RESEARCH ARTICLE

Chiroptical Switching and Quantitative Chirality Sensing with (Pseudo)halogenated Quinones

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Abstract: (Pseudo)halogenated quinones react smoothly with chiral amines, amino alcohols and amino acids toward push-pull conjugates with optical sensing and switching applications. The chiroptically active conjugates can serve as redox switches between two reversibly interconverting states with remarkably different UV and CD signatures. The addition of sodium borohydride generates a hydroquinone derivative that is quantitatively re-oxidized to the original quinone upon exposure to air. This chiroptical quinone/hydroquinone redox switch system combines several attractive features such as simple set-up, use of inexpensive chemicals, short response time, and thermal and photochemical stability. A conceptually new sensing approach that is based on integrated chiroptical amplification and redox switching enables on-the-fly deconvolution of otherwise overlapping CD spectra and is used for quantitative *er* analysis of challenging samples containing constitutional isomers in varying enantiomeric compositions.

Introduction

Quinones are ubiquitous small molecules in nature and have found widespread use in numerous applications that are testimony to the unique physiological, medicinal, photophysical and chemical properties of this fascinating pool of compounds (Figure 1).

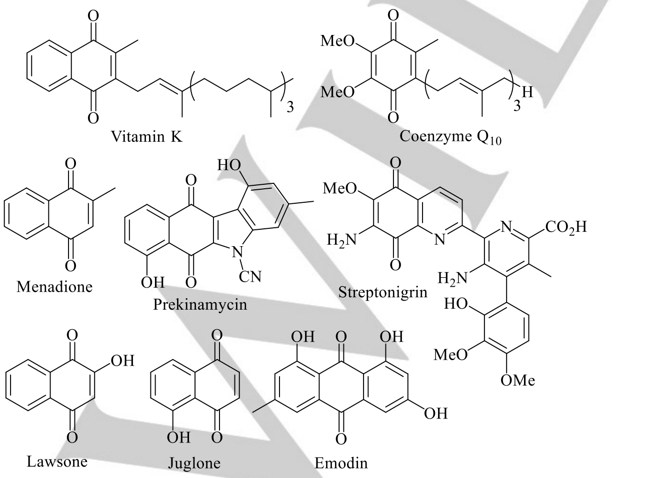


Figure 1. Structures of biologically active quinones.

They play essential roles in important biological processes including aerobic respiration,[1] photosynthesis,[2] cellular signaling,[3] and metabolic transformations,[4] and embody a frequently encountered structural unit in Vitamin K,[5] Coenzyme Q10,[6] Menadione,[7] Streptonigrin,[8] Prekinamycin[9] and other biologically active compounds.[10] Quinones also serve as versatile chemical building blocks,[11] dyes,[12] redox catalysts,[13] and are used in energy harvesting,[14] electrochemical water-splitting,[15] and metal-free energy storage[16] technologies.

This striking diversity of quinone utility and function in chemistry, engineering and biology encouraged us to investigate whether the distinguishing optical and electrophilic properties could be exploited in new ways to conquer additional chemical space for this eminent class of compounds. We envisioned that quinones exhibiting replaceable halide or pseudohalide substituents would allow smooth covalent capture of a variety of nucleophilic chiral compounds and thus trigger a strong chiroptical response originating from the proximate positioning of the molecular asymmetry onto its chromophoric ring structure. This chemistry was expected to occur fast and quantitatively under mild conditions with preservation of the fully conjugated dione structure. The substitution of an electron-withdrawing halide or cyanide by an electron-donating moiety, for example an amine, should significantly alter the optical properties as it generates strong push-pull conjugation across the quinone scaffold. Because the carbon-nitrogen bond formation is based on an addition-elimination sequence, it does not produce a new chirality center. As a result, complicated diastereomeric mixtures are not produced which assures that the interpretation and quantitative analysis of any optical changes measured remain simple. With these chemical and optical design features in mind, we hypothesized that the placement of a chiral amine or another suitable *N*-nucleophile directly at the quinone ring will induce strong UV and CD signals with potential for quantitative chirality sensing, a field that has received increasing attention in recent years.[17-19] Chiroptical switches that exist in the form of two reversibly interchangeable states have considerable potential in a variety of applications including molecular recognition, optical displays, imaging, data storage, logic gates, and asymmetric catalysis. Intriguing examples of redox-triggered polymers,[20] metal coordination complexes,[21-25] and other small molecular systems[26-30] have been introduced.

Encouraged by these developments, we expected that the attachment of a chiral amine to an achiral quinone probe would not only enable quantifiable chirality sensing but also provide a simple platform for chiroptical redox switching that is easily controlled by an external stimulus. We now show that inexpensive, commercially available quinones react very quickly with chiral amines, amino alcohols and amino acids in organic solvents or aqueous solutions toward chiroptically active push-pull conjugates. The reaction is fast, occurs at room temperature, is insensitive to moisture and spontaneously generates characteristic UV and CD signals above 300 nm which allow direct quantitative determination of the concentration, enantiomeric excess and absolute configuration of these compounds without any work-up.

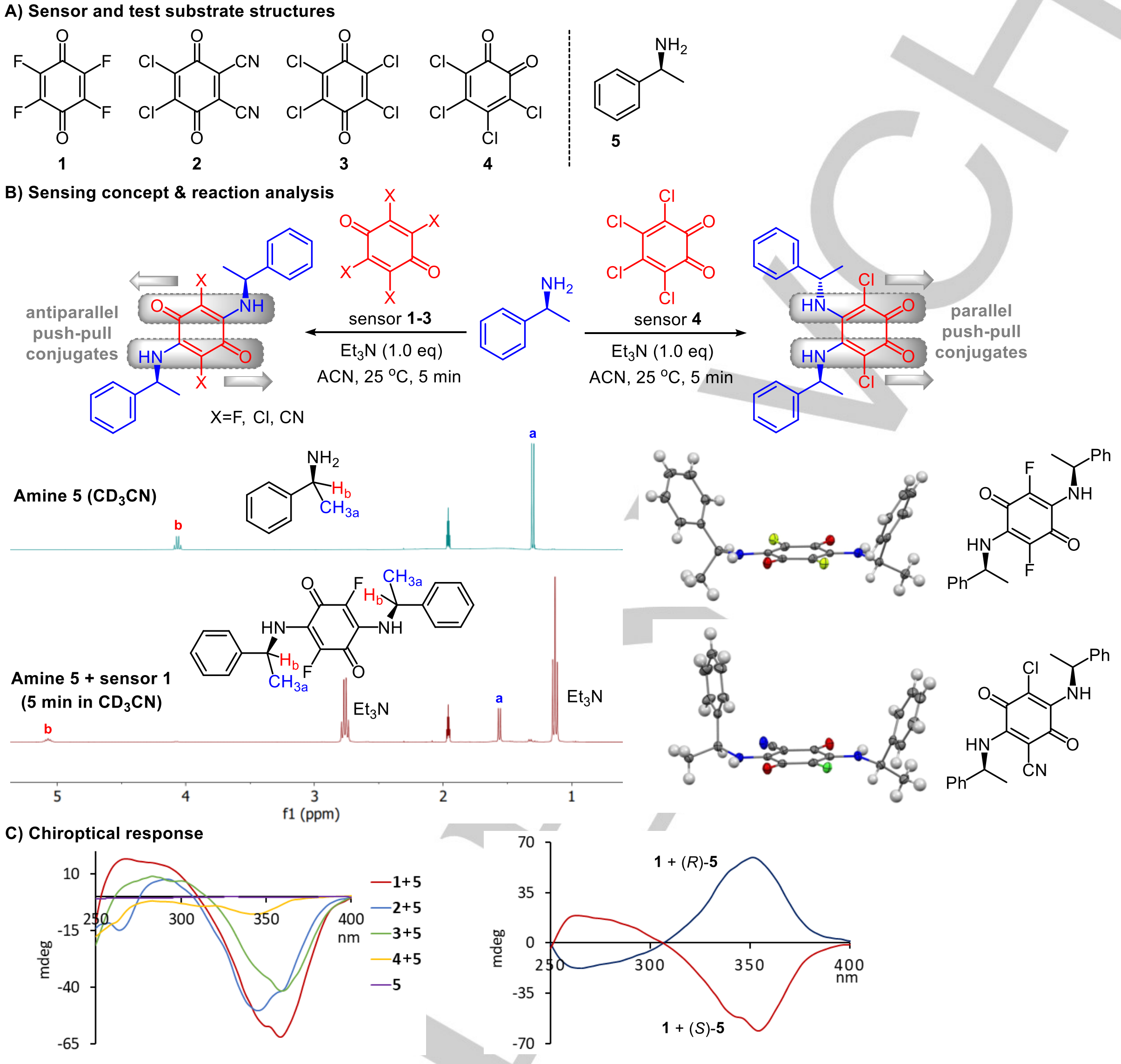


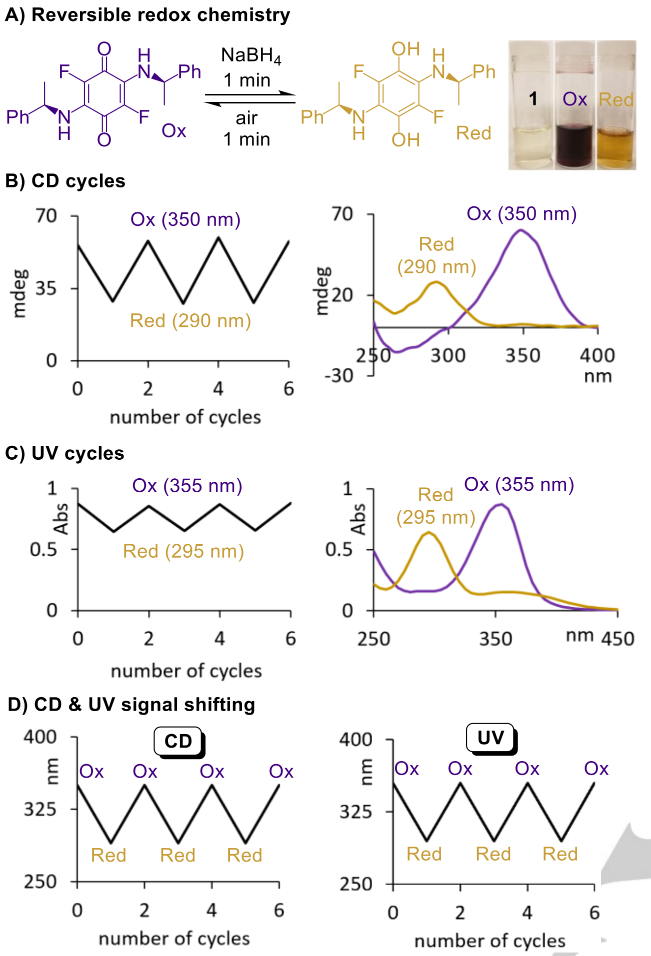
Figure 2. A) Structures of the quinones **1-4** and (*S*)-phenylethylamine, **5**. B) Sensing strategy and reaction analysis including crystal structures of (*S,S*)-2,5-difluoro-3,6-bis((1-phenylethyl)amino)-1,4-benzoquinone and (*S,S*)-2-chloro-5-cyano-3,6-bis((1-phenylethyl)amino)-1,4-benzoquinone. C) Circular dichroism spectra of the substitution products obtained from **1-4** and **5** at 0.13 mM in acetonitrile. The lack of a CD signal of free (*S*)-**5** under the same conditions is shown for comparison.

The practicality and accuracy of this optical chirality sensing approach is demonstrated with 20 samples covering a wide enantiomeric composition range and varying analyte concentrations. The amine adducts also undergo reversible redox switching upon alternating addition of sodium borohydride and exposure to air between two stable states with remarkably different UV and CD signatures. The chiroptical quinone/hydroquinone switch displays several attractive features such as simple operation, use of inexpensive materials, ease of preparation, fast response, thermal and photochemical stability, and it shows no sign of degradation or signal decay after three redox cycles. In contrast with noncovalent analyte sensing that is based on reversible metal coordination or supramolecular assemblies,[31-36] the stoichiometric covalent binding and redox switching theme exploited herein is fast and avoids formation of complicated complexes with highly convoluted optical readouts that can be anticipated when more than one chiral target compound needs to be analyzed. We show how this advance can be used to streamline er analysis of challenging samples containing constitutional isomers.

Results and Discussion

Chirality sensing and optical redox switching. At the onset of this study, we decided to prove the feasibility of our hypothesis with the readily available tetrasubstituted benzoquinones **1**-**4** and 1-phenylethylamine, **5**, as the test substrate (Figure 2A). Our initial screening efforts showed that each quinone reacts with two equivalents of **5** at room temperature and NMR analysis revealed that the double substitution reaction is complete within 5 minutes while detectable amounts of by-products were not observed (Figure 2B). We were able to grow single crystals of the reaction products generated with **1** and **2** by slow evaporation of dichloromethane/hexane solutions. The crystallographic analysis verified the regioselective formation of 1,4-disubstituted products displaying two antiparallel push-pull conjugates. The click chemistry nature of the reaction between **5** and **1**-**4** greatly facilitates chiroptical sensing and switching applications as any work-up and product isolation is unnecessary. We therefore subjected the unaltered reaction mixtures obtained with (*S*)-**5** and the quinone probes in acetonitrile after a short stirring period directly to CD analysis after dilution to submillimolar concentrations with the same solvent (Figure 2C). Strong negative Cotton effects at long wavelengths were observed with the paraquinones derived from **1**-**3** while the amination of the orthoquinone **4** gave relatively weak signals under identical conditions. We then included the *R*-enantiomer of **5** in the same protocol and obtained the corresponding positive Cotton effect as expected (see Figure 2).

The reaction between the quinones **1**-**4** and 1-phenylethylamine, **5**, coincides with a drastic color change (see Supporting Information). For example, the off-white color of a solution of **1** in THF turns to dark purple within five minutes upon addition of **5** and triethylamine. After screening several reducing agents and conditions we found that reduction of the push-pull quinone conjugate with sodium borohydride immediately gives a dark yellow solution which was assigned to the corresponding hydroquinone. The structures of the oxidized and reduced states were confirmed by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy and crystallographic analysis (SI).[37] Exposure of the solution to air regenerated the original color within a minute (Scheme 1). The reversibility, short response time and the impressive colorimetric changes encouraged us to further investigate chiroptical switching with this system. A reaction mixture of probe **1**, (*R*)-phenylethylamine and Et_3N was subjected to reduction/oxidation cycles using $NaBH_4$ and air, respectively, in a THF/methanol solution. The optical changes were measured by UV and CD spectroscopy. The oxidized state, which is visible by the dark purple color, shows a strong UV absorption at 355 nm. The reduction produces a new major UV absorption at 295 nm and a minor one at 375 nm. Re-oxidation was achieved in less than one minute by agitating the solution with air, regenerating the characteristic purple color of the solution and the original UV signal at 355 nm while the bands at 295 and 375 nm disappeared. We monitored the same redox sequence by CD spectroscopy. The redox switching is accompanied by a dual chiroptical response as both the intensity and the wavelength of the CD maxima are significantly changing. Reduction of the quinone conjugate produced a substantial blue shift of the large CD amplitude at 350 nm of the purple oxidized state by 60 nm. The dark yellow hydroquinone which was formed spontaneously displayed a CD signal at 290 nm with approximately half intensity. NMR and chiroptical measurements showed that the oxidation and reduction steps are fast and occur quantitatively. The operation of this chiroptical switch is straightforward and does not require cumbersome precautions. In fact, the individual redox states were exposed to light during all experiments and did not show any sign of photochemical degradation. We then conduced several switching cycles with this system and found no sign of signal decay after three consecutive redox sequences (Scheme 1). It is noteworthy that this chiroptical quinone/hydroquinone switch is easily set up with inexpensive chemicals, and it exhibits thermal and photochemical stability together with distinctive color, UV and CD signal transformations that occur in less than one minute upon addition of the external stimuli.



Scheme 1. Chiroptical redox switching using $NaBH_4$ and air as external stimuli. Reduction: $NaBH_4$ in MeOH (33.3 mM) was added to the quinone solution in THF (16.7 mM) to afford the hydroquinone in less than 1 min at room temperature. Oxidation: The hydroquinone sample was agitated with air for 1 min at room temperature to afford the original quinone. See SI for more details.

Chirality sensing scope. Having studied the chiroptical redox switching utility, we selected the tetrafluorobenzoquinone **1**, which gave the strongest chiroptical response upon binding of amine **5**, to further explore the general scope and utility of the chirality sensing concept illustrated in Figure 2. We found that the reaction and the subsequent CD analysis can be completed within a few minutes and without any precautions. Screening of ACN, $CHCl_3$, THF or EtOH as solvent showed essentially the same strong CD induction (see SI). The CD assay is actually quite practical and robust; it can be conducted under air and in the presence of moisture or even in aqueous solutions if necessary. This enables sensing of free amino acids that do not need to be derivatized to improve solubility in organic solvents, *vide infra*. Encouraged by this operational simplicity and the initial chirality sensing results with **5**, we continued testing a variety of other amines, some carrying an aromatic group which may contribute to the CD induction, for example via π-π stacking with the quinone moiety, but also the purely aliphatic substrates **15**-**19**. Strong CD signals at long wavelengths were obtained with the same protocol in all cases including 2-methylphenethylamine, **19**, which carries the chirality center remote from the amino group (see SI and Figure 3 for selected examples). It is noteworthy that the generation of a large CD amplitude above 300 nm is generally considered beneficial because it eliminates possible interferences that may arise from the presence of chiral impurities during quantitative *er* analysis.

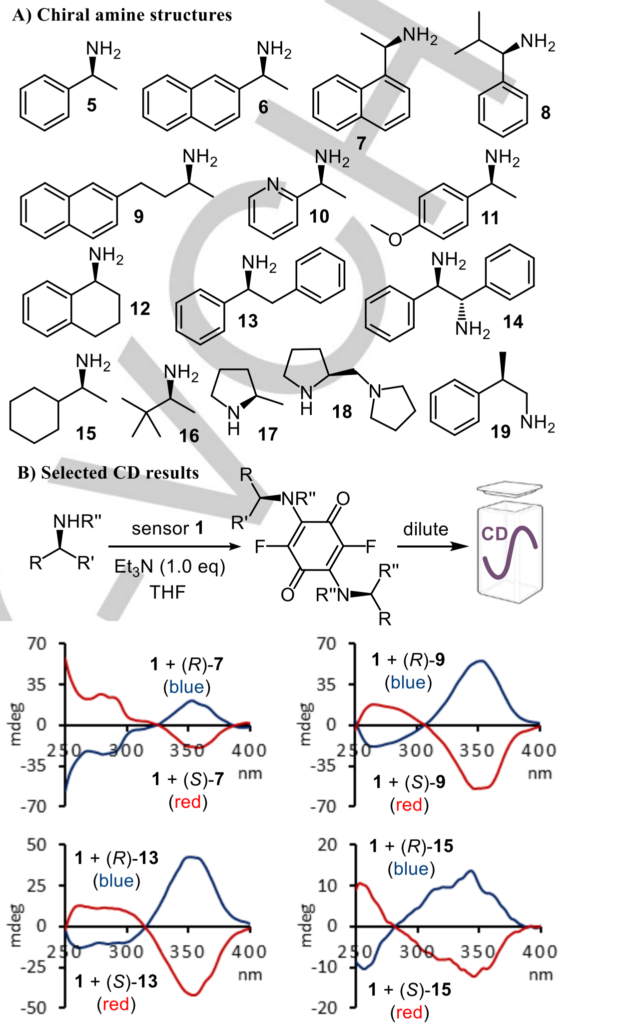


Figure 3. Structures of chiral amines tested (only one enantiomer is shown) and selected CD spectra obtained by sensing of **7**, **9**, **13** and **15**, respectively, with **1** in THF. Reaction conditions: A solution of the chiral amine (3.33 mM), Et_3N (3.33 mM) and **1** (1.67 mM) in 1.5 mL of tetrahydrofuran was stirred for 5 minutes at room temperature. The CD analyses of the reactions with these amines were conducted at 0.10-0.15 mM in THF, see SI for details.

We then extended essentially the same protocol to the amino alcohols **20**-**28** and used an aqueous acetonitrile pH 8.5 borate buffer solution for the sensing of the amino acids **29**-**40** (Figure 4). In accordance with our chiral amine sensing study, these additional 21 substrates were selected to encompass structures exhibiting a small aromatic ring as well as some that are devoid of a chromophore and therefore increasingly challenging. Nevertheless, distinct CD effects were obtained without exception just by fast mixing of the assay components and CD analysis without further delay (see SI).[19,38-43]

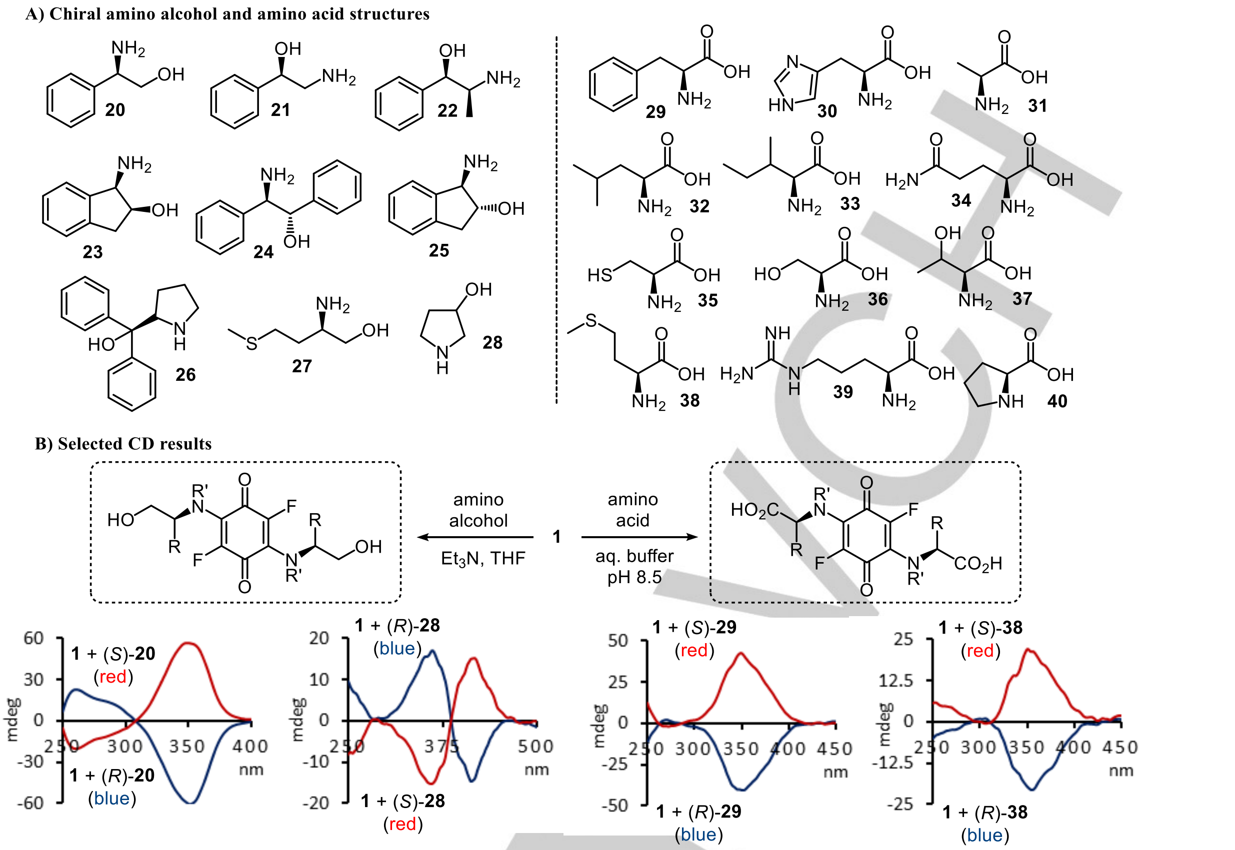


Figure 4. Structures of chiral amino alcohols and amino acids tested (only one enantiomer is shown) and selected CD spectra obtained by sensing with **1** in THF or aqueous borate pH 8.5 buffer. Amino alcohol reaction conditions: A solution of a chiral amino alcohol (3.33 mM), Et_3N (3.33 mM) and **1** (1.67 mM) in 1.5 mL of tetrahydrofuran was stirred at 25 ºC for 5 minutes. Amino acid sensing: A solution of **1** (1.00 mM) and an amino acid (2.00 mM) in 2.5 mL of acetonitrile:aqueous pH 8.5 borate buffer (4:1 v/v, 10.0 mM) was stirred at 25 ºC for 5 minutes. The CD analyses of the reactions with the amino alcohols **20** and **28** were conducted at 0.10-0.15 mM in THF. The amino acid sensing was performed at 0.07 mM in ACN:aqueous pH 8.5 borate buffer 4:1 (v/v), see SI for details.

Quantitative *er* and concentration sensing. Having successfully applied the quinone **1** to a total of 36 structurally diverse compounds we chose to investigate the possibility of quantitative chirality sensing. We realized that this would be most impactful if simultaneous determination of the enantiomeric ratio *and* of the overall concentration of a chiral analyte were possible. Fortunately, we found that the sensing reaction yields a strong UV change at ~350 nm (Figure 5). Because we avoid formation of a new chirality center during the C-N bond formation the quantitative analysis of this steadily increasing UV signal is greatly simplified. In fact, this optical probe response is not enantioselective, i.e. the same UV response is obtained irrespective of the enantiomeric sample composition. As a result, the profound CD signal induction can be correlated to the *er* and the characteristic UV change to the total concentration of both enantiomers, by using the same sample. This is practical and a user-friendly solution to a generally cumbersome task because CD spectrophotometers typically generate CD and UV spectra together. Interestingly, the induced CD signal increases linearly with the enantiomeric excess of the sample. Because two analyte molecules are attached to the quinone core one can expect a mixture of (*R*,*R*)-, (*S*,*S*)- and (*R*,*S*)-isomeric products when both enantiomers are present in the original sample. However, the heterochiral product is centrosymmetric and a meso compound that is naturally CD-inactive. The resulting linearity of the CD signal induction simplifies the chiroptical sensing analysis. NMR analysis of the reaction between **1** and racemic **5** showed that the three possible stereoisomeric 2,5-difluoro-3,6-bis((1-phenylethyl)amino)-1,4-benzoquinones are approximately formed in the statistically favored 1:2:1 ratio, indicating negligible asymmetric induction once the first amine is bound, see SI.

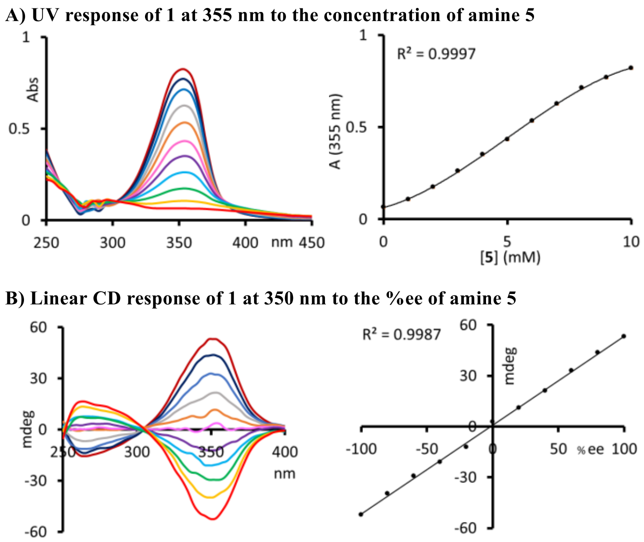


Figure 5. Correlation of the UV and CD responses of **1** to the concentration and enantiomeric composition of 1-phenylethylamine. The UV and CD measurements were performed after dilution with THF as described above, see SI for details.

With a thorough understanding of the mechanistic underpinnings of our chirality sensing method, we prepared twenty amine samples containing **5** or **17**, representing an aromatic and an aliphatic substrate, in widely varying concentrations and enantiomeric ratios. These mixtures were applied in the general protocol described above for simultaneous UV/CD analysis. The sample concentrations and enantiomeric ratios were determined using the chiroptical signals at 350 nm, and the sign of the CD response was used to assign the absolute configuration of the major enantiomer by comparison with the previously obtained reference CD spectrum. This worked well without exception. For example, we determined an *er* of 20.7 (*S*) : 79.3 (*R*) and a total concentration of 4.8 mM for a 5.0 mM sample with 20.0% of the *S*-enantiomer and 80.0% of (*R*)-**5** (entry 1). The UV/CD analysis of a solution of **5** at 6.0 mM with an *S/R* ratio of 82.0 : 18.0 gave 5.9 mM and an enantiomeric composition of 85.5 : 14.5 (entry 2). Similar results were obtained with the ten 2-methylpyrrolidine samples (entries 11-20). The absolute error margins are within a few percent which is generally considered acceptable for high-throughput screening applications.[19]

Table 1. Determination of the concentration, enantiomeric ratio, and absolute configuration of samples of phenylethylamine (entries 1-10) and 2-methylpyrrolidine (entries 11-20) by simultaneous UV and CD analysis with reagent **1**.

Entry	Sample composition			Sensing results		
	AC	Conc. (mM)	*S/R*	AC	Conc. (mM)	*S/R*
1	*R*	5.0	20.0:80.0	*R*	4.8	20.7:79.3
2	*S*	6.0	82.0:18.0	*S*	5.9	85.5:14.5
3	*S*	6.5	60.0:40.0	*S*	7.0	60.6:39.4
4	*S*	7.0	70.0:30.0	*S*	7.0	72.5:27.5
5	*S*	7.5	90.0:10.0	*S*	7.8	97.6:2.4
6	*R*	8.0	35.0:65.0	*R*	8.2	32.6:67.4
7	*R*	8.0	25.0:75.0	*R*	8.0	18.8:81.2
8	*R*	4.0	22.0:78.0	*R*	3.6	21.3:78.7
9	*R*	8.0	5.0:95.0	*R*	8.1	2.0:98.0
10	*S*	5.0	60.0:40.0	*S*	4.6	58.0:42.0
11	*R*	5.0	20.0:80.0	*R*	4.9	25.0:75.0
12	*S*	6.0	82.0:18.0	*S*	5.4	82.5:17.5
13	*S*	6.5	60.0:40.0	*S*	6.2	57.0:43.0
14	*S*	7.0	70.0:30.0	*S*	7.0	70.5:29.5
15	*S*	7.5	90.0:10.0	*S*	7.5	92.5:7.5
16	*R*	8.0	35.0:65.0	*R*	7.8	38.0:62.0
17	*R*	8.0	25.0:75.0	*R*	7.8	28.5:71.5
18	*R*	4.0	22.0:78.0	*R*	3.6	25.0:75.0
19	*R*	8.0	5.0:95.0	*R*	8.4	5.5:94.5
20	*S*	5.0	60.0:40.0	*S*	4.7	56.5:43.5

The concentrations and enantiomeric ratios were determined using the UV and CD responses of the probe at 350 nm. The absolute configuration (AC) of the major enantiomer was assigned by comparison of the observed Cotton effects to a reference sample.

Integration of chiroptical sensing and switching. The introduction of the first small-molecule probes that unite chirality sensing and redox switching properties has important implications and generates new applications. We envisioned that the integration of chiroptical sensing and redox state manipulation would enable *er* analysis of challenging compound mixtures, for example samples containing constitutional isomers in varying enantiomeric ratios which to the best of our knowledge has not been reported to date. To prove that this is possible, we chose amines **6** and **7** as analytes and we prepared the new quinone **41**. In contrast with **1**-**4** which have two reaction sites and bind two substrates, 2-(benzylamino)-3,5,6-trifluorocyclohexa-2,5-diene-1,4-dione, **41**, exhibits only one replaceable fluoride and therefore reacts with 1:1 stoichiometry. This avoids formation of complicated sensing mixtures that would be expected with **1**-**4** when samples containing different compounds need to be analyzed. Nevertheless, **41** still produces an antiparallel push-pull conjugate which proved to be an advantageous chirality sensing motif during this study.

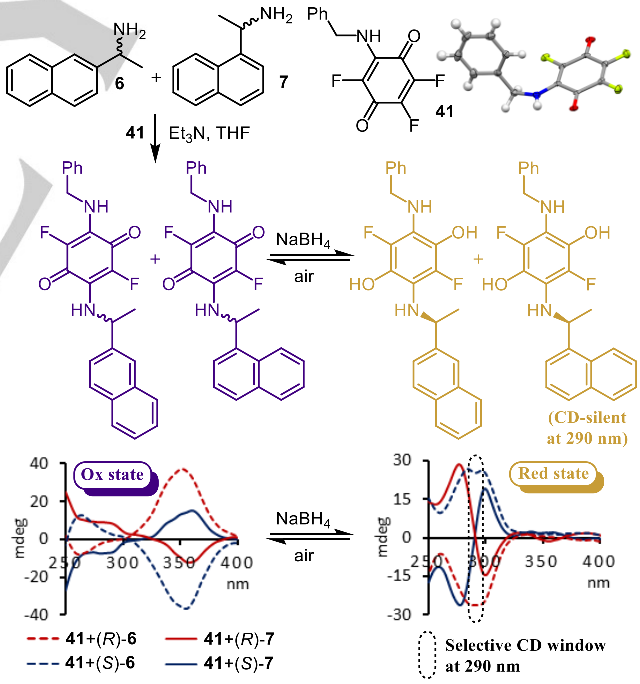


Figure 6. Spectral deconvolution by integrated chirality sensing and redox switching with quinone **41** and mixtures of amines **6** and **7**. The redox switching coincides with a color change from deep purple to yellow. Reaction conditions: Probe **41** (8.33 mM), Et_3N (8.33 mM) and the amine (8.33 mM) were dissolved in 1.5 mL of THF and stirred at 25 °C for 10 minutes. Reduction: $NaBH_4$ in MeOH (25.0 mM) was added to the reaction mixture to afford the corresponding hydroquinone at 25 °C in less than 1 min. Oxidation: The hydroquinone sample was agitated with air at room temperature for 1 min to afford the original quinone. See SI for details.

As expected, we found that chirality sensing of the constitutional isomers **6** and **7** with **41** yields strong CD spectra but with substantial overlap. Traditional chiroptical analysis of nonracemic mixtures of these amines would produce highly convoluted spectral information that is difficult to decipher and quantify. Fortunately, redox switching from the oxidized to the reduced state generates a complementary scenario that addresses this problem. The hydroquinone derivative of **7** obtained by reduction with $NaBH_4$ is CD-silent at 290 nm while the hydroquinone product obtained with **6** has a strong and easily quantifiable CD amplitude at this wavelength (Figure 6). The redox chemistry thus generates crucial sensing data obtained on-the-fly with simply by adding the reductant to the same reaction mixture. We were able to use the CD readouts measured at 290 nm in the reduced state to determine *er* values of **6** by linear regression without interference from the other amine product. With that information in hand, we used the composite CD output obtained at 356 nm in the oxidized state to calculate the enantiomeric ratio of **7**. The success of this concept is demonstrated with 10 samples containing both amines in varying enantiomeric compositions (Table 2).

Table 2. Chiroptical redox *er* sensing of nonracemic mixtures of amines **6** and **7**.

Sample composition				Sensing results			
Amine 6		Amine 7		Amine 6		Amine 7	
R/S	AC	*R/S*	AC	*R/S*	AC	*R/S*	AC
90.0/10.0	*R*	80.0/20.0	*R*	96.5/3.5	*R*	80.5/19.5	*R*
20.0/80.0	*S*	85.0/15.0	*R*	15.0/85.0	*S*	87.5/13.5	*R*
60.0/40.0	*R*	5.0/95.0	*S*	67.0/33.0	*R*	11.0/89.0	*S*
25.0/75.0	*S*	40.0/60.0	*S*	27.5/72.5	*S*	39.5/60.5	*S*
5.0/95.0	*S*	90.0/10.0	*R*	1.0/99.0	*S*	89.5/10.5	*R*
65.0/35.0	*R*	70.0/30.0	*R*	60.0/40.0	*R*	65.5/34.5	*R*
85.0/15.0	*R*	98.0/2.0	*R*	81.0/19.0	*R*	100/0.0	*R*
98.0/2.0	*R*	65.0/35.0	*R*	92.0/8.0	*R*	69.0/31.0	*R*
30.0/70.0	*S*	25.0/75.0	*S*	30.0/70.0	*S*	21.5/78.5	*S*
15.0/85.0	*R*	80.0/20.0	*R*	11.0/89.0	*R*	85.0/15.0	*R*

The enantiomeric ratios of **6** and **7** in the mixtures were determined using CD signals generated with probe **41** in the oxidized (356 nm) and reduced (290 nm) states. The absolute configuration (AC) of the major enantiomer was assigned by comparison of the observed Cotton effects to a reference sample.

Conclusion

In summary, we have shown that amines, amino alcohols and amino acids quickly add to (pseudo)halogenated quinones to produce push-pull conjugates exhibiting distinct colorimetric, UV and CD properties. The carbon-nitrogen bond formation is based on an addition/elimination sequence and therefore does not produce a new chirality center. As a result, the UV changes are not dependent on the sample *er* and can be correlated to the overall concentration of these compounds. At the same time, strong circular dichroism signals are induced that allow determination of the absolute configuration by comparison of the sign of the Cotton effect with a reference sample while the enantiomeric ratio is quantified using the amplitude of the CD maximum. The UV and CD signals produced *in vitro* appear above 300 nm which is advantageous to eliminate interferences that could arise from the presence of chiral impurities. The sensing reaction is fast, occurs at room temperature without by-product formation, tolerates a variety of solvents, and it is insensitive to moisture. Altogether, this protocol is broadly applicable as demonstrated with more than thirty aliphatic and aromatic target compounds, operationally simple, robust, avoids any form of work-up, is sufficiently accurate while much faster and less costly than traditional chromatographic methods, and amenable to high-throughput analysis with commercially available UV/CD plate readers. Alternatively, the chiroptically active push-pull conjugates can serve as redox switches exhibiting two stable states that can be interconverted at will with external stimuli. The addition of sodium borohydride generates a hydroquinone which is quantitatively re-oxidized to the original quinone upon exposure to air. The corresponding redox couple has remarkably different UV and CD signatures and the switching coincides with a stark colorimetric change. This chiroptical quinone/hydroquinone redox switch combines several attractive features such as simple set-up, use of inexpensive chemicals, short response time, thermal and photochemical stability, and it shows no sign of degradation or signal decay after three redox cycles. Moreover, integrated chiroptical sensing and switching, shown here for the first time, enables on-the-fly spectral deconvolution of otherwise overlapping CD spectra. This conceptually new approach is shown to streamline currently cumbersome chirality analysis and molecular recognition workflows with challenging compound mixtures, for example samples containing constitutional isomers in varying enantiomeric ratios. The unique chiroptical switching properties of (pseudo)halogenated quinones discovered in this study may also have considerable promise in rapidly growing technologies based on optical imaging or tunable multicolor materials.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: chirality • chiroptical switching • circular dichroism • sensors • stereoisomers

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Quinones are used for quantitative UV/CD sensing of the concentration and enantiomeric excess of more than thirty aliphatic and aromatic chiral amines, amino alcohols and amino acids. The integration of redox switching into the sensing protocol allows spectral deconvolution of otherwise overlapping CD spectra that are obtained with challenging compound mixtures.