Enantioselective Sensing of Carboxylic Acids with a Bis(urea)oligo(phenylene)ethynylene Foldamer

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Abstract

The development of molecular probes for optical sensing of chiral compounds has received increasing attention in recent years, in particular because of the potential to accelerate asymmetric reaction analysis. In this study, we prepared conformationally flexible oligo(phenylene)ethynylene foldamers carrying peripheral bis(trifluoromethyl)phenylurea units that undergo hydrogen bonding with chiral carboxylic acids. This interaction results in a chiral amplification process across the stereodynamic sensor scaffold which coincides with characteristic circular dichroism signals at high wavelengths. The induced chiroptical signals allow quantitative determination of the enantiomeric excess of the substrate which was demonstrated with nonracemic samples of tartaric acid. The chirality sensing assay is fast, sufficiently accurate for high-throughput screening purposes and adaptable to parallel analysis with multiwell plate readers.

Keywords: Chirality, enantiomeric excess, circular dichroism, urea sensor, carboxylic acids

Introduction

Chirality plays an essential role in literally all branches of chemistry and at the interface with the health, environmental and materials sciences. The detection and stereoselective analysis of chiral compounds have become central tasks in numerous asymmetric synthesis and drug development programs. Encouraged by the success of hydrogen bond donors in asymmetric organocatalysis,[1] very useful chiral solvating agents displaying a chiral bis(urea),[2] bis(thiourea)[3] or bis(selenourea)[4] motif have been introduced to enantioselective NMR analysis.[5] Chiroptical sensing is becoming a practical alternative to traditional chiral chromatography and NMR methods,[6] in particular when asymmetric reactions need to be examined.[7] To this end, our laboratory recently introduced a stereodynamic arylboronic acid/urea sensor that allows determination of yield and enantiomeric excess directly from crude reaction mixtures.[7d]

Several chiroptical sensors exhibiting a stereodynamic oligo(phenylene)ethynylene backbone have been reported and applied in chirality amplification and ee studies with amines, aldehydes and amino alcohols.[8] The arylacetylene moiety has become a quite popular scaffold in recent years and been incorporated into a wide variety of materials and devices including molecular turnstiles and gyroscopes.[9] The intriguing applications of oligo(phenylene)ethynylenes and the sensing potential of the urea motif inspired us to design the stereodynamic foldamers **1** and **2**, Figure 1. Both structures consist of three 'frictionless' aryl-alkyne rods and two terminal urea groups. In the free form, **1** and **2** do not exhibit a circular dichroism (CD) signal and populate axially chiral (and achiral) conformations that rapidly interconvert at room temperature. The sensing concept is based on possibly synergistic hydrogen bonding between the terminal urea units and a chiral guest to induce chirality amplification across the oligo(phenylene)ethynylene backbone. The molecular recognition event thus creates a chiral bias

and preferential population of a CD active conformation of the sensor. This imprinting of the substrate chirality onto the extended chromophoric π-system of the host was expected to result in a strong chiroptical signal that reveals the absolute configuration and the enantiomeric composition of the analyte. We now describe the synthesis of these new sensors and their use for quantitative ee sensing of tartaric acid and other chiral carboxylic acids.

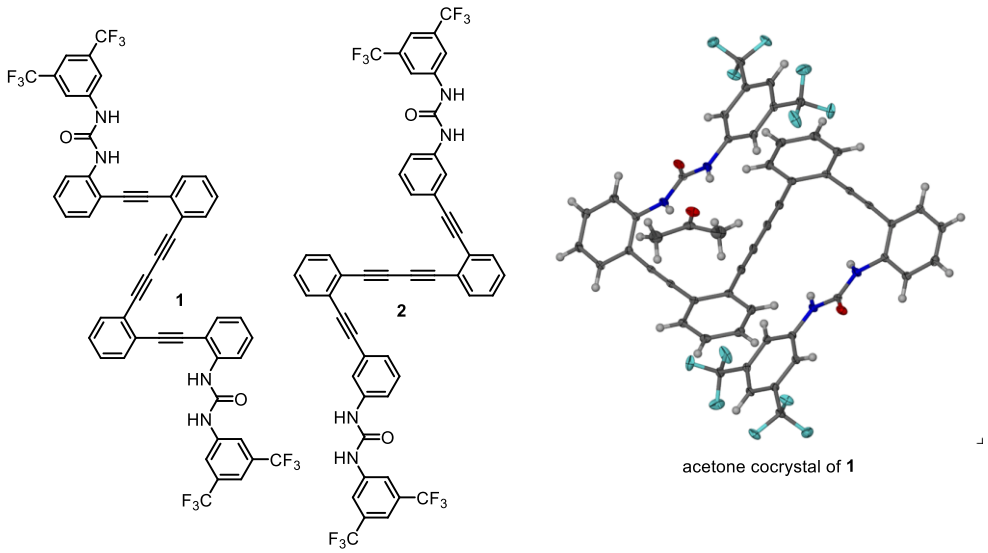


Figure 1. Structures of the bis(urea) foldamers **1** and **2** and co-crystal structure of **1** with acetone.

Experimental Section

Sensor synthesis

The compounds **4**, **5** and **6** were prepared following a previously described procedure.[10]

1-(3,5-Bis(trifluoromethyl)phenyl)-3-(2-iodophenyl)urea, 10. A solution of **8** (1.27 g, 5.78 mmol) and **7** (983 mg, 3.85 mmol) in dichloromethane (7 mL) was stirred at room temperature for 5 hours. The precipitate was collected by vacuum filtration and suspended in cold dichloromethane. The suspension was stirred for 10 minutes, filtered and the residue was dried under vacuum to give 1.4 g (3.03 mmol, 79%) of a white solid. ^{1}H-NMR (400 MHz, acetone-d_6): δ (ppm) = 6.90 (1H, m), 7.38 (1H, m), 7.61 (1H, s), 7.65 (1H, s), 7.87 (1H, d, J=8.0 Hz), 8.02

(1H, d, *J*=8.1 Hz), 8.21 (2H, s), 9.42 (1H, s). ^{19}F-NMR (acetone-d_6): δ (ppm) = -63.7 (s). ^{13}C-NMR (100 MHz, acetone-d_6): δ (ppm) = 90.6, 114.9 (m), 118.2 (m), 123.3 (m), 124.1 (q, $J_{C\text{-}F}$ = 271.8 Hz), 125.7, 128.9, 131.6 (q, $J_{C\text{-}F}$ = 33.1 Hz), 139.2, 139.4 (m), 141.9 (m), 152.0. Anal. Calcd. $C_{15}H_9F_6IN_2O$: C, 38.00; H, 1.91; N, 5.91. Found: C,38.04; H, 2.00; N, 5.97.

1,1'-(((Buta-1,3-diyne-1,4-diylbis(2,1-phenylene))bis(ethyne-2,1-diyl))bis(2,1-phenylene))bis(3-(3,5-bis(trifluoromethyl)phenyl)urea), 1. A mixture of **6** (72 mg, 0.29 mmol), **10** (682 mg, 1.44 mmol), CuI (5.49 mg, 0.03 mmol) and $Pd(PPh_3)_4$ (33.3 mg, 0.03 mmol) was stirred at room temperature in Et_3N:ACN (1:1 v/v, 8 mL) for 12 hours. The reaction was quenched with brine and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography on silica gel (2% acetone in hexanes) afforded 114.1 mg (0.12 mmol, 42%) of a white solid. ^{1}H-NMR (400 MHz, acetone-d_6): δ (ppm) = 6.97-7.01 (2H, m), 7.31-7.47 (10H, m), 7.51-7.57 (4H, dd, *J*=7.8 Hz, 15.6 Hz), 8.11 (4H, s), 8.20 (1H, s), 8.25 (2H, d, *J* = 8.5 Hz), 9.44 (1H, s). ^{19}F-NMR (acetone-d_6): δ (ppm) = -63.5 (s). ^{13}C-NMR (100 MHz, acetone-d_6): δ (ppm) = 77.2, 81.6, 89.1, 93.7 (m), 111.1 (m), 114.6 (m), 117.9 (m), 118.8 (m), 122.4, 123.4, 128.4 (q, $J_{C\text{-}F}$ = 272.3 Hz), 126.2, 128.5, 129.5, 129.8, 131.3 (q, $J_{C\text{-}F}$ = 32.9 Hz), 131.7, 132.1, 132.6, 140.0, 141.7, 151.7. Anal. Calcd. $C_{50}H_{26}F_{12}N_4O_2$: C, 63.70; H, 2.78; N, 5.94. Found: C, 63.84; H. 2.62; N, 5.86.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-(3-iodophenyl)urea, 11. A solution of **9** (121 mg, 0.55 mmol) and **7** (100 mg, 0.36 mmol) in dichloromethane (5 mL) was stirred at room temperature for 5 hours. The precipitate was collected by vacuum filtration and suspended in cold dichloromethane. The suspension was stirred for 10 minutes, filtered and the residue was dried under vacuum to give 254 mg (0.54 mmol, 97%) of a white solid. ^{1}H-NMR (400 MHz, acetone-d_6): δ (ppm) = 7.10 (1H, m), 7.41 (1H, d, *J* = 8.4 Hz), 7.49 (1H, d, *J* = 8.1 Hz), 7.62 (1H, s), 8.10

(1H, s), 8.19 (2H, s), 8.81 (1H, s), 8.48 (1H, s). ^{19}F-NMR (acetone-d_6): δ (ppm) = -65 (s). ^{13}C-NMR (100 MHz, acetone-d_6): δ (ppm) = 93.6, 114.9 (m), 118.1, 118.2 (m), 123.5 (q, $J_{C\text{-}F}$ = 271.9 Hz), 127.5 (m), 130.6, 131.5 (q, $J_{C\text{-}F}$ = 32.9 Hz), 131.6 (m), 140.6 (m), 141.7 (m), 152.0 (m). Anal. Calcd. $C_{15}H_9F_6IN_2O$: C, 38.00; H, 1.91; N, 5.91. Found: C, 38.01; H, 2.11; N, 5.79.

1,1'-(((Buta-1,3-diyne-1,4-diylbis(2,1-phenylene))bis(ethyne-2,1-diyl))bis(3,1-phenylene))bis(3-(3,5-bis(trifluoromethyl)phenyl)urea), 2. A mixture of **6** (202.7 mg, 0.81 mmol), **11** (1.15 g, 2.43 mmol), CuI (15.3 mg, 0.08 mmol) and $Pd(PPh_3)_4$ (92.4 mg, 0.08 mmol) was stirred at room temperature in Et_3N:ACN (1:1 v/v, 8 mL) for 12 hours. The reaction was quenched with brine and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography on silica gel (2% acetone in hexanes) afforded 153.8 mg (0.16 mmol, 40%) of a yellow solid. ^{1}H-NMR (400 MHz, acetone-d_6): δ (ppm) = 7.16-7.22 (4H, m), 7.31-7.42 (6H, m), 7.54-7.57 (4H, m), 7.61-7.64 (2H, m), 7.80 (2H, d, J = 3.7 Hz), 8.06-8.17 (4H, m), 8.40 (2H, s), 8.78 (2H, s). ^{19}F-NMR (acetone-d_6): δ (ppm) = -63.6 (s). ^{13}C-NMR (100 MHz, acetone-d_6): δ (ppm) = 77.4, 81.3, 87.3, 94.2, 114.7 (m), 118.1 (m), 119.7, 121.9, 123.1, 123.5 (q, $J_{C\text{-}F}$ = 271.7 Hz), 123.9, 126.2, 126.8, 128.4, 129.0, 129.5, 131.5 (q, $J_{C\text{-}F}$ = 33.0 Hz), 131.8, 131.9, 132.8, 139.4, 141.9, 152.1. Anal. Calcd. $C_{50}H_{26}F_{12}N_4O_2$: C, 63.70; H, 2.78; N, 5.94. Found: C, 63.75; H, 2.64; N, 5.54.

Chirality sensing

A stock solution of the sensor **2** (0.005 M) in $CHCl_3$:acetone (4:1) was prepared and portions of 0.5 mL were transferred into 4 mL vials. Solutions of substrates (0.25 M) in $CHCl_3$ (0.5 mL) were prepared. For substrates **12** to **15**, two equivalents of base were added (34.8 µL of Et_3N for **12**, and 37.3 µL of 1,8-diazabyclo[5.4.0]undec-7-ene, DBU, for **13** to **15**). For substrate **16**, one equivalent of base was added (18.7 µL of DBU). To each vial containing 0.5 mL of sensor stock

solution was added either 2 equivalents (20 μL, 0.005 mmol) of a diacid or 4 equivalents of an α-hydroxy acid (40 μL, 0.01 mmol). The mixture was stirred for 10 minutes at 25 ºC and CD analysis was conducted after sample concentrations were adjusted to 1.5 x 10^{-4} M with diethyl ether. The CD spectra were collected at 25 ºC with a standard sensitivity of 100 mdeg, a data pitch of 2 nm, a bandwidth of 1 nm, a scanning speed of 500 nm min^{-1}, and a response of 0.5 s using a quartz cuvette (1 cm path length). The data were baseline-corrected and smoothed using a binomial equation. Control experiments with free substrates showed no CD signal in the region of interest at similar concentrations.

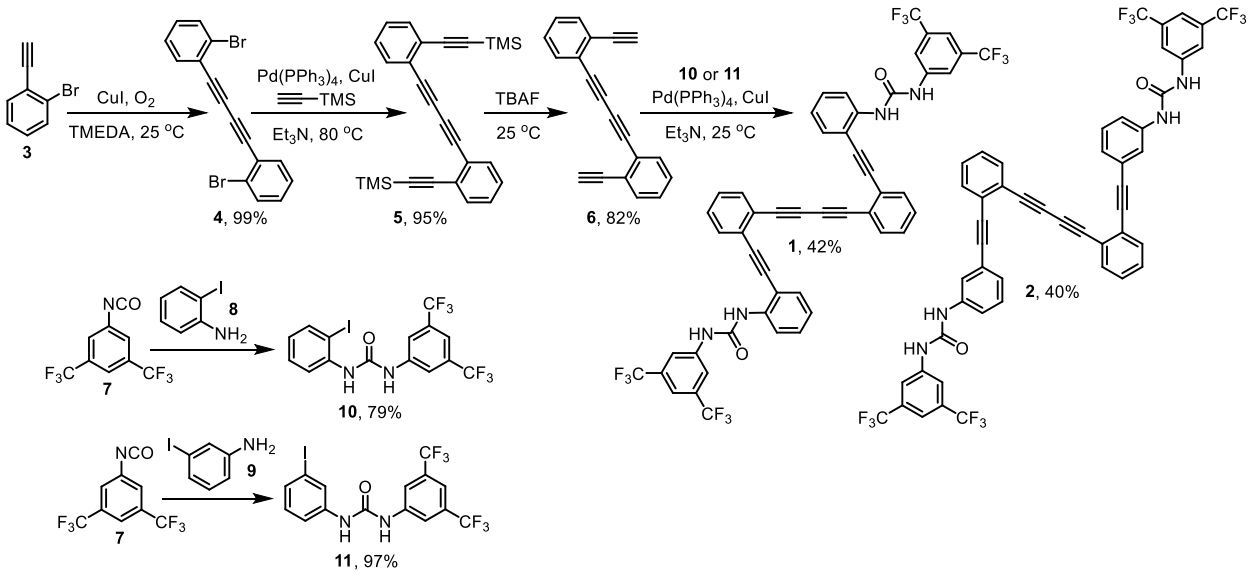
Crystallography

A single crystal was obtained by slow evaporation of a solution of **1** in 2% acetone in hexanes. Single crystal X-ray analysis was performed at 100 K using a Siemens platform diffractometer with graphite monochromated Mo- Kα radiation (λ = 0.71073 Å). Data were integrated and corrected using the APEX 3 program. 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 parameter. Crystal data: $C_{50}H_{26}F_{12}N_4O_2$, $2(C_3H_6O)$, M = 1058.90, colorless prism, 0.76, 0.45, 0.08 mm^3, triclinic space group, *P-1*, a = 10.7462(15), b = 11.6544(16), c = 12.0253(17) Å, V = 1197.0(3) $Å^3$, Z = 1.[11]

Results and discussion

At the onset of this study, we prepared the arylacetylene core **6** which is shared by both sensor designs, Scheme 1.[10] Oxidative dimerization of 2-bromophenylacetylene, **3**, gave the dialkyne **4** in quantitative yields. Palladium catalyzed Sonogashira cross-coupling with trimethylsilylacetylene and deprotection with tetrabutylammonium fluoride, TBAF, then produced **5** and **6**, respectively, in good yields. The terminal 3,5-bistrifluoromethylphenylurea

units **10** and **11** were prepared by addition of the corresponding iodoanilines **8** or **9** to the arylisocyanate **7**, and then employed in the Shonogashira reaction with **6** to afford **1** and **2** in 40-42% yield.



Scheme 1. Synthesis of **1** and **2**.

We noticed that dissolution of the probes requires small amounts of acetone which is probably necessary to disrupt intermolecular hydrogen bonding between the urea units. We were able to grow a single crystal of **1** from hexanes/acetone (98:2). Crystallographic analysis revealed a nonplanar sensor structure together with acetone in the crystal lattice, Figure 1. We then employed the five carboxylic acids **12-16** in chiroptical sensing experiments with the two bis(urea) probes, Figure 2. Unfortunately, sensor **1** did only give a weak CD response to the enantiomers of mandelic acid but remained CD-silent in the presence of the other analytes which might be attributed to steric interference during hydrogen bonding interactions with the ortho-substituted arylurea units. By contrast, we observed strong induced circular dichroism (ICD) signals in all cases using sensor **2** and diethyl ether as the bulk solvent, Figure 3. This probe

generates CD maxima above 300 nm which is generally preferable to eliminate potential interferences from chiral impurities.

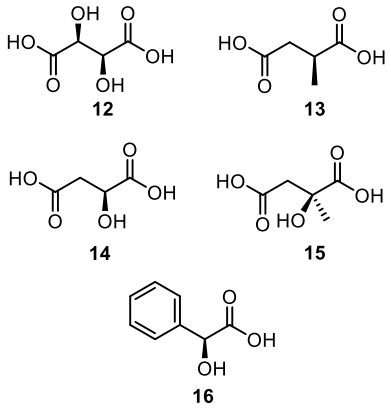


Figure 2. Structures of the carboxylic acids tested. Only one enantiomer is shown.

Attractive features of this chiroptical sensing assay in addition to the strong red-shifted CD effects that originate from the arylacetylene framework are the operational simplicity and time efficiency. Solutions of the sensor and the analyte together with either triethylamine or DBU as base are simply combined, stirred for 10 minutes and then further diluted for CD analysis. The molecular recognition and the imprinting of the analyte chirality onto the sensor scaffold are complete within a few minutes, producing a stable ICD signal. This simple mix-and-measure protocol can easily be adapted to automated multi-well plate technology. The use of the bis(urea) probe **2** is expected to enable parallel ee screening of hundreds of samples with CD plate readers. Undoubtedly, this would further increase the inherent time efficiency of this chiroptical assay in particular in comparison with traditional HPLC techniques. The workflow of the sensing assay is outlined in Figure 3.

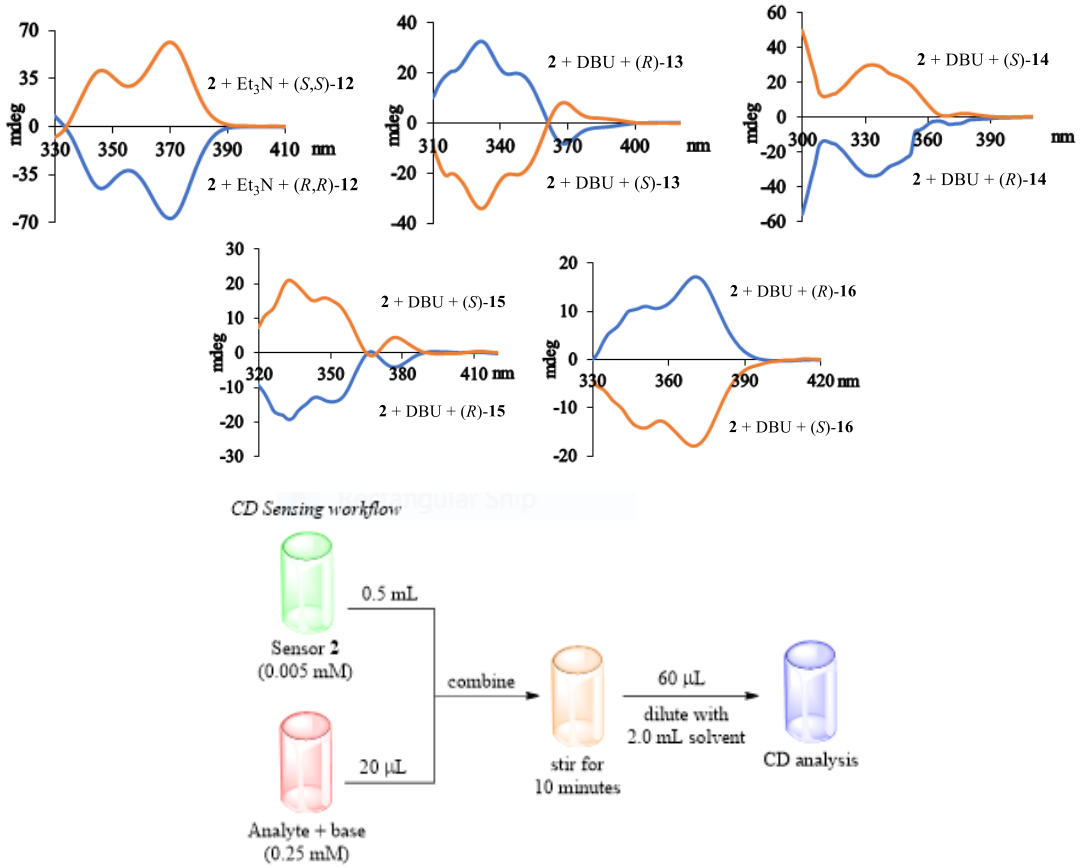


Figure 3. Top: Circular dichroism spectra obtained with **2** and carboxylic acids **12-16** in the presence of Et_3N or DBU. Bottom: Workflow of the chiroptical sensing assay.

The hydrogen bonding interaction between the urea protons in the sensor and the carboxylate groups of the analytes, for example malic acid **14**, is clearly visible from the ^1H NMR titration experiment shown in Figure 4. The urea protons undergo strong downfield shifts upon addition of a half to two equivalents of **14** from 7.95 and 8.51 ppm to 8.98 and 9.62 ppm, respectively. The molecular recognition is also accompanied by a slight downfield shift of the aliphatic protons in **14**. The methine proton at the chiral center in malic acid shifts from 4.26 ppm to 4.33 ppm while the two adjacent diastereotopic protons are shifted from 2.78-2.82 ppm to 2.83-2.86 ppm. Additional NMR and Job plot analysis with tartaric acid gave the same strong downfield shifts for the urea protons and corroborate that a 2:1 hydrogen bond adduct is formed

within a few minutes, see SI. Unfortunately, attempts to identify sensor-analyte adducts by ESI-MS and the formation of co-crystals by slow evaporation of sensor analyte mixtures using chloroform with various co-solvents (acetone, ethyl acetate, THF, diethyl ether) and by varying base additives (DBU, dimethylaminopyridine, 1,4-diazabicyclo[2.2.2]octane, Et_3N) to generate insights into the chiral amplification process via crystallographic analysis were not successful.

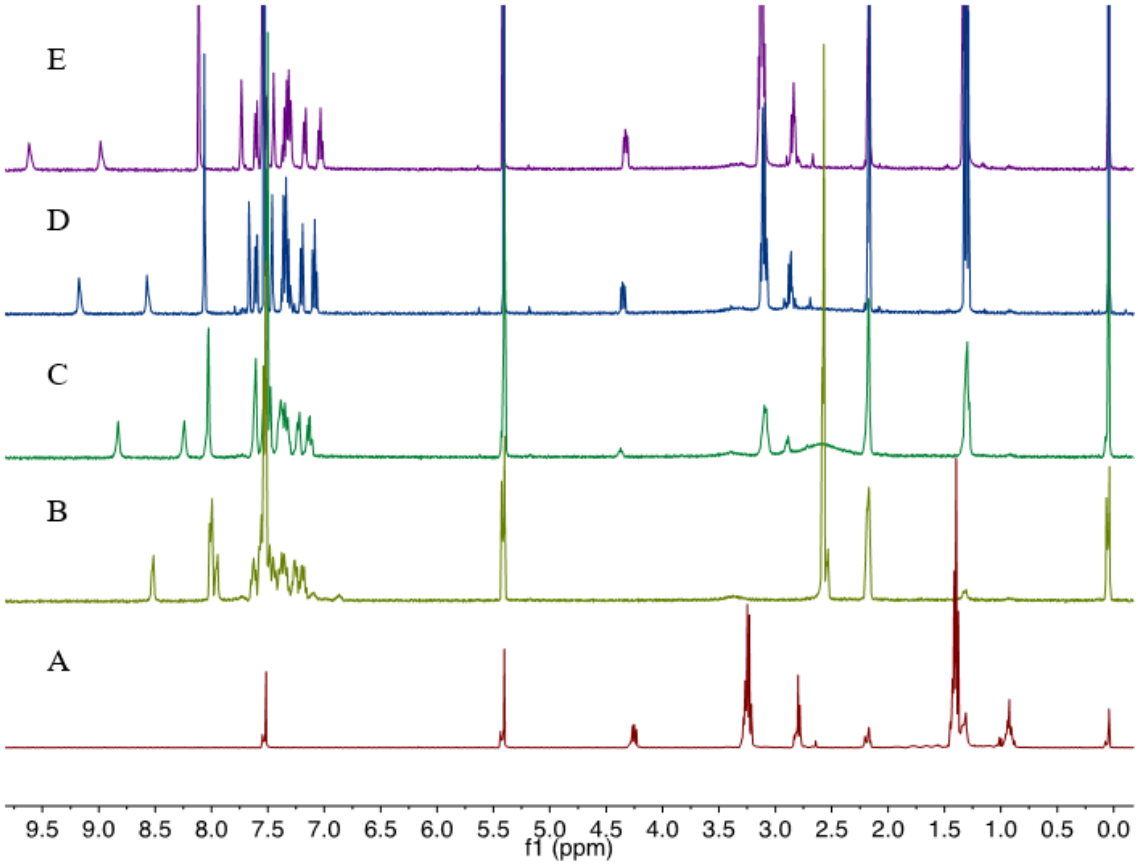


Figure 4. ^1H NMR analysis of the hydrogen bonding interaction between **2** and **14** using a mixture of deuterated chloroform and acetone (4:1) as solvent and triethylamine as base. A: (*S*)-malic acid and 2 eq. of Et_3N. B: Sensor **2**. C: Sensor and diammonium (*S*)-malate (0.5 eq.). D: Sensor and diammonium (*S*)-malate (1 eq.). E: Sensor and diammonium (*S*)-malate (2.0 eq.).

We then investigated the feasibility of quantitative ee determination. First nonracemic mixtures of **12** were prepared and subjected to chiroptical sensing with **2**. Plotting the induced CD amplitudes at 370 nm versus the sample ee's revealed a perfectly linear correlation, Figure 5. With this calibration curve in hand, we analyzed five arbitrarily mixed samples containing tartaric acid in both low and high ee's, Table 1. After mixing with the bis(urea) probe in the presence of triethylamine for a few minutes, the solutions were directly applied to CD analysis following the workflow schematic shown above. The absolute configuration of the major enantiomer in each sample was correctly determined from the sign of the induced CD signal and the enantiomeric composition was calculated based on the magnitude of the ICD at 370 nm with good accuracy. For example, the sensing analysis of tartaric acid samples containing the (*S,S*)- or (*R,R*)-enantiomer in 78.0 and 94 %ee gave 73.1 and 94.2 %ee, respectively, see entries 1 and 5 in Table 1.

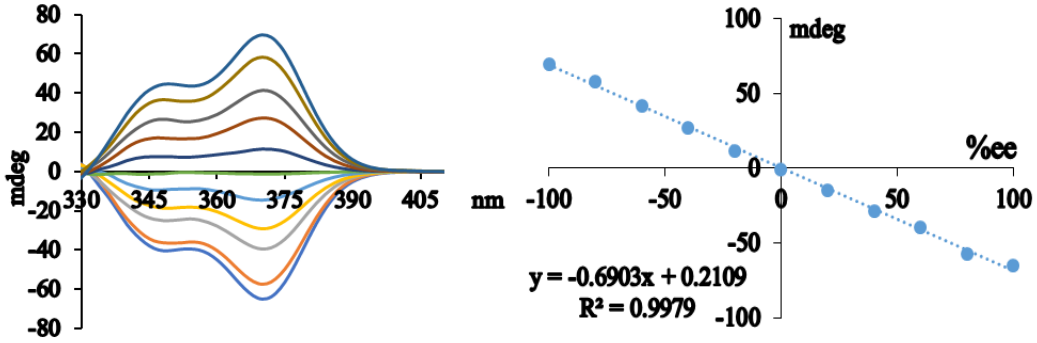


Figure 5. CD spectra of the mixture obtained with **2**, Et_3N, and scalemic samples of **12** and linear relationship between the CD amplitude at 370 nm and the sample ee.

Table 1. Experimentally determined ee's of five scalemic samples of **12** using the ICD maxima of **2** at 370 nm.

Sample Composition		Chiroptical Sensing		%Error
Abs. Config.	%ee	Abs. Config.[a]	%ee[b]	
S,S	78.0	*S,S*	73.1	4.9
S,S	46.0	*S,S*	39.6	6.4
R,R	16.0	*R,R*	16.3	0.3
R,R	76.0	*R,R*	79.3	3.3
R,R	94.0	*R,R*	94.2	0.2

[a]Based on the sign of the CD response. [b]Based on the amplitude of the ICD at 370 nm.

Conclusion

In summary, we have introduced an oligo(phenylene)ethynylene foldamer with two terminal urea units to chiroptical sensing of carboxylic acids. Formation of a hydrogen bond complex between the stereodynamic probe and the analyte yields characteristic CD signals originating from the arylacetylene framework at high wavelengths. The induced chiroptical signals can be used for quantitative ee analysis which was demonstrated with five nonracemic samples of tartaric acid. This chirality sensing assay is operationally simple, fast and easily adjusted to high-throughput screening technology and multi-well plate CD readers.

Acknowledgements

This work was supported by the U.S. National Science Foundation (CHE-1464547 and CHE-1764135).

Conflict of Interests

The authors declare no competing conflict of interests.

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11 The CCDC number 1853292 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.