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Enantioselective Sensing of Amines Based on [1 + 1]-, [2 + 2]-, and [1 + 2]-Condensation with Fluxional Arylacetylene-Derived Dialdehydes

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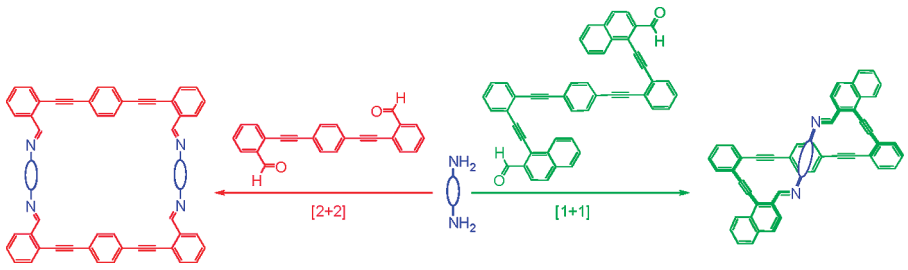
ABSTRACT



Four induced circular dichroism (ICD) probes exhibiting a stereodynamic arylacetylene framework and terminal aldehyde units have been prepared. The CD silent sensors generate a strong chiroptical response to substrate-controlled induction of axial chirality upon selective [1 + 1]-, [2 + 2]-, and [1 + 2]-condensation. The intense Cotton effects can be exploited for in situ ICD analysis of the absolute configuration and ee of a wide range of amines.

Conformationally flexible receptor molecules that adopt an axially or helically chiral arrangement upon binding to a chiral substrate have received increasing attention in recent years.[1] Imprinting of the chiral information of carboxylic acids or other analytes onto supramolecular assemblies,[2] molecular bevel gears,[3] propellers,[4] and other well-defined arrangements[5] can give rise to remarkable induced circular dichroism (ICD) signals.[6] Using carefully studied ICD probes that form hydrogen bond adducts[7] and metal complexes[8] with distinct chiral amplification, Berova, Nakanishi, Canary, and others have demonstrated that the corresponding Cotton effects can be used for reliable

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configurational and conformational analysis of a wide range of substrates. Rosini and Toniolo have successfully used this concept for the assignment of the absolute configuration of chiral amino acids, carboxylic acids, and alcohols that were covalently attached to a stereodynamic biphenyl probe.[9]

In recent years, we have investigated the stereodynamic properties of a wide range of axially chiral compounds[10] and used 1,8-diquinolyl- and 1,8-diacridylnaphthalenes as UV and fluorescence sensors for quantitative analysis of the enantiomeric composition of carboxylic acids, amino acids, amines, and amino alcohols.[11] These sensors provide accurate information about the ee and amount of a wide range of substrates often at micromolar concentrations.[12] We then realized that rapidly racemizing chromophoric probes exhibit strong Cotton effects if the binding event locks the stereodynamic sensor into a single chiral conformation.[13] For example, 1,4-bis(2(2-formylphenylethynyl)phenylethynyl)benzene, **1**, reacts with chiral diamines to a highly CD active macrocycle showing substrate-controlled induction of three chiral axes upon diimine formation.[14]

To date, few compounds bearing a diarylacetylene motif which typically undergoes fast rotation about the triple bond at room temperature have been reported.[15] The molecular bias for almost frictionless rotation has been exploited for the development of molecular turnstiles[16] and gyroscopes.[17] Based on the potential of 1,3-diarylacetylenes as versatile stereodynamic units in molecular devices, probes, and other applications, we decided to evaluate a series of arylacetylene-based frameworks having a well-defined intramolecular separation and relative orientation of terminal formyl groups. The molecular geometry of these structures would either favor or prevent [1 + 1]-cyclocondensation with diamines. We now report that the design of the CD silent arylacetylene moiety of four stereodynamic dialdehydes directs the reaction with diamines toward a [1 + 1]- or [2 + 2]-assembly that provides a distinct chiroptical response to a substrate-controlled chiral amplification process. We assumed that bridging of 1,4-di(2-formylphenyl)buta-1,3-diyne, **2**, and 1,4-bis(2-formylphenylethynyl)benzene, **3**, through cyclocondensation with a diamine would be geometrically impossible and thus favor formation of a large macrocyclic tetraimine via [2 + 2]-cyclocondensation (Figure 1). By contrast, 1,4-bis-(2(2-formyl-1-naphthylethynyl)phenylethynyl)benzene, **4**, and 1,4-bis(2(2-formylphenylethynyl)phenylethynyl)anthracene, **5**, were expected to favor a [1 + 1]-assembly.

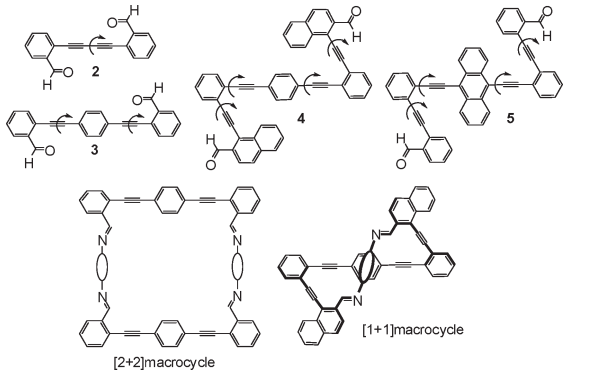

Figure 1. Structures of dialdehydes **2** to **5** (top) and [1 + 1]- and [2 + 2]-assembled macrocycles (bottom).

Dialdehyde **2** was readily available through oxidative homocoupling of 2-ethynylbenzaldehyde as described in the literature (Scheme 1).[18] The elongated analogue **3** was prepared by Sonogashira coupling of 2-bromobenzaldehyde and 1,4-diethynylbenzene in 80% yield. Slow evaporation of a solution of **2** in dichloromethane gave single crystals suitable for X-ray diffraction. The crystallographic analysis of **3** showed the expected linear geometry and the lack of steric hindrance to rotation about the aryl−alkyne bonds. As discussed above, we expected that the geometry of **2** and **3** would afford tetraimine macrocycles upon

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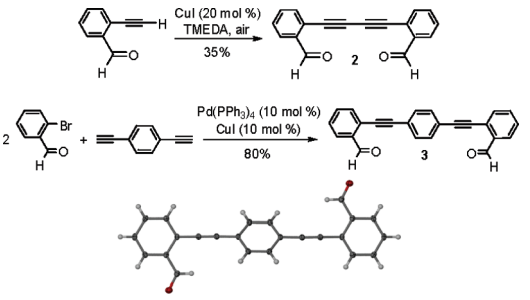
Scheme 1. Synthesis of **2** and **3** and Crystal Structure of **3**



[2 + 2]-cyclocondensation with diamines.[19] The reaction between stoichiometric amounts of either enantiomer of *trans*-diaminocyclohexane and **2** was monitored by NMR spectroscopy showing quantitative disappearance of the formyl protons. Formation of the expected [2 + 2]-macrocycle was evident from ESI-MS analysis, but the condensation with 1,2-diamino-1,2-diphenylethane yielded an acyclic product (see Supporting Information (SI)). Importantly, the **2**-derived imines obtained with the enantiomers of *trans*-diaminocyclohexane and other amines gave measurable Cotton effects (Figure 2 and SI).

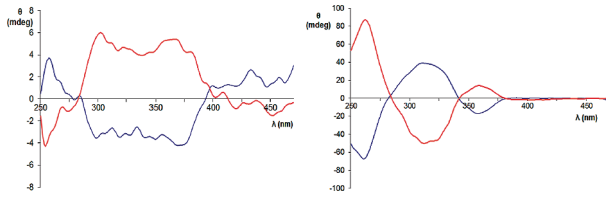


Figure 2. CD Spectra of the condensation products obtained from **2** (left) or **3** (right) and (1*R*,2*R*)-diaminocyclohexane (blue) and its (1*S*,2*S*)-enantiomer (red). The reactions were performed at 3.75 mM in chloroform at room temperature. For CD analysis the samples were diluted to 2.82×10^{-4} and 1.32×10^{-4} M, respectively.

Encouraged by the results obtained with **2**, we continued to screen the condensation between **3** and several amines (Figure 3). We were pleased to find that this dialdehyde undergoes [2 + 2]-cyclocondensation with all diamines tested and generates acyclic diimines with amines **10**–**16**. Both the enantiomeric tetraimines and diimines formed show remarkable Cotton effects that can be used for quantitative ee analysis of the amine substrates (Figure 2 and SI). To demonstrate the use of **3** in enantioselective sensing applications, a calibration curve was constructed using scalemic mixtures of diaminocyclohexane, **6**. The corresponding **3**-derived macrocyclic tetraimines were prepared in chloroform at 3.75 mM, and the samples were diluted to 7.48×10^{-4} M for CD analysis. Plotting of the CD amplitudes measured at 300 nm versus %ee revealed a linear relationship. Four scalemic samples of **6** having −90.0%, −46.0%, 30.0%, and 86.0% ee were then prepared and treated with sensor **3** as described above. Using the linear regression equation calculated from the calibration curve and the measured CD amplitudes of these samples, the enantiomeric excess was determined. Experimentally obtained data were within 3.9% of the actual values; see SI.[20]

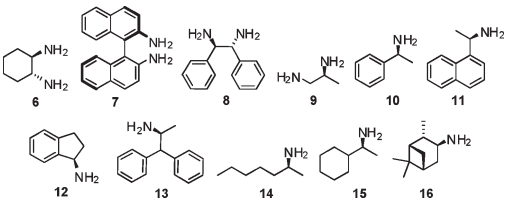
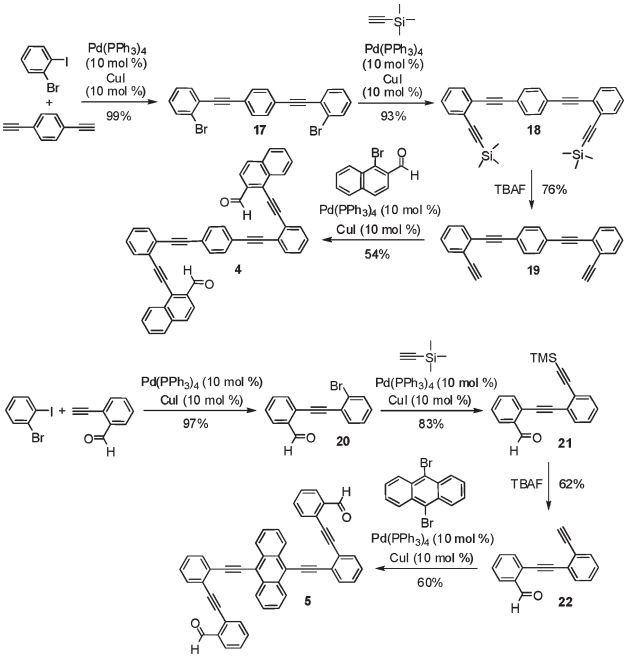


Figure 3. Structures of amine and diamine substrates.

Palladium catalyzed Sonogashira coupling of 2-bromoiodobenzene and 1,4-diethynylbenzene gave dibromide **17** in quantitative amounts (Scheme 2). Cross-coupling with ethynyltrimethylsilane then furnished **18** in 93% yield which was deprotected with TBAF to produce dialkyne **19**. Finally, coupling of **19** and 2 equiv of 1-bromo-2-naphthaldehyde in the presence of 10 mol % of $Pd(PPh_3)_4$ and CuI produced **4** in 54% yield. A somewhat similar strategy was used to prepare the branches of compound **5** prior to the construction of the central rod. First, 2-((2-bromophenyl)ethynyl)benzaldehyde, **20**, was obtained in almost quantitative yields by Sonogashira coupling of 2-iodobromobenzene and 2-ethynylbenzaldehyde. Alkynylation

Scheme 2. Synthesis of Sensors **4** and **5**



with ethynyltrimethylsilane and subsequent deprotection then gave **21** and **22** in 83% and 62% yield, respectively. 2-(2-Ethynylphenylethynyl)benzaldehyde, **22**, was then attached to the anthracene core by palladium catalyzed cross-coupling with 9,10-dibromoanthracene to give **5** in 60% yield.

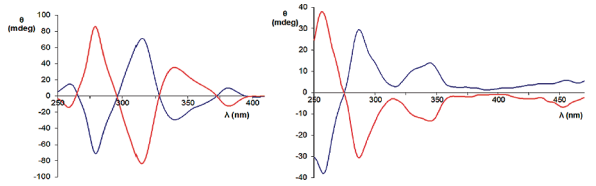


Figure 4. CD spectra of the [1 + 1]-macrocycle obtained using **4** and (1*R*,2*R*)-**6** (blue) or (1*S*,2*S*)-**6** (red) at 9.75×10^{-5} M in $CHCl_3$ (left). CD spectra of the acyclic [1 + 2]-cyclocondensation product produced from **5** and (*R*)-**13** (blue) or (*S*)-**13** (red) at 3.39×10^{-4} M in $CHCl_3$ (right).

The suitability of dialdehydes **4** and **5** for enantioselective sensing of the amines shown in Figure 4 was then evaluated. As expected, mass spectrometric analysis of the reaction mixtures obtained with diamimes **6**–**9** proved the formation of [1 + 1]-macrocycles while the monoamines generate [1 + 2]-cyclocondensation products. In situ CD analysis of the diimines showed strong Cotton effects that can be attributed to population of a highly CD active axially chiral conformer (Figure 4). MM2 calculations of the dimines obtained by cyclocondensation of sensors **4** and **5** with (1*S*,2*S*)-**6** showed that this distinctive chiral amplification is controlled by the central chirality of the amine substrate, and we anticipated that the induced chiroptical properties of the diimines formed should provide quantifiable information on the absolute configuration and the enantiomeric composition of the substrate (Figure 5). Indeed, we were able to obtain linear calibration curves using these two sensors and either diamine **8** or monoamine **13**. As described above, the linear regression equation calculated from these calibration curves and the measured CD amplitudes of the diimines generated from scalemic mixtures of amines **8** and **13** gave experimentally obtained data that were within 7.4% of the actual values; see Supporting Information.

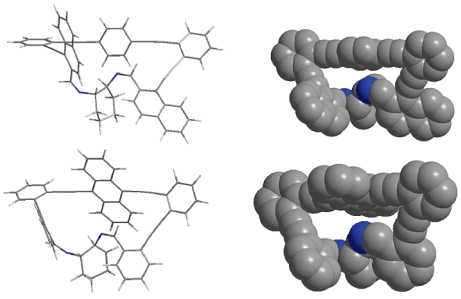


Figure 5. MM2 Computation of the structures of the diimines derived from (1*S*,2*S*)-**6** and **4** (top) or **5** (bottom). For better clarity, the hydrogens are omitted in the space filling model.

In summary, we have introduced four CD silent probes exhibiting a stereodynamic arylacetylene framework and two terminal aldehyde units. The well-defined geometry of these compounds favors either [1 + 1]- or [2 + 2]-cyclocondensation with diamines while monoamines generate acyclic [1 + 2]-diimines. Computational analysis suggests that the strong Cotton effects observed upon di- and tetraimine formation are due to substrate-controlled induction of axial chirality. These sensors provide a means for metal-free enantioselective CD analysis of a wide range of chiral amines. The use of sensitive ICD sensors **2**–**5** avoids cumbersome isolation of reaction products prior to analysis, and it eliminates the need for an elaborate synthesis of an enantiomerically pure chiral probe.

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Supporting Information Available. Synthetic details, compound characterization, and MS, CD, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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