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Stereodynamic Quinone-Hydroquinone Molecules that Enantiomerize at sp^3 -Carbon via Redox-Interconversion

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Abstract

Since the discovery of molecular chirality, non-superimposable mirror-image organic molecules have been found to be essential across biological, chemical processes, and increasingly in materials science. Generally, carbon centers containing four different substituents are configurationally stable, unless bonds to the stereogenic carbon atom are broken and reformed. Herein, we describe sp^3 -stereogenic carbon-bearing molecules that dynamically isomerize, interconverting between enantiomers without cleavage of a constituent bond, nor through remote functional group migration. The stereodynamic molecules were designed to contain a pair of redox-active substituents, quinone and hydroquinone groups, which allow the enantiomerization to occur *via* redox-interconversion. In the presence of an enantiopure host, these molecules undergo a deracemization process that allows observation of enantiomerically enriched compounds. This work reveals a fundamentally distinct enantiomerization pathway available to chiral compounds, coupling redox-interconversion to chirality.

Graphical Abstract

Introduction

The chirality of molecules with sp^3 -hybridized carbon atoms bearing four different substituents is a ubiquitous and well-studied phenomena in stereochemistry.¹ The enantiopurity of molecules with chiral features is vital in biology,² materials science,³ and, of course, it is fundamental to chemistry. As such, chemists have been continuously

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ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website. Experimental methods, characterization of all compounds, and copies of spectra can be found in the Supporting Information. X-Ray crystallographic data for compounds **1a**, **2a**, **2b**, **3a**, **3b**, and **1b** (**4b**) are available, free of charge, from the Cambridge Crystallographic Data Center via <https://www.ccdc.cam.ac.uk/structures/>. CCDC number 1559706 (**1a**), 1559708 (**2a**), 1559707 (**2b**), 1559705 (**3a**), 1559704 (**3b**), and 1559709 (**1b/4b**).

challenged to generate chiral elements in molecules with high levels of stereochemical purity.⁴ Yet, molecular chirality can also be dynamic,^{5,6} with the loss of enantioenrichment, a signature of the process of racemization. Spontaneous enantiomeric enrichment is rare, and associated with intriguing molecular mechanisms.⁷ Most often, racemization or enantiomerization at an sp^3 -carbon atom is a function of bond cleavage at a stereogenic center. Solvolysis, homolytic, or heterolytic bond cleavage illustrate the canonical mechanisms for enantiomer interconversion at sp^3 -carbon atoms (Figure 1A). Although less common, enantiomerization at an sp^3 -carbon atom can also occur without breaking a constitutive bond. Examples include migration of labile functional groups that are remote from a stereogenic center (Figure 1B).^{8,9} Herein, a molecular system that exhibits stereodynamic behavior based on the phenomenon of redox-interconversion is reported.

In considering the design of molecules that could exhibit enantiomerization without bond cleavage, we were drawn to the well-known redox pair of quinone and hydroquinone (Figure 2A). These compounds have been studied extensively for their fundamental interest¹⁰ due to their critical roles in biochemistry. In nature, for example, quinoid species in various oxidation states have been characterized in photosynthesis as mediators of electron transfer¹¹ and as species coupled to reversible disulfide bond formation in proteins.¹² In synthetic applications, quinones are often employed as electron shuttles in reactions that are either reductive or oxidative in nature.^{13,14} Furthermore, the redox-properties of these molecules have been used in applications ranging from in vivo imaging, and biomimetic studies to clinical diagnostics.^{15–21} Importantly, the 1:1 mixture of quinone and hydroquinone, often called “quinhydrone,” has been described as a charge transfer complex.²² Synthetic “intramolecular quinhydrone” variants are also known (Figure 2A),²³ including chiral variants,^{24,25} although to the best of our knowledge their stereodynamic features have not been reported. In particularly inspiring work, Curtin and Paul showed that diverse quinones and hydroquinones can interconvert (Figure 2B), reaching equilibrium as a function of their redox potentials.²⁶

These curiously related phenomena stimulated our study of chiral quinone-hydroquinone structures, exemplified by **1** and *ent*-**1** (Figure 2C), and their possible stereodynamic behavior that could involve enantiomerization at the sp^3 -carbon without cleavage of a constituent bond. Some specific questions emerging from the consideration of **1** and *ent*-**1** thus include: (a) whether or not individual enantiomers can be observed as configurationally stable species, and (b) what might be their mechanism of racemization? Deliberately, compounds **1** and *ent*-**1** are constrained from achieving an intramolecular coplanar relationship between the ring moieties; a feature we hypothesized at the outset might attenuate rapid, intramolecular interconversion. Of course, bimolecular quinhydrone formation remains possible with these systems, although we speculated that this aspect might be tunable as a function of substituents, as exemplified in the tris(*tert*-butyl)-bearing compound **1a/ent-1a** (Figure 2C).

Results and Discussion

Our studies began with the synthesis of bis(hydroquinone) compounds **2a** and **2b**, and the corresponding bis(quinone) of each, **3a** and **3b** (Scheme 1). Upon preparing independent

solutions of 1:1 mixtures of **2a** and **3a**, and of **2b** and **3b**, equilibration occurs in each case. In the example of [**2a** + **3a**], the system reaches equilibrium with the formation of the targeted chiral redox system in solution (**1a**; Scheme 1, Eq 1). Strikingly, rather than a statistical mixture, the species are observed in equilibrium concentrations of **2a/3a/1a** 11:13:76, as determined by integration of the ^1H NMR spectrum. For [**2b** + **3b**], the analogous formation of **1b** is observed with the product distributions measured to be **2b/3b/1b** = 15:13:72 (Scheme 1, Eq 2). Chiral compounds of type **1** can be prepared in various solvents. The solution ^1H NMR and ^{13}C NMR spectra, presented in the Supporting Information, reveal unambiguously unsymmetrical species **1a** and **1b**.

The solid state characterization of **1**, **2**, and **3** showed diagnostic features but also unexpected differences (Figure 3A). X-Ray crystallographic analysis of **2a** and **2b** provided unambiguous evidence for the symmetrical bis(hydroquinone) species with characteristically long C–O bond lengths between 1.384(2) Å and 1.390(2) Å. Analogous studies of the bis(quinone)s **3a** and **3b** revealed structures with expected shorter C–O bond lengths between 1.204(7) Å and 1.235(8) Å. In contrast, the chiral quinone-hydroquinone **1a** exhibited unsymmetrical features, with a hydroquinone moiety showing longer C–O bond lengths of 1.368(2) Å and 1.369(2) Å and a quinone moiety with shorter C–O bond lengths of 1.237(2) Å and 1.240(2) Å.

In addition to these C–O bond lengths, the observed C–C bond lengths are in good agreement with the expected bond orders and, ultimately, the corresponding redox state of each ring (See Table S1–S2 for the measurements of all the C–O/C–C bond lengths). The unsymmetrical structural parameters of **1a** thus resemble the hydroquinone and quinone moieties of the parent compounds of **2a** and **3a**, respectively. On the other hand, single crystals obtained from compound **1b** revealed a symmetrical structure **4b** with similar lengths for all C–O bonds of 1.304(5) Å and 1.307(4) Å (Figure 3A), which stands in stark contrast to the anticipated unsymmetrical species **1b**. These measurements are approximately the midpoint between those typical of hydroquinones and quinones, and are similar to the previously reported semiquinones.²⁷ Furthermore, the solid state EPR spectrum of the crystalline sample exhibits a Gaussian-shaped signal with a peak-to-peak line width of 16 G (Figure 3B), consistent with the spectrum of a solid state radical species.^{27–29} These data are consistent with a contribution to the spectrum resulting from the presence of the bis(semiquinone) biradical **4b**, a tautomeric isomer of the unsymmetrical quinone-hydroquinone **1b** (Figure 3A). In addition, it is also possible that supramolecular combinations of unsymmetrical monoradical species, semiquinone-benzoquinone (**5b**) and semiquinone-hydroquinone (**6b**) (Figure 3B), are present and contributing to the overall observations. In these cases all semiquinone moieties are stabilized via a network of intermolecular hydrogen bonds.

This observation then stimulated us to pursue a quantitative assessment of any radical species contributing to the tautomeric equilibrium. Using the diphenylpicrylhydrazyl radical (DPPH) as a standard, quantitative solid state EPR measurements revealed that the EPR-active radical species (Figure 3B) accounts for only 0.073% of **1b**, suggestive of a very small contribution to the overall structure. Powder diffraction analysis also revealed that the bulk solid sample mostly consists of one component (See Supporting Information for details,

Fig. S35), presumably the closed shell species. Based on these findings, our interpretation is that the X-ray diffraction structure of **4b** is the result of a disordered, superposition of the quinone and hydroquinone moieties in crystal packing of racemic **1b** (Figure 3B), with a small contribution from a radical species.³⁰ Similarly, the EPR spectrum of a solid sample of *tert*-butyl-bearing compound **1a** also exhibits a small signal, perhaps in contrast to its unambiguous and unsymmetrical X-ray crystallographic structure. This observation may be consistent with fluxional redox properties for both **1a** and **1b**, and equilibration among the unsymmetrical quinone-hydroquinone enantiomers of **1** and the corresponding semiquinone species in the solid state (Figure 3B). These phenomena are also consistent with the supramolecular features of both **1a** and **1b** in the solid state, where each exhibits a tight network of ‘head-to-tail’ hydrogen bond interactions, with O–O distances of 2.746(4) Å to 2.810(2) Å.

The phenomena also resemble the well-known examples of hydrogen bond-stabilized semiquinone intermediates studied in the laboratory,^{22,27,31–33} and extant in photosynthesis.¹¹ Finally in terms of these structures, both the macroscopic features in the solid state (Figure 4A), and the UV-Vis spectra measured in both solution and solid state (Figure 4B and Fig. S10, respectively), of compounds **1–3** bear strong analogy to the parent hydroquinone, quinone, quinhydrone, and “intramolecular quinhydrone” variants.^{23–25}

A second feature in the X-ray crystallographic analysis of **1a** is that, within the racemic conglomerate, a single enantiomer appears within each hydrogen bonded supramolecular assembly (Figure 3A). This behavior in the solid state, along with our original hypothesis about the possibility of observing enantiomerically enriched hydroquinone-quinone scaffolds, prompted a study of **1** from a stereochemical perspective (Fig. 3). Since (±)-**1b** is prepared by comproportionation of **2b** and **3b**, we hypothesized that the enantiomers of **1b** could also interconvert, a dynamic phenomenon that can be studied with HPLC techniques.^{34,35} In cases where enantiomerization takes place within the timescale of chromatographic separation, an elevated baseline can be observed between the enantiomers as a result of on-column interconversion.^{36–41} We found that both enantiomers of **1b** are readily separated on a CHIRALPAK[®] IC stationary phase (Figure 5A). Chromatograms acquired at elevated temperatures also revealed characteristic plateau formation between the enantiomers, which corroborated our hypothesis that **1b** and *ent*-**1b** are stereodynamic under these conditions (Figure 5B). Analogous plateau formation was observed with compound **1a** and *ent*-**1a** (See Supporting Information for details, Fig. S20–22). No side reactions or decomposition of the compounds was observed under the on-column conditions at elevated temperatures (See Supporting Information for details, Fig. S27). Accordingly, we then considered that strong non-covalent interactions between chiral selector molecules and racemic interconverting analytes could lead to enrichment of the favorably bound analyte enantiomer, resulting in a net deracemization.⁴² This phenomenon has been demonstrated previously with the on-column deracemization of axially chiral molecules.^{43,44} In the case of **1b** and *ent*-**1b**, a large enantiomer separation factor ($\alpha = 5.91$) at low eluent polarity, enabled deracemization of **1b** on the basis of non-covalent interactions with the chiral stationary phase, which we then observed under stopped flow conditions (Figure 5C). When (±)-**1b** was allowed to stand on-column at 12 °C for 13 h, a stereochemically static ratio (*i.e.*, on-

column equilibrium) was reached, and upon resumption of elution by the mobile phase, significant enrichment to an enantiomeric ratio of 18:82 was observed (Figure 5C). This ratio corresponds to $\Delta\Delta G_{285\text{ K}}^{\circ}=0.86\text{ kcal mol}^{-1}$ (3.59 kJ mol^{-1}) of the diastereomeric adducts with the chiral stationary phase.

The enantiomerization, and indeed the deracemization of **1b**, described above constitutes an inversion of configuration at an sp^3 -stereogenic center during which all constituent bonds remain intact. The mechanistic landscape for this stereodynamic, formal redox interconversion could be more diverse than initially noted, and possible scenarios are presented in Fig. 4. Perhaps the most well-precedented mechanistic possibility does indeed involve redox-interconversion through the charge-transfer complexes associated with quinhydrone species,^{26,45} which may also involve proton-coupled electron transfer.^{46–48} As noted above (Figure 4B), UV-Vis spectroscopy reveals the possibility of quinhydrone-like complexes in solution. In the case of **1**, these known pathways may also be associated with the intermediacy of the bis(semiquinone) biradical **4** or its related monoradical species **5/6** (Figure 6A).

While a constitutive bond cleavage scenario involving the sp^3 -stereogenic center might also be proposed *via* a traditional enolization mechanism (Figure 6B), incubation of **1b** in a variety of deuterated solvents does not lead to the formation of a C–D bond under the conditions we evaluated. However, other polar mechanisms could be operative. For example, compounds like **1** are a mere bond rotation away from setting up either a 1,2-addition to form a hemiketal intermediate^{49,50} or a 1,4-addition adduct (Figure 6C). A few examples of related hemiketal structures are known (Figure 6D), and this class of intermediates could presumably be involved in the enantiomerization process. Notably, independent of mechanism, these scenarios also constitute enantiomerization of the sp^3 -carbon atom, without cleavage of a constituent bond, and with formal redox-exchange of substituents.

Conclusions

In conclusion, through synthesis of quinone-hydroquinone-bearing stereogenic carbon centers, we have observed a distinct enantiomerization process and provided evidence for their inherent stereodynamic behavior. The demonstration of enantiomeric enrichment suggests opportunities for chiral mixed redox species that could engage in stereoselective interactions with homochiral hosts, such as biological targets. Also, these molecules may be relevant to the study of stereochemically controlled electron transfer processes, or dynamic kinetic resolution reactions in synthetic chemistry. For now, these fundamental studies provide an example of enantiomerization of sp^3 -stereogenic carbon center without breaking its constituent bond, and ground the principle of redox-racemization for future evaluation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Interconversions in chiral organic compounds and quinone-hydroquinone redox pairs
(A) Known pathways for converting a molecule with one sp^3 -stereogenic carbon center to its enantiomer. **(B)** Top, enantiomerization *via* base-mediated intramolecular acyl-transfer. Bottom, equilibration of enantiomeric macrocycles in a prochiral rotaxane thread.

Figure 2. Known and postulated quinone-hydroquinone redox pairs

(A) Left, quinhydrone, a well-studied quinone-hydroquinone charge transfer complex. Right, examples of covalently connected quinone-hydroquinone molecules, ‘in-tramolecular quinhydrone’. (B) Pairs of quinhydrone derivatives in redox-equilibrium. (C) Our design of stereodynamic molecules and their enantiomerization *via* redox-interconversion of quinone-hydroquinone substituents.

Figure 3. Characterization of quinone- and hydroquinone-containing molecules 1–6

(A) Top, crystallographic structures of compounds **2a**, **3a**, **1a** and their corresponding carbon-oxygen bond lengths in Å. Left, compound **2a** (C7A–O1A, C4A–O2A): 1.390(2), 1.384(2). Middle, compound **3a** (C7A–O1A, C4A–O2A, C13A–O3A, C10A–O4A): 1.204(7), 1.207(7), 1.235(8), 1.220(1). Right, compound **1a** (C7–O1, C4–O2, C13–O4, C10–O3): 1.369(2), 1.368(2), 1.237(2), 1.240(2). Bottom, crystallographic structures of compounds **2b**, **3b**, **1b** (**4b**) and their corresponding carbon-oxygen bond lengths in Å. Left, compound **2b** (C7–O1, C4–O2): 1.390(2), 1.389(2). *The hydrogen atoms associated with O1 and O2 are disordered with respect to the crystallographic symmetry elements. Middle, compound **3b** (C7–O1, C4–O2, C13–O3, C10–O4): 1.209(8), 1.224(8), 1.215(7), 1.226(7). Right, compound **1b** (**4b**) (C7–O1, C4–O2): 1.304(5), 1.307(4). All hydrogen atoms

connected to carbon atoms are omitted for clarity. See Supporting Information for full bond lengths of the quinone-hydroquinone motifs (Table S1–S2). (B) Top, a tautomeric equilibrium between **1a**, **4a**, and **5a/6a** in solid state. Analysis of the sample in the solid state by EPR (298 K) is consistent with the presence of the radical species **4a**, **5a/6a**. Right, ‘head-to-tail’ hydrogen bonds within the crystallographic packing of compound **1a** shows O–O distance of 2.810(2) and 2.792(2) Å. Only a single enantiomer, (*S*)-**1a**, is observed in the space group. Bottom, a tautomeric equilibrium between **1b**, **4b**, and **5b/6b** in solid state. Analysis of the sample in the solid state by EPR (298 K) is consistent with the presence of the radical species **4b**, **5b/6b**. Right, electron density difference map of a single crystal obtained from **1b**. Thermal ellipsoids are shown at 50% probability levels. Hydrogen atoms are shown as arbitrary spheres. The observed X-ray crystallographic structure shows compound **4b** as the result of disordered, superposed quinone and hydroquinone moiety in crystal packing of racemic **1b**. A ‘head-to-tail’ hydrogen bond within the crystallographic packing shows O–O distance of 2.746(4) Å (See Supporting Information, Fig. S34).

Figure 4. Further characterization of quinone- and hydroquinone-containing molecules 1–6 (A) Left, *p*-hydroquinone, **2a**, and **2b** are off-white solids. Middle, *p*-benzoquinone, **3a**, and **3b** are bright yellow solids. Right, quinhydrone is dark greenish solid. Quinone-hydroquinone **1a** and **1b** are dark purple solids. (B) An overlay of UV-Vis spectroscopy absorbance, log(ε), of **1b** (red) and quinhydrone (blue) in MeOH (0.17 mM) that shows a broad absorbance band (approximately 425–600 nm) as an evidence of charge transfer interaction in **1b**.

Figure 5. HPLC investigation of stereodynamic quinone 1b

(A) HPLC analysis of **1b** at 12 °C that shows both enantiomers, **1b** and *ent*-**1b**.

CHIRALPAK[®] IC (250 mm, i.d. 4.6 mm, particle size 5 μ m), hexanes:2-propanol (85:15, v/v), 0.5 mL min⁻¹, λ = 254 nm, retention times of enantiomers:

$t_{ret}^1=9.56$ min, $t_{ret}^2=25.20$ min. (B) The HPLC traces at 30, 40, and 50 °C show increasing formation of a plateau between both enantiomers as a result of on-column interconversion. Dashed-line shows interpolated baseline for each trace. CHIRALPAK[®] IC (250 mm, i.d. 4.6 mm, particle size 5 μ m), hexanes:2-propanol (85:15, v/v), 0.5 mL min⁻¹, λ = 254 nm. (C)

At lower polarity of mobile phase the enantiomer separation factor was increased to

$\alpha=k_2'/k_1'=5.91$ (upper trace). In a stopped flow HPLC experiment (lower trace), ($\pm$)-**1b** was flushed onto the chiral column and equilibrated for 13 h at 12 °C. Subsequent elution resulted in enrichment of the more retained enantiomer with 18:82 er. CHIRALPAK[®] IC (250 mm, i.d. 4.6 mm, particle size 5 μ m), hexanes:2-propanol (95:5, v/v), 0.5 mL min⁻¹, λ = 254 nm, retention times of enantiomers: $t_{ret}^1=24.25$ min, $t_{ret}^2=112.25$ min, t_0 = 6.31 min (1,3,5-tri-*tert*-butylbenzene), $k_1'=(t_{ret}^1-t_0)/t_0=2.84$, $k_2'=16.79$.

Figure 6. Possible mechanisms of formal redox enanti-omerization

(A) Redox-interconversion mechanism involving semiquinone intermediate. (B) Enolization mechanism. (C) Polar addition-elimination mechanism. (D) Previously isolated hemiketal molecules of relevance to the polar mechanistic scenario with hemiketal intermediates.

Product distributions determined by ^1H NMR spectroscopy

Scheme 1.
Formation of chiral quinone-hydroquinone 1