A highly congested *N,N′*-dioxide fluorosensor for enantioselective recognition of chiral hydrogen bond donors†

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A rigid C_2-symmetric 1,8-diacridylnaphthalene *N,N′*-dioxide fluorosensor has been developed for enantioselective recognition of chiral hydrogen bond donors such as amines and amino acids.

Routine analysis of the enantiomeric composition of a sample usually entails chiral chromatography, chiroptical methods, electrophoresis with chiral additives or NMR spectroscopy with chiral shift reagents. Enantioselective sensing based on fluorescence spectroscopy offers a variety of advantages over these techniques including different detection modes (fluorescence quenching, enhancement, and lifetime), high sensitivity, low cost of instrumentation, waste reduction, and time efficiency. Stereoselective luminescent sensing based on indicator-displacement assays has recently been reported to provide a promising entry to high-throughput screening of chiral catalysts.[1] Because of the high sensitivity inherent to fluorescence spectroscopy only a very small amount of the sensor is required, which makes this technique cost-effective and practicable. To date, enantioselective fluorescence sensors including chiral macrocycles,[2] dendrimers,[3] or oligomers[4] have been reported.[5] Enantioselectivity in energy transfer reactions between a variety of chiral quencher molecules and photoexcited chiral lanthanide chelates has also been observed by time-resolved or steady-state circularly polarized luminescence measurements.[6]

In continuation of our studies of the stereodynamics of axially chiral 1,8-dipyridyl- and 1,8-diquinolylnaphthalenes,[7] we decided to investigate the use of highly congested 1,8-dihetarylnaphthalenes that do not undergo enantiomerization for stereoselective sensing. We assumed that the incorporation of selectively substituted and inherently fluorescent acridyl groups into the peri positions of naphthalene would result in conformationally stable bidentate 1,8-bis(9,9′-diacridyl)naphthalenes that could be highly useful enantioselective sensors. Optimization of the ground state of 1,8-bis(3,3′-(3,5-dimethylphenyl)-9,9′-diacridyl)naphthalene *N,N′*-dioxide, **1**, by PM3 calculations shows a rigid structure of cofacial acridyl rings that are almost perpendicular to the naphthalene moiety, thus providing an attractive C_2-symmetric coordination environment for enantioselective recognition of hydrogen bond donors, Fig. 1.

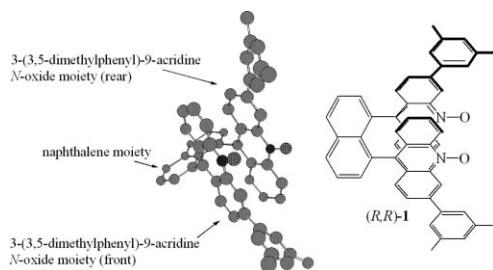The structure of this new class of *N,N′*-dioxides is designed to (a) embed interactions with chiral molecules into a highly stereoselective environment, and to (b) utilize fluorescence spectroscopy to monitor stereoselective recognition. Enantiopure *N,N′*-dioxide **1** was prepared using a recently reported synthetic strategy towards highly congested 1,8-diacridylnaphthalenes[8] followed by chiral HPLC on a Chiralpak AD column, Scheme 1. The CD spectra of the enantiomers of **1** are shown in Fig. 2.

Slow acetonitrile evaporation of a solution of **1** resulted in the formation of a co-crystal with water.‡ The congested geometry of **1** affords antiparallel acridyl rings forming a chiral cleft. Notably, the distance between the two *N*-oxide groups is 4.30 Å. The acridyl rings are slightly splayed away from each other by about 3.2° and the torsion angle between the acridyl rings was determined as 24.8°, Fig. 3.

Based on crystallographic studies of other congested 1,8-diheteroarylnaphthalenes conducted in our laboratories, the twisting of the acridyl rings of *N,N′*-dioxide **1** can be expected to vary while the splaying angle remains constant. The geometry of **1** thus results in a one-dimensional flexibility, *i.e.* the distance between the cofacial acridyl rings barely changes, whereas the opening of the C_2-symmetric cleft, *i.e.* the gap between the 3,5-dimethylphenyl moieties, is flexible to accommodate analytes of varying size.
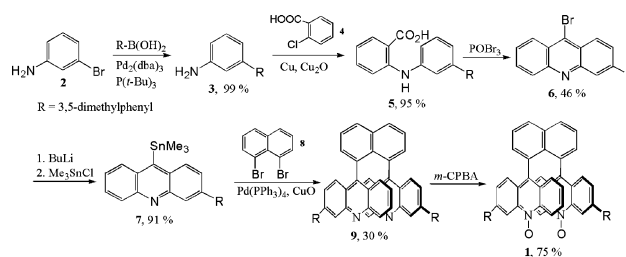
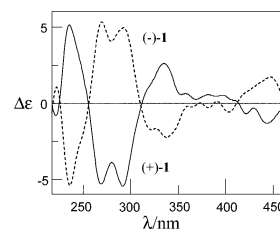**Scheme 1** Synthesis of 1,8-diacridylnaphthalene *N,N′*-dioxide **1**.
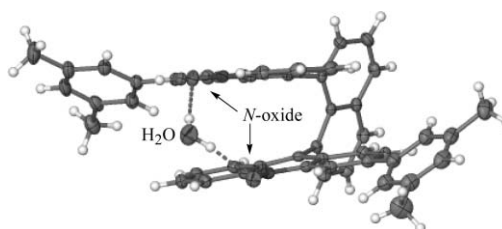
Fig. 2 CD spectra of the enantiomers of **1**.

Fig. 1 PM3-calculated ground state of (*R,R*)-**1**.

Fig. 3 Single crystal X-ray structure of **1**-H_2O. Selected bond lengths (Å): *O*–*O′* 4.32, *N*–*N′* 3.84, *O*–*H* 1.99.
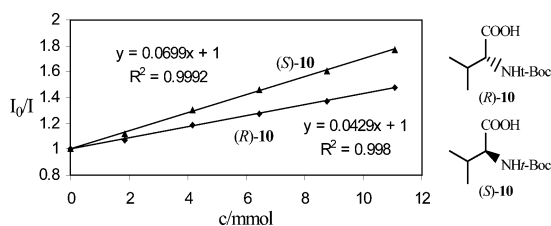
Fig. 4 Stern–Völmer plot of 3.5×10^{-5} M $(+)$-**1** in the presence of (R)- and (S)-N-t-Boc-valine, **10**, in acetonitrile.

The single crystal structure of N,N'-dioxide **1** demonstrates its ability to participate in hydrogen bonding and to embed substrates in its chiral environment. Since crystallographic analysis of **1** suggests that it would undergo strong interactions with hydrogen bond donors we decided to employ chiral bidentate analytes **10** and **11** in fluorescence titration experiments. Titration studies using $(+)$-**1** at 3.5×10^{-5} M (excitation at 490 nm, emission maximum at 571 nm) and various amounts of (R)- and (S)-N-t-Boc-valine, **10**, in acetonitrile showed enantioselective fluorescence quenching and an enantioselectivity factor (K^S_{SV}/K^R_{SV}) of 1.63, Fig. 4.

By contrast, Stern–Völmer plots using *trans*-1,2-diaminocyclohexane, **11**, in acetonitrile (excitation at 475 nm, emission maximum at 571 nm) revealed enantioselective fluorescence enhancement and an enantioselectivity factor $(K^{RR}_{SV}/K^{SS}_{SV})$ of 1.50, Fig. 5.

Acetonitrile can be expected to undergo hydrogen bonding with analytes **10** or **11** which would dimish interactions with the sensor and thus enantioselective recognition. We therefore repeated the titrations using **11** in toluene. As expected, a slightly increased enantioselectivity factor $(K^{RR}_{SV}/K^{SS}_{SV})$ of 1.60 was obtained.

While fluorescence enhancement induced by diaminocyclohexane may be a consequence of increased rigidity of **1** upon complexation to **11**,[9] enantioselective fluorescence quenching of excited N,N'-dioxide **1** in presence of amino acid **10** may be attributed to static quenching (*i.e.* constant fluorescence lifetimes) *via* non-radiative relaxation of diastereomeric hydrogen-bond adducts.[10] The stereoselective interactions between $(+)$-**1** and the enantiomers of **10** and **11** in the concentration range of 10^{-3} to 10^{-1} M result in fluorescence changes following the Benesi–Hildebrand equation.[11] Benesi–Hildebrand plotting gave an association constant of 236 M^{-1} for $(+)$-**1** and (R)-**10**, and 460 M^{-1} for $(+)$-**1**–(S)-**10**. Association constants between $(+)$-**1** and (R,R)-**11** or (S,S)-**11** were determined as 280 M^{-1} and 180 M^{-1}, respectively. Enantioselective sensing of compounds that do not exhibit bulky substituents near the chiral center remains a major challenge in fluorescence sensing. Accordingly, an enantioselectivity factor of only 1.28 for **11** has been reported using a 1,1'-binaphthyl-derived fluorosensor.[4] The selectivity of **1** for the
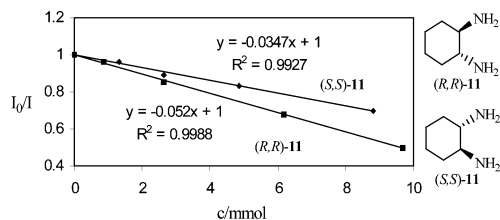
enantiomers of amino acid **10** and diamine **11** is therefore quite promising for future sensing studies.

In summary, we have developed a new class of C_2-symmetric fluorosensors for enantioselective recognition of chiral hydrogen bond donors. In contrast to fluorophores previously developed for enantioselective sensing, the 1,8-diacridylnaphthalene N,N'-dioxide-derived sensor exhibits a highly congested structure that can embed substrates of varying size closely into its chiral framework. Further studies of the usefulness of axially chiral 1,8-diacridylnaphthalene N,N'-dioxides for enantioselective fluorosensing of mono- and bifunctional chiral compounds are currently underway in our laboratories.

Notes and references

‡ Crystal structure data for **1**-H$_2$O-CH$_3$CN: Formula C$_{28}$H$_{23}$N$_2$O$_{1.5}$, $M = 411.5$, crystal dimensions $0.5 \times 0.4 \times 0.4$ mm, monoclinic, space group $C2/c$, $a = 24.551(2)$ Å, $b = 13.388(1)$ Å, $c = 13.719(1)$ Å, $\beta = 107.204(2)°$, $V = 4307.46$ Å^3, $Z = 8$, $\rho_{calcd} = 1.2689$ g cm^{-3}, $2\theta_{max} = 54°$, $T = 186$ K, 4690 independent reflections ($R_{int} = 3.68\%$), of which 3491 were above $4\sigma(F)$. $R1 = 0.0568$, $wR2 = 0.1576$ with $I > 2\sigma(I)$, $R_\sigma = 0.0328$, GooF = 1.090, $\Delta\rho_{max} = 0.61$ e Å^{-3}, $\Delta\rho_{min} = -0.47$ e Å^{-3}. Single crystal X-ray diffractions of **1** were performed at -87 °C using a Siemens platform diffractometer with graphite monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). Data were integrated with the Siemens SAINT program and corrected for the effects of absorption using SADABS. The structures were solved by direct methods and refined with full-matrix least-square analysis using SHELX-97-2 software. Non-hydrogen atoms were refined with anisotropic displacement parameters and all hydrogen atoms were placed in calculated positions and refined with a riding model. CCDC 218159. See http://www.rsc.org/suppdata/cc/b4/b407718k/ for crystallographic data in .cif or other electronic format.

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Fig. 5 Stern–Völmer plot of 3.5×10^{-5} M $(+)$-**1** in the presence of (R,R)- and (S,S)-**11** in acetonitrile.