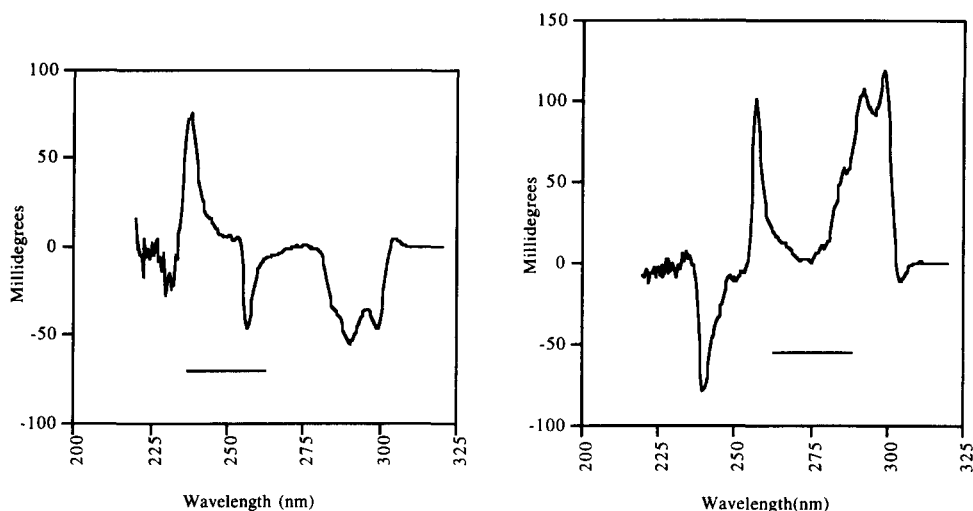


(drawn as the *RRRR* enantiomer)



AM1 Structure of **1**

The experimentally determined CD spectra for the enantiomers of **1** are shown in Figure 1. The first spectrum is that of the more quickly eluted enantiomer. Because the CD spectra are expected to be mirror

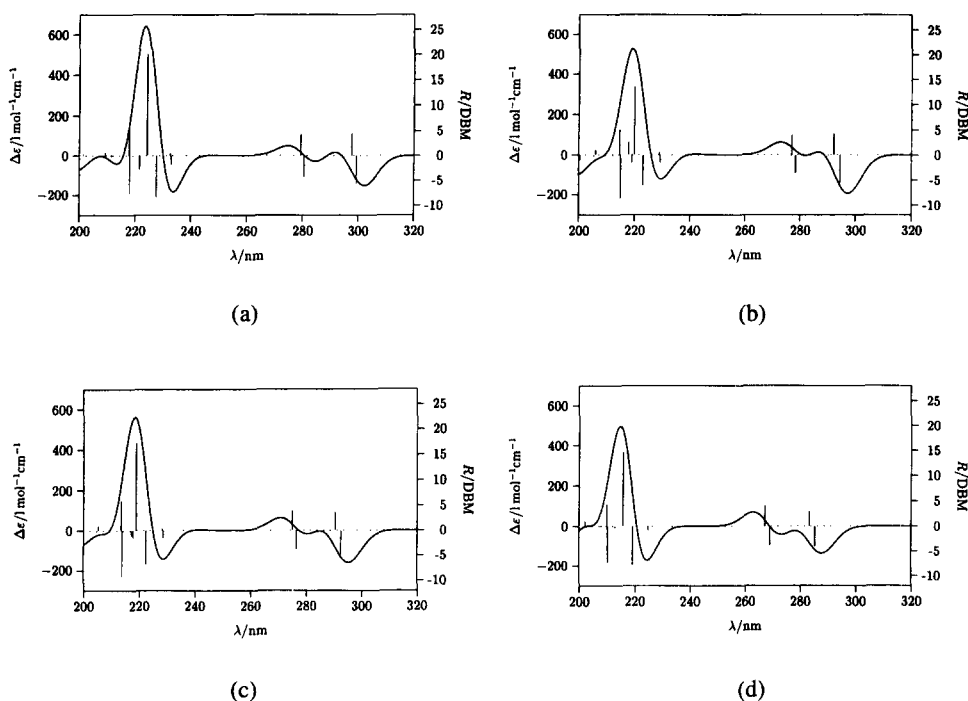


**Figure 1.** Experimental CD spectra of the enantiomers of **1**.<sup>5</sup> The first spectrum is that of the compound eluted first from an (*R,R*)-Whelk-O 1 chromatography column.

images, the CD spectra of only one enantiomer needs to be calculated. By comparison with the experimental spectra, one can assign the absolute configuration of both samples. This approach has proven quite successful in other cases.<sup>6,7</sup>

The CD spectra are calculated in the following way. First, the structure of one enantiomer is needed. Starting from bond lengths and angles taken from the literature<sup>8</sup>, geometry optimizations were performed using the semiempirical methods MNDO<sup>9</sup>, AM1<sup>10</sup>, and PM3<sup>11</sup> as implemented in the program MOPAC 6.0.<sup>12</sup> The three-dimensional structure of the *RRRR* enantiomer of **1** obtained with AM1 is shown next to the two-dimensional drawing of **1**. This structure was further optimized by an ab initio calculation at the HF/3-21G level using the program Gaussian 94.<sup>13</sup> The structures differ in the angle between the two dibenzofuran planes. With MNDO this angle is 36°; with AM1 and PM3, 22° and with 3-21G, 4.5°. In a crystal structure of **1**, this angle is 4.05°.<sup>14</sup>

The CD spectra which belong to these structures were then determined. The calculation of the rotational strengths was performed using the semiempirical method CNDO/S<sup>15</sup> as implemented in the program package DZDO/MCD3SP.<sup>16,17</sup> For the CI calculation, 169 singly excited singlet configurations were used. These were generated by exciting one electron from one of the thirteen highest occupied orbitals into one of the thirteen lowest unoccupied orbitals. In order to generate the spectra the rotational strengths were multiplied with gaussian functions with a halfband width of 6.07 nm in the range below 180 nm; 6.72 nm between 180 nm and 235 nm;



**Figure 2.** Calculated CD spectra for the RRRR enantiomer of **1** with CNDO/S using (a) the MNDO structure, (b) the AM1 structure, (c) the PM3 structure and (d) the 3-21G structure.

and 7.68 nm beyond 235 nm.<sup>18</sup>

The calculated spectra are shown in Figure 2. If one compares these spectra with each other one can see that the signs of the principal bands agree in all cases. With respect to the position and the intensity of these bands no great differences occur. In the experimental spectrum of the enantiomer of **1** with the smaller retention time, a broad negative band occurs at about 290 nm which may be split due to molecular vibrations. At 240 nm a positive Cotton effect and at 260 nm a negative Cotton effect are observed. The latter one is a little less intense than the former. The spectrum of the other enantiomer is approximately the mirror image of the first one, as expected. The differences are probably due to concentration effects. The three experimental bands can be assigned to the bands at 300, 230 and 220 nm in the calculated spectra. Their signs agree with the signs in the spectrum for the enantiomer of **1** less strongly bound to the Whelk-O CSP. Therefore, this enantiomer is assigned the *RRRR* configuration.

In summary, we have assigned the absolute configurations of the enantiomers of **1** by using a comparison of the experimental and calculated CD spectra. This work establishes a basis for the stereochemical assignment of other molecular tweezers of this class using CD spectroscopy. Further studies of enantiomer recognition and other applications of this class of compounds are in progress. Results will be reported in due course.

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### References and Notes

- Harmata, M.; Barnes, C.L. *J. Am. Chem. Soc.* **1990**, *112*, 5655.
- Harmata, M.; Kahraman, M.; Tyagarajan, S.; Barnes, C.L.; Welch, C.J. *J. Incl. Phenom.* (in press).
- Chromatographic analysis was performed using a Kratos ABI Spectroflow 400 pump, a Rheodyne Model 7010 injector fitted with a 10mL sample loop, a Kratos Spectroflow 783 variable wavelength absorbance monitor, and a Hewlett-Packard HP 3396 integrating recorder. Chromatographic conditions: column = (R,R) Whelk-O 1 (1 cm x 25 cm); mobile phase = 5%IPA/hexane; flow rate = 4 mL/min; detection = UV 280 nm. A sample of racemic dibenzofuran cleft (10 mg) was dissolved in mobile phase (2 mL). Injection of progressively increasing volumes of this solution showed that baseline resolution could still be achieved with an injection size of 400 uL (2 mg) with a run time of about 8 min. Collected fractions from four injections of 400 uL were pooled and assayed using a 4.6 mm x 25 cm analytical (R,R) Whelk-O column, revealing enantiopurity greater than 98% ee for both fractions.
- Pirkle, W.H.; Welch, C.J. *J. Chromatogr. A* **1994**, *683*, 347.
- CD measurements were carried out under constant nitrogen flow at 25.1 °C in an AVIV Circular Dichroism Spectrometer (AVIV Associates, Model 62DS) with a 450 watt suprasil Xenon lamp. Spectra were taken as a solution in methylene chloride (0.016M for the first eluted enantiomer and 0.025M for the second eluted enantiomer) using a 2 mm cuvette.
- Bringmann, G.; Gulden, K.P.; Busse, H.; Fleischhauer, J.; Kramer, B.; Zobel, E.; *Tetrahedron* **1993**, *49*, 3305.
- Fleischhauer, J.; Koslowski, A.; Kramer, B.; Zobel, E.; Bringmann, G.; Gulden, T.; Ortmann, B.P. *Z. Naturforsch* **1993**, *48b*, 4899.
- Pople, J.A.; Beveridge, D.L. *Approximate Molecular Orbital Theory*; McGraw-Hill: New York, 1970.
- Dewar, M.J.S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899.
- Dewar, M.J.S.; Zoebisch, E.G.; Healy, E.F.; Stewart, J.J.P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
- Stewart, J.J.P. *J. Comp. Chem.* **1989**, *10*, 209.
- Stewart, J.J.P. *Quant. Chem. Progr. Exch.* **1990**, *9*, 455.
- Gaussian 94*, Revision C.3: Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Gill, P.M.W.; Johnson, B.G.; Robb, M.A.; Cheeseman, J.R.; Keith, T.; Petersson, G.A.; Montgomery, J.A.; Raghavachari, K.; Al-Lahan, M.A.; Zakrzewski, M.G.; Ortiz, J.V.; Foresman, J.B.; Cioslowski, J.; Stefanov, B.B.; Nanayakkara, A.; Challacombe, M.; Peng, C.Y.; Ayala, P.Y.; Chen, W.; Wong, M.W.; Andres, J.L.; Replogle, E.S.; Gomperts, R.; Martin, R.L.; Fox, D.J.; Binkley, J.S.; Defrees, D.J.; Baker, J.; Stewart, J.P.; Head-Gordon, M.; Gonzalez, C.; Pople, J.A., Gaussian Inc, Pittsburgh, PA, 1995.
- Harmata, M.; Pusalkar, S.; Barnes, C.L. (manuscript in preparation).
- Ellis, R.L.; Kuehnlenz, G.; Jaffé, H.H. *Theor. Chem. Acta* **1972**, *26*, 131.
- The programs DZDO and MCD3SP were written by J. Downing and J. Michl, University of Colorado at Boulder, and modified by J. Fleischhauer, W. Schleker and B. Kramer.
- Downing, J.; Waluk, J.W.; Stanovnik, B.; Tisler, M.; Vercek, B.; Michl, J. *J. Org. Chem.* **1985**, *50*, 302.
- Meyers, A.I.; Nguyen, T.; Stoianova, D.; Sreerama, N.; Woody, R.W.; Koslowski, A.; Fleischhauer, J. *Chirality* (in press).

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