# Chiroptical Properties of Organic Radical Cations. The Electronic and Vibrational Circular Dichroism Spectra of α-Tocopherol Derivatives and Sterically Hindered Chiral Hydroquinone Ethers

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Qualitatively and quantitatively reliable electronic and vibrational circular dichroism (ECD and VCD) spectra of chiral organic radical cations were obtained for the first time with α-tocopherol derivatives and sterically hindered chiral hydroquinone ethers. The isolation and spectral measurements of chiral radical cation salts were made possible by using nitrosonium or antimony derivatives as electron-transfer oxidants, which can cleanly oxidize the substrate donors without giving any byproducts in the sample solution. Such reliable ECD spectra enabled us to fully examine the chiroptical properties of organic radical cations and also compare them with those of the corresponding neutral compounds. The observed VCD spectra of neutral and radical cationic species of chiral hydroquinone ether were nicely simulated by density functional theory (DFT) calculations, from which the relative contribution of each radical cation conformer in solution was evaluated. Thus, the combined synthetic, spectroscopic, and theoretical protocol, composed of chiral modification, clean oxidation to form stable radical cations, ECD/VCD spectral analyses, and DFT calculations, was demonstrated to be a powerful, indispensable tool for elucidating a comprehensive picture of radical cationic species in solution.

## Introduction

Chiral photochemistry has attracted considerable attention in recent years.[1,2] Enantiodifferentiating photosensitization is one of the most successful strategies for obtaining moderate-to-high enantioselectivities by manipulating environmental factors such as temperature, solvent, pressure, and concentration.[3] Asymmetric photoisomerizations performed within modified zeolite supercages[4] and asymmetric photocyclization/additions of achiral substrates in chiral crystals[5] have also been studied extensively. In contrast, asymmetric (photo)reactions via radical ionic species, produced through an electron-transfer (ET) process, have been investigated much less, although a couple of recent investigations have shown that asymmetric ET reactions do occur but give low stereoselectivity.[6] This is rather surprising, because radical cations are widely recognized as important intermediates in physical and organic chemistry,[7] in particular, in redox,[8] electrophilic aromatic substitution,[9] and addition−elimination reactions.[10] Furthermore, radical cations[11] and charge-transfer complexes[12] are known to play crucial roles in biological systems and are indeed characterized for a variety of biologically active compounds. Photoinduced ET reactions, by exciplex or excited charge-transfer complexes, are considered to be important from both synthetic and mechanistic points of view, but the stereoselectivity obtained in asymmetric ET photoreactions has been low, and the mechanism of chiral information transfer upon ET is still unclear.[13]

Electronic circular dichroism (ECD) spectroscopy is an essential and powerful tool for obtaining the chiroptical and stereochemical information of natural and synthetic optically active compounds, and in recent years, a great deal of chiroptical property data have been accumulated.[14] Nevertheless, practically no systematic endeavor has hitherto been devoted to the ECD spectral study of chiral organic radical cations, apart from the preliminary study on a tocopherol derivative described here.[15] There are several reports on ECD spectra of transient redox species generated electrochemically and measured in situ.[16] However, this spectroelectrochemical technique has not been applied to the detection of radical ions and may have some limitations in fully examining the chiroptical properties of radical ions, because the spectral overlap with the original neutral species cannot be avoided, particularly at the shorter wavelengths, and the contribution of possible chiral contaminants cannot rigorously be excluded. In the present study, we report the unequivocal ECD spectra of stable organic radical cations, which are compared with those of the corresponding neutral species. We further performed vibrational circular dichroism (VCD) spectral measurements and the relevant ab initio calculations at the Hartree−Fock (HF) and DFT levels in order to elucidate the relative contribution of the possible conformers in the solution phase. These studies provide us with the indispensable chiroptical and stereochemical information about usually much less stable organic radical cations and further contribute to the assignment of radical cationic species observed by the recently developed time-resolved CD spectral technique[17]

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and, also, to the mechanistic understanding of asymmetric electron-transfer reactions.

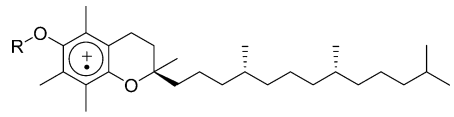
Our own approach to authentic ECD and VCD spectra of organic radical cations, free from artifacts, is to synthesize candidate donor compounds that are expected to generate stable radical cations upon ET oxidation in solution. For that purpose, we chose trimethyloxonium hexachloroantimotate and nitrosonium salts as single-electron-transfer (SET) oxidants and annulated hydroquinone ethers as readily oxidizable substrates to obtain stable and isolable chiral radical cations and reveal their chiroptical properties. Furthermore, these stable radical cations are of great interest from the viewpoint of designing chiral magnetic materials, because a novel magneto-optical phenomenon was predicted theoretically but has yet been not fully supported experimentally, and only a limited number of chiral-molecule-based magnetic materials have been synthesized.[18] Hence, the first unambiguous ECD and VCD spectra and relevant chiroptical properties of organic radical cations reported here are not only scientifically interesting but also important for the development of such magneto-optical materials.

## Results and Discussion

*p*-Dimethoxybenzenes are known to give the corresponding radical cations upon mild oxidation, which are relatively stable and well-characterized.[19] Hence, we first introduced a chiral auxiliary to anisole by the Mitsunobu coupling reaction to yield (1*S*,2*S*,5*R*)-*p*-neomenthyloxyanisole and (1*S*,2*S*,4*S*)-*p*-isobornyloxyanisoles, which were then subjected to SET oxidation with triethyloxonium hexachloroantimonate ($Et_3O^+SbCl_6^-$) in dichloromethane. An addition of $Et_3O^+SbCl_6^-$ to the solution of chiral anisole under an argon atmosphere produced a new absorption band at wavelengths around 450 nm, which is assignable to the $d_0-d_2$ transition of the relevant radical cation on the basis of the reported spectrum of the parent *p*-dimethoxybenzene radical cation.[19] We preliminary reported the CD spectra of these solutions and discussed the Cotton effect (CE) of the chiral organic radical cations semiquantitatively.[20] It was revealed that both the neutral and oxidized forms of chiral alkoxyanisole derivatives exhibit CE of the same sign with analogous ellipticities and anisotropy ($g$) factors in the $^1L_b$ band regions. However, because of the subsequent sluggish reactions, such as chlorination and protonation of the aromatic ring,[28] it was difficult to analyze these first CD data more quantitatively, and hence, the in-depth examinations of the structure and conformation of the radical cation in solution from the obtained CD spectra have not been done. Nevertheless, the use of the SET oxidant was obviously advantageous over the conventional technique of using strong acids, in particular, for the preparation and quantitative spectral measurement of radical cations.

**1. Electronic CD Spectra of α-Tocopherol Derivatives and their Radical Cations.** We first chose tocopherol and the related chromanols as substrate donors for the SET oxidation, not only because this class of compounds is known to be biologically active and behave as a natural antioxidant,[21] but also because the first and only chiral organic radical cation for which the CD spectrum was claimed to have been measured was prepared from vitamin E acetate.[15] Tocopherols have attracted much attention, especially in the fields of peroxyl radical chemistry and of oxidations in vitro[22] and in organic solvents.[23] More recently, the EPR and ENDOR spectra of radical cations of vitamin E-related compounds measured in various solvents revealed that these radical cations are very short-lived and are spontaneously converted to the corresponding neutral radicals through the release of a proton.[29] Optical rotation of α-tocopherol is strongly solvent dependent (e.g., the specific rotation of (2*R*,4′*R*,8′*R*)-α-tocopherol, $[\alpha]_{365}$,[25] varies from +0.32° in ethanol to −3.0° in benzene.[24] There is only one ECD spectrum assigned to a radical cation of α-tocopherol acetate (Chart 1).[15,25] In the study, optically active α-tocopherol acetate, (2*R*,4′*R*,8′*R*)-**1a**, was partially oxidized in trifluoroacetic acid to its radical cation (**1a**$^{\bullet+}$), and the ECD measurement of the resulting solution gave a negative CE of $\Delta\epsilon_{ext} = -65\ M^{-1}\ cm^{-1}$ at 465 nm. However, this is an extraordinarily large $\Delta\epsilon$ value compared to those reported for neutral tocopherol and relevant optically active alkylbenzenes: $\Delta\epsilon \approx 10^{-2}\ M^{-1}\ cm^{-1}$.[26] Our own attempts to oxidize α-tocopherol acetate **1a** with a slight-to-large excess amount (up to 10 equiv) of nitrosonium tetrafluoroborate or triethyloxonium hexachloroantimonate in dichloromethane (eqs 1 and 2)[27] were unsuccessful, for which the relatively high

**CHART 1: Radical Cations of Derivatives of α-Tocopherol**



**1a**$^{\bullet+}$ R = Ac
**1b**$^{\bullet+}$ R = Me

$$ArH + NO^+BF_4^- \rightarrow ArH^{\bullet+}(BF_4^-) + NO \quad \text{(eq 1)}$$

$$2ArH + 3Et_3O^+SbCl_6^- \rightarrow 2ArH^{\bullet+}(SbCl_6^-) + [EtCl, Et_2O, SbCl_3] \quad \text{(eq 2)}$$

oxidation potential of the acetate may be responsible, at least in part. Strong acids were often used in various oxidation reactions, but recent studies have revealed the formation of concomitants, such as reduced species and undesirable byproducts derived therefrom.[28] If they are chiral, as is often the case, the obtained CD spectrum of the radical cationic species of interest will not be reliable or reproducible. In the oxidation of vitamin E and its derivatives, the radical cations are stable only for a brief period of time as reactive intermediates and readily deprotonate to give the corresponding neutral radical species.[29] Furthermore, α-tocopherol possesses a fused dihydropyran coplanar to the aromatic ring, which prevents the full relaxation of the produced radical cationic species and eventually accelerates the possible secondary (oxidation) reaction(s). We further examined other oxidants (e.g., antimony pentachloride or trifluoromethanesulfonic acid in dichloromethane) under various conditions but failed to produce a radical cation that is stable enough to obtain a fully consistent CD spectrum (∼30 min). Hence, we performed a trace experiment under the reported conditions (trifluoroacetic acid/dichloromethane = 2:1) and measured the CD spectrum of the oxidized species of **1a** immediately after the treatment, which is shown in Figure 1 (middle right, dashed line). Contrary to the previous report,[15] the solution exhibited an oppositely signed (positive) CE.[30] Thus, the observation of EPR signals does not immediately guarantee that the detected radical cation of interest is the major species responsible for the CD signals, particularly in such a complex mixture resulting from strong acid oxidation. We would rather suggest that protonated **1a**, which is likely to be abundantly formed under the highly acidic condition, gives a slightly red-shifted absorption and CD signal. Therefore, chiral vitamin E analogue **1b** was newly synthesized. This compound is expected to be readily oxidized to the corresponding radical cation under a much milder condition using either nitrosonium tetrafluo-

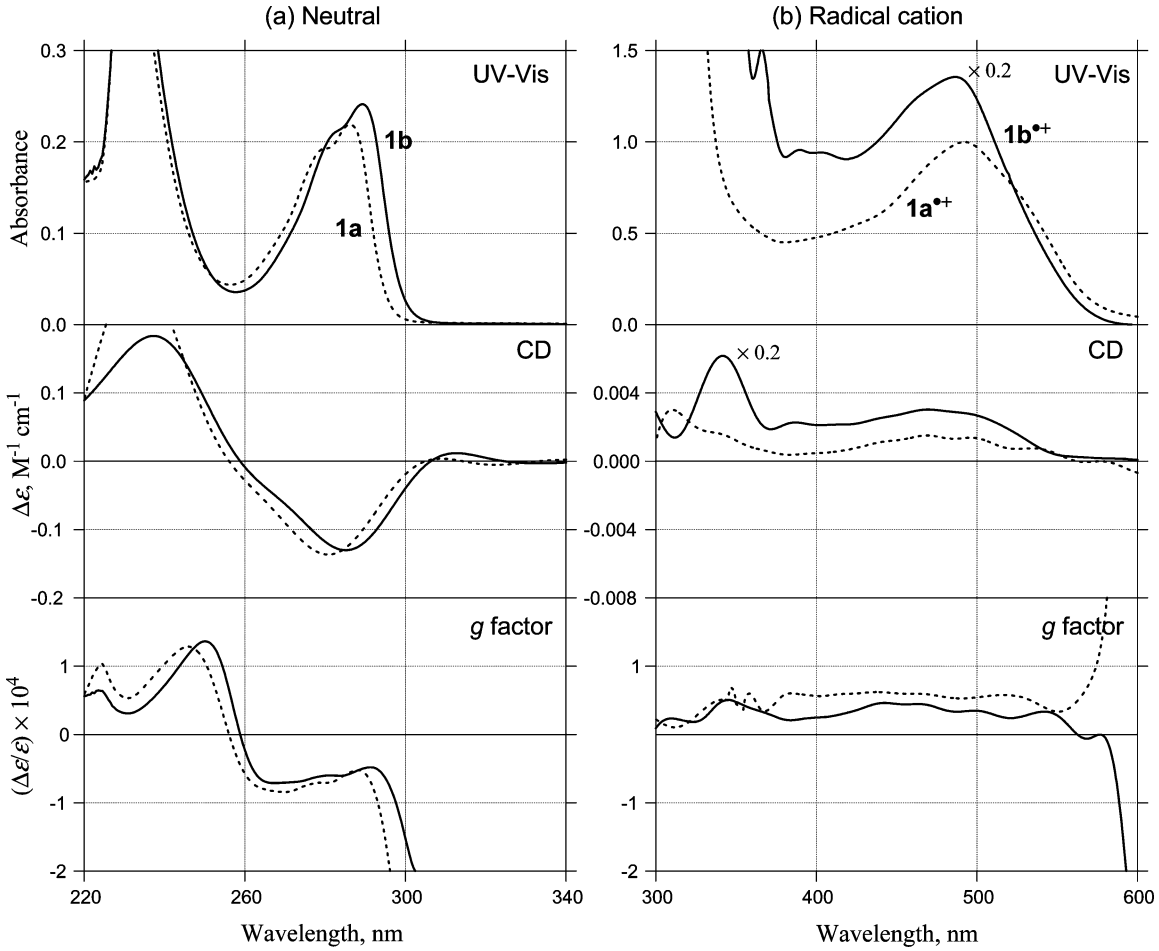



**Figure 1.** Electronic absorption (UV−vis) and ECD spectra and anisotropy (*g*) factors of neutral (left panels) and radical cationic (right panels) α-tocopherol derivatives (dashed lines for **1a** and **1a**$^{\bullet+}$; solid lines for **1b** and **1b**$^{\bullet+}$) in dichloromethane at 25 °C under an argon atmosphere. The UV−vis and ECD spectra were recorded at $1.0 \times 10^{-4}$ M, except for the UV−vis spectra of the radical cations which were recorded at $1.0 \times 10^{-3}$ M. The radical cations of **1a** and **1b** were obtained by treating the neutral donors with $CF_3CO_2H$ and $NO^+BF_4^-$, respectively. The vertical scale ($\Delta\epsilon$) of the ECD spectra of the radical cationic species is tentative, as we assume a quantitative formation of the radical cation.

roborate or triethyloxonium hexachloroantimonate (eqs 1 and 2), because its achiral analogue, prepared recently, has an oxidation potential as low as 1.05 V (versus SCE, as compared with $E$ = ca. 1.5 V for $NO^+$)[31] in dichloromethane.[32] In such an oxidation strategy, we can greatly reduce the amount of contaminants and even eliminate the byproducts (such as NO, EtCl, and $SbCl_3$) by evaporation if necessary and exclude the possible contamination by the arenium ion (protonated arene). As expected, we could obtain the radical cation in ca. 70% yield (estimated from the absorbance of the solution) within 30 min by mixing **1b** with $Et_3O^+SbCl_6^-$ in dichloromethane at 0 °C. The absorption maximum of methyl ether **1b** is slightly red-shifted from that of acetate **1a** in dichloromethane (probably due to the lower oxidation potential of **1b** (vide infra)), yet keeps the same spectral shape. As can be seen from Figure 1 (middle traces), the CD spectra of neutral (2*R*,4′*R*,8′*R*)-α-tocopherol acetate **1a** and methyl ether **1b** show quite similar profiles, exhibiting the absorptions attributable to the $^1L_b$ band at ∼280 nm with a fairly strong negative CE with comparable intensities of $\Delta\epsilon \approx -0.14$.[33] This CD spectrum of neutral **1a** is in good agreement with the one previously reported.[15]

The CD spectrum of **1b**$^{\bullet+}$ obtained by oxidation with $NO^+BF_4^-$ is shown in Figure 1, along with that of the neutral donor **1b**. Radical cation **1b**$^{\bullet+}$ exhibited a positive CE around 480 nm for the $d_0-d_2$ transition. Judging from the benzene chirality and sector rules,[26] as well as the conformational resemblances of **1a** with **1b** and **1a**$^{\bullet+}$ with **1b**$^{\bullet+}$, we can now safely conclude that the previous report of a CD signal of the radical cation of vitamin E acetate was erroneous. Although the amount of the radical cation formed upon oxidation of **1a** was small, the analogous *g* factor observed indicates that the CE, and the structure, of **1a**$^{\bullet+}$ is practically the same as that of **1b**$^{\bullet+}$. It is a good sign that the use of SET oxidants greatly reduces the contamination by artifacts in the production and subsequent CD measurement of radical cations from the qualitative and semiquantitative points of view. However, even in the **1b**$^{\bullet+}$ case, its instability did not allow us to fully determine the reliable $\Delta\epsilon$ value.

**2. Electronic Circular Dichroism Spectra of 9,10-Bis[(*R*)-1-methylpropyloxy]-1,4:5,8-dimethano-1,2,3,4,5,6,7,8-octahydroanthrancene (2b) and its Radical Cation (2b**$^{\bullet+}$**).** *Ab Initio Calculations of Annulated Hydroquinone Ethers.* Of several stable organic radical cations[27,28,34] that were structurally well-characterized by X-ray crystallography, those derived from sterically hindered hydroquinone ethers (**2** and **3**), possessing two 1,3-cyclopentanediyls or 1,4-cyclohexanediyls, are suitable for CD spectral examination. This is because (i) these radical cations can be prepared under relatively mild conditions and are totally stable not only in the solid state but also in dichloromethane solution at ambient temperatures for more than a month under inert conditions, (ii) the electrochemical and UV−vis spectral properties were known for dimethyl analogues and should not greatly be affected by chiral modification, and

(iii) chiral ether moiety(ies) can be readily introduced to the aromatic ring by conventional coupling reactions.

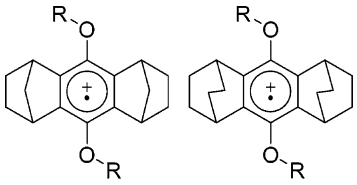
It is known that the two methoxy groups, perpendicular to the aromatic plane, are in either syn or anti conformation, and the two are equilibrated with each other in the neutral donors.[34] Thus, the observed CD should be a sum of the signals from the two conformers. The relative contributions of the syn and anti conformers in **2** and **3** were crudely estimated by ab initio calculations, using the Boltzmann populations obtained from the calculated Gibbs free energies of the structure-optimized conformers (See Table S1 in Supporting Information). The optimization was performed with the economical HF/3-21G* basis set for each conformer employed, which was followed by high-level energy calculations using DFT methods at the B3LYP/6-311+G(2d,p) level. The calculated energies were further corrected for the zero-point energy obtained in frequency calculations at HF/3-21G* level with a scaling factor of 0.94.[35] For the known dimethyl derivatives (**2a** and **3a**), the calculated free energies were comparable to the syn and anti isomers, predicting a roughly 1:1 syn/anti ratio. However, the X-ray crystallographic studies found only the anti conformers in crystalline **2a** and **3a**,[34] which can be accounted for by the significant role played by the packing forces. In contrast, the corresponding radical cations favor the anti conformation over the syn conformation to a great extent.

We further moved on to the chiral hydroquinone derivatives (**2b**,**c** and **3b**,**c**) with (*R*)- and/or (*S*)-1-methylpropyl auxiliaries.[36] Interestingly, ab initio calculations yielded distinctly different energy profiles and structure preferences for **2b** and **3b**, despite the same homochiral modification. Thus, bis(cyclopentanediyl)-annulated **2b** prefers the anti form, while the bis(cyclohexanediyl)-annulated homologue **3b** favors the syn form. In the oxidized radical cation form, however, both **2b** and **3b** exclusively prefer the anti conformation. Merely for comparison purposes, meso donors **2c** and **3c**, possessing antipodal (*R*)- and (*S*)-1-methylpropyl groups, were also subjected to calculations giving a similar tendency. However, we will not further analyze or discuss the results obtained with these achiral donors, because the stereoselective synthesis of the meso donors is rather complicated, and no ECD or VCD signals are expected to occur.

Among the species examined, **2b** is conformationally the most intriguing in both the neutral and radical cationic states, showing populations to the energetically less favorable syn conformer in 10% and 12%, respectively. Higher-level calculations at the B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) levels afforded the relative contribution of the syn in 21% for neutral **2b** and 4% for **2b**$^{\bullet+}$. Such a critical balance between the conformers is not a drawback but an advantage for precisely analyzing how the conformational changes affect the ECD and VCD spectral behavior in solution (vide infra), and hence, we decided to exploit this substrate for further experimental studies.

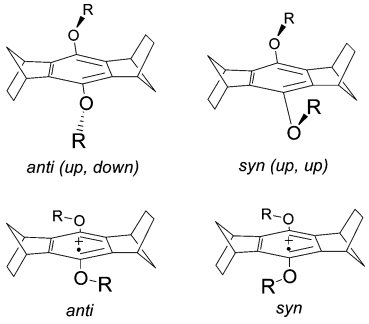
*Electrochemical Oxidation of 9,10-Bis[(R)-1-methylpropyloxy]-1,4:5,8-dimethano-1,2,3,4,5,6,7,8-octahydroanthrancene (**2b**).* Donor **2b** was prepared by the Mitsunobu coupling of 9,10-dihydroxy-1,4:5,8-dimethano-1,2,3,4,5,6,7,8-octahydroanthrancene[34] with (*S*)-(+)-2-butanol. The desired (*R*,*R*)-**2b** was obtained in >99% optical purity.[37] The dimethyl analogue **2a** is known to be electrochemically oxidized at a redox potential of 1.11 V versus SCE.[34] Hence, the chiral analogue **2b** (1 mM) was subjected to electrochemical oxidation with platinum electrodes in anhydrous dichloromethane containing 0.2 M tetra-*n*-butylammonium hexafluorophosphate as a supporting electrolyte. A reversible cyclic voltammogram (CV) and a linear sweep oxidation wave (OSWV) were obtained (See Figure S1 in Supporting Information), and the calibration with added ferrocene gave the oxidation potential of **2b**: $E_{1/2} = 1.19$ V versus SCE. This is slightly higher than that for the dimethyl analogue **2a**, but small enough to be oxidized by convenient SET oxidants such as $NO^+$ or $Et_3O^+SbCl_6^-$ (eqs 1 and 2). This slight shift of $E_{1/2}$ may be attributed to steric effects, because the larger substituents in **2b** may hinder the alkoxy group from taking the favorable conformation coplanar to the aromatic ring.

**CHART 2: Stable Radical Cations of Sterically Hindered Hydroquinone Ethers**




**a**: R = Me
**b**: R = (*R*)-1-MePr
**c**: R = (*R*)- and (*S*)-1-MePr

**CHART 3: Conformations of Neutral and Radical Cationic Chiral Hydroquinone Ethers 2b and 2b$^{\bullet+}$**




*Chemical Oxidations of **2b** and CD Spectra of Neutral **2b** and Radical Cation **2b**$^{\bullet+}$.* To avoid ambiguity and obtain the absolute $\Delta\epsilon$ value of a radical cation, we employed chiral derivatives of stable radical cations **2**$^{\bullet+}$ and **3**$^{\bullet+}$, whose parent compounds (**2a**$^{\bullet+}$ and **3a**$^{\bullet+}$) were known to be isolable as pure salts (Chart 2). We will report the use of this isolated radical cation for the first chiroptical measurements of the organic radical cation (vide infra).

The electronic CD and UV−vis spectra of the neutral donor **2b** in dichloromethane are shown in Figure 2, along with the anisotropy (*g*) factor. The observed CD extrema are in good agreement with the absorption maxima for both $^1L_b$ and $^1L_a$ bands (279 and 243 nm), affording negative CEs of $\Delta\epsilon \approx -0.13$ (Table 1). The $\Delta\epsilon$ values are significantly smaller than those reported for related chiral aromatic ethers. For example, the $^1L_b$ bands of *p*-neomenthyloxyanisole and *p*-isobornyloxyanisole display much larger $\Delta\epsilon$'s of +1.2 and +1.8, respectively.[20] The unusually small $\Delta\epsilon$ value for **2b** may be attributed at least in part to the mixed conformers with opposite CD signs. This idea is supported by our preliminary ab initio calculations at the HF level and indeed proved by VCD measurements combined with DFT calculations (vide infra). The observed *g* factors are on the order of $10^{-4}$, which is typical for chiral benzenes with simple substitutents.[26] A negative CE for the $^1L_b$ transition is reasonable in view of the empirical benzene chirality rule.[26]

Chiral donor **2b** was readily oxidized by either 1.5 equiv of triethyloxonium hexachloroantimonate or 1 equiv of nitrosonium tetrafluoroborate in dichloromethane to give a clear orange

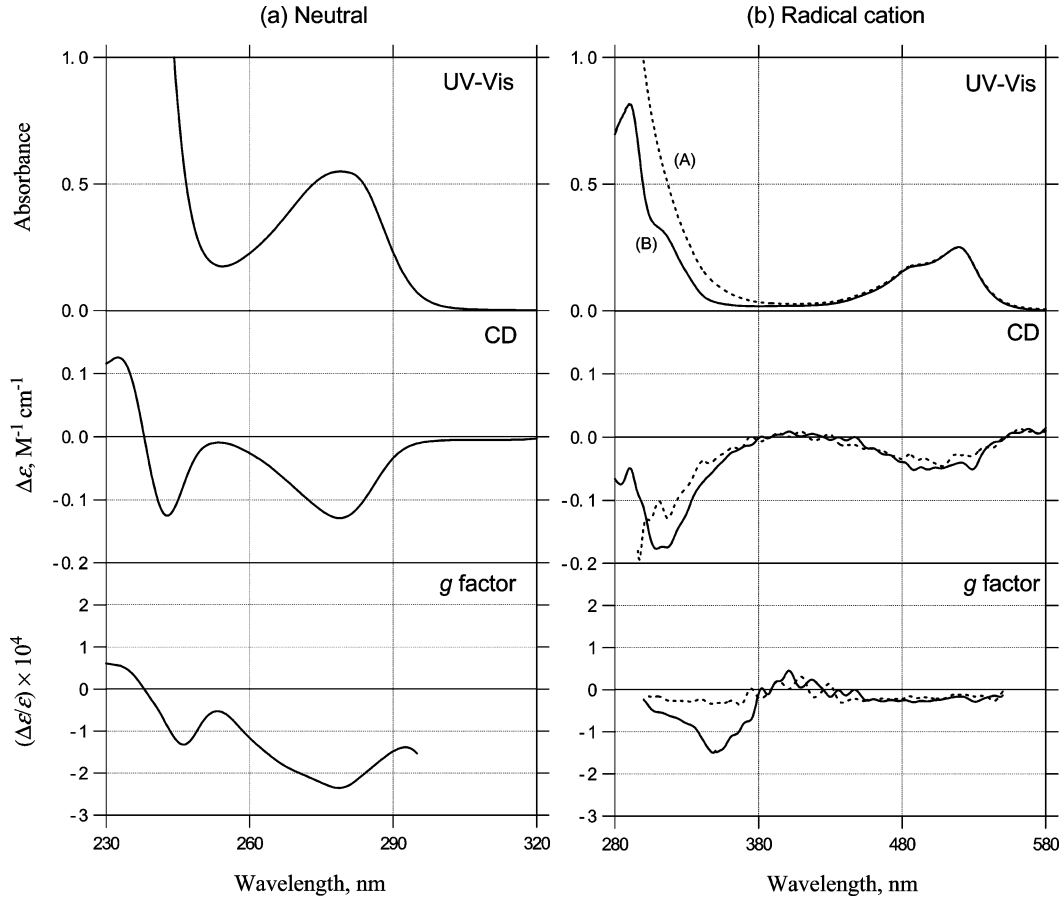



**Figure 2.** Electronic absorption (UV−vis) and circular dichroism (CD) spectra and anisotropy ($g$) factors of (a) neutral **2b** ($10^{-3}$ M) and (b) radical cation **2b**$^{\bullet+}$ ($10^{-4}$ M) in dichloromethane at 25 °C under argon atmosphere. The counteranion of **2b**$^{\bullet+}$ was either $SbCl_6^-$ (dashed line) or $BF_4^-$ (solid line).

**TABLE 1: UV−Vis and Circular Dichroism Spectra of Chiral Radical Cations and Their Parent Compounds**[a]

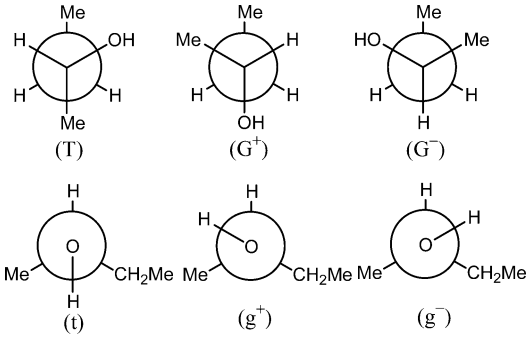
| compd | configuration | oxidant | UV−vis $\lambda_{max}$/nm (log $\epsilon$)[b] | CD $\lambda_{ext}$/nm ($\Delta\epsilon$)[b] |
|---|---|---|---|---|
| **1a** | R,(R,R) | | 286 (3.34) | 281 (−0.142) |
| | | | <230 | 234 (+0.271) |
| **1a**$^{\bullet+}$ | R,(R,R) | $CF_3CO_2H$ | 492 (>2.4) | 496 (∼+0.01)[c] |
| **1b** | R,(R,R) | | 289 (3.38) | 285 (−0.137) |
| | | | <230 | 237 (+0.177) |
| **1b**$^{\bullet+}$ | R,(R,R) | $NO^+BF_4^-$ | 487 (>3.0) | 470 (∼+0.01)[c] |
| **2b** | R,R | | 279 (2.74) | 279 (−0.129) |
| | | | 232 (3.89) | 243 (−0.125) |
| **2b**$^{\bullet+}$ | R,R | $NO^+BF_4^-$ | 520 (3.40) | 529 (−0.081) |
| | | | 485[d] (3.23) | 488 (−0.082) |
| | | | 315[d] (3.48) | 315 (−0.274) |

[a] Measured in dichloromethane at 25 °C under argon atmosphere. [b] Molar extinction coefficient $\epsilon$ and molar circular dichroism $\Delta\epsilon$. [c] Quantitative formation of **1a**$^{\bullet+}$ or **1b**$^{\bullet+}$ assumed; hence, the $\Delta\epsilon$ value could be larger. [d] Shoulder.

solution at −20 °C to room temperature under argon.[38] This solution was stable for a long period of time even at ambient temperature, if protected from air. The new broad absorption band centered at 520 nm is assigned to the $d_0-d_2$ transition of radical cation **2b**$^{\bullet+}$ from the spectral comparison with its methyl analogue (**2a**$^{\bullet+}$)[34] and the *p*-dimethoxybenzene radical cation.[19] Two different salts of **2b**$^{\bullet+}$ were isolated by the following procedures. Method 1: A solution of **2b** was mixed with 1.5 equiv of $Et_3O^+SbCl_6^-$ under argon in dichloromethane, and the resulting mixture was stirred for 1 h at 0 °C. After the evaporation of the solvent in vacuo, the residue was redissolved in anhydrous dichloromethane and filtered under an inert atmosphere to eliminate the precipitates. Anhydrous ether was added to the solution to give the salt as a precipitate, which was filtered and washed with dry ether under argon. Method 2: **2b** and $NO^+BF_4^-$ (1 equiv) were mixed in dichloromethane, and the suspension was stirred at 0 °C. As the $NO^+$ salt gradually dissolved, the color of the solution became darker. The resulting solution was treated as in Method 1 to yield the $BF_4^-$ salt of **2b**$^{\bullet+}$. These two salts were more than 98% pure, as determined by the iodometric titration. These salts were redissolved in dichloromethane, and the solutions were subjected to the UV−vis and ECD spectral measurements under argon.

The two radical cation salt solutions showed exactly the same UV−vis spectra in the $d_0-d_2$ transition region around 520 nm but revealed significant differences at shorter wavelengths, most probably because of the overriding absorption by the counteranion. The CD spectra of **2b**$^{\bullet+}$ with different counteranions were measured, and the results are shown in Figure 2b (traces A and B). The two spectra are almost superimposable in the $d_0-d_2$ transition region but deviate appreciably at shorter wavelengths. Because $SbCl_6^-$ is not transparent at shorter wavelengths, the $\Delta\epsilon$ values of **2b**$^{\bullet+}$ were determined from the CD spectrum of the $BF_4^-$ salt as −0.081, −0.082, and −0.274 at 529, 488, and 315 nm, respectively. Both neutral and radical cationic (*R*,*R*)-**2b** species exhibit the negative CE for the two major bands. It is noted that the $d_0-d_2$ transition of radical cation **2b**$^{\bullet+}$ gives an unexpectedly small anisotropy ($g$) factor of $-2 \times 10^{-5}$ at ca. 500 nm, which is roughly 10 times smaller than those of the allowed transitions of neutral **2b**. This is simply due to the higher transition probability ($\epsilon$) of the $d_0-d_2$ transition of **2b**$^{\bullet+}$.

**CHART 4: Conformers of (*R*)-2-Butanol with Different Dihedral Angles around the C−C−C*-C and H−C*-O−H Bond**




**3. Vibrational Circular Dichroism Spectra of 9,10-Bis-[(*R*)-1-methylpropyloxy]-1,4:5,8-dimethano-1,2,3,4,5,6,7,8-octahydroanthrancene (2b) and its Radical Cation (2b$^{\bullet+}$).** *Neutral Donor.* In the foregoing experiments, we measured the first reliable electronic CD spectra of organic radical cations, although this alone does not immediately provide us with enough information to elucidate the structure and conformation of the relevant radical cations; we therefore further measured the VCD spectra of the relevant species in solution, which were compared with the calculated spectra.

It is not very easy in general to know the population and structural details of such conformers that are equilibrated with each other in solution by using conventional spectroscopic techniques such as UV−vis, electron paramagnetic resonance (EPR), or NMR measurements. For example, the conformational dynamics of α-tocopherol in solution have recently been studied in detail by $^{13}$C NMR spectroscopy.[39] However, this elegant methodology cannot be applied to the radical cation species. EPR spectroscopy is a very sensitive technique to detect radical cations, but it is usually used for the detection of transient species in a solid matrix and is not suitable for studying the conformer distribution in solution, particularly when several conformers are present. The combined use of DFT calculations and VCD spectroscopy[40] has been recognized in recent years as a powerful tool for determining the absolute configuration, as well as the predominant conformations of ground state (or neutral) chiral molecules in the solution phase. DFT theory[41] can provide vibrational frequencies and intensities, the accuracy of which is comparable to post-self-consistent field (post-SCF) calculations taking electron correlation into account. Standard software such as *Gaussian 98*[42] now includes the calculation of VCD intensities as well. This allows us to use VCD for the reliable determination of the absolute configuration and conformational analysis in solution for simple chiral molecules such as 2-butanol[43] and α-deuterioethanol.[44] Recently, such techniques have been further applied to a variety of systems,[45] but only for the rather simple stable compounds.

The absolute configuration of 2-butanol is of particular importance in stereochemistry, because a large number of chiral compounds are related to this simple chirogenic group. Thus, the conformational preference of 2-butanol is also a crucial recent topic, which has been studied carefully by using VT-polarimetry,[46] NMR spectroscopy,[47] Raman spectra combined with MM3 calculations[48] and VCD spectroscopy combined with DFT calculations.[43] These experiments indicate that the *T* conformer, possessing the anti C−C−C*-C bond, is lowest in energy, but the other two conformers (i.e., gauche plus ($G^+$) and minus ($G^-$)) are also populated in the ratio $T$:$G^+$:$G^-$ = ca. 5:4:1 (Chart 4). In the VCD−DFT study,[43] additional conformers around the H−C*−O−H bond (i.e., *t*, $g^+$, and $g^-$) were also taken into account to give information about more detailed conformer structures and their distributions. It should be noted, however, that, although the VCD−DFT approach is a versatile and reliable tool for analyzing the structure of chiral molecules[49] and has indeed been successful in determining the solution-phase conformation of small molecules,[50] it is not always suitable for larger molecules with many more degrees of freedom. Hence, we first examined the validity of such an approach to the relatively large molecule **2b** and then expanded the method to the radical cationic species **2b**$^{\bullet+}$.

A dichloromethane-$d_2$ solution of **2b** (0.22 M), placed in a $BaF_2$ cell (2 cm $\phi$), was subjected to VCD measurement. The path length of the cell was separately determined as 72 $\mu$m. The VCD signals with a 4 cm$^{-1}$ resolution were accumulated for 3 h to afford a reasonable spectrum, which was corrected for the solvent signals. Figure 3a illustrates the VCD and simultaneously obtained IR spectra of neutral **2b**.

Ab initio calculations of neutral donor **2b** were performed at two different levels (Table S2 in Supporting Information). First, the geometrical optimization of each conformer was done by HF calculation, which is faster and more economical than the DFT and post-SCF calculations. This was followed by frequency calculations at the same level and a single-point energy calculation at the B3LYP/6-311G+(2d,p) level. Theoretical absorption and VCD spectra were simulated with Lorentzian band shapes of 6 cm$^{-1}$ full-width at half-mean, and the frequencies were scaled by a factor of 0.97 or 0.91 for the B3LYP/6-31G(d) or HF/3-21G* calculations, respectively. The hydroquinone ether **2b** may take 12 different conformations, because there is syn−anti isomerism of two alkoxyls with respect to the aromatic plane and also anti (*T*), gauche plus ($G^+$), and gauche minus ($G^-$) rotamers around the C−C−C*−C bond for each of the two 1-methylproyl groups. These isomers are distinguished by the following abbreviations: anti-$G^+G^+$, anti-$G^+T$, anti-$G^+G^-$, anti-*TT*, anti-$TG^-$, anti-$G^-G^-$, syn-$G^+G^+$, syn-$G^+T$, syn-$G^+G^-$, syn-*TT*, syn-$TG^-$, and syn-$G^-G^-$. Similar optimizations were done by the DFT method, which is relatively fast and affords satisfactory results as precise as post-SCF calculations. Thus, almost all of the IR peaks calculated for each conformer can be assigned to the observed signals (see Supporting Information).

The VCD spectra calculated for all possible conformers are shown in Figure 4 (right), along with the Boltzmann populations calculated from their Gibbs free energies. Each conformer displays a significantly different simulated VCD spectrum, and no single conformer can correctly reproduce the observed VCD profile. This is also true for the IR signals (see Figure S2 in Supporting Information). The observed VCD and IR spectra are best simulated in frequency and intensity by using the DFT method: Compare spectrum a with b in Figure 4 (see Figure S2 for the IR counterparts). The HF calculations gave less satisfactory results: Compare spectrum a with d in Figure 4. As expected, even if the contribution from the minor conformers (of <10% population) is neglected, the simulated VCD spectrum c (and e) show satisfactory matches. It is concluded, therefore, that the DFT calculation can generate a reasonable VCD spectrum of a relatively large neutral molecule such as **2b** by taking into account the conformer population that is estimated from the calculated Gibbs free energy of each conformer.

*Radical Cation.* Because radical cation **2b**$^{\bullet+}$ is totally stable under inert atmosphere (vide supra), highly reliable and reproducible VCD and IR spectra could be measured in solution. Although the measurements were run under inert conditions,

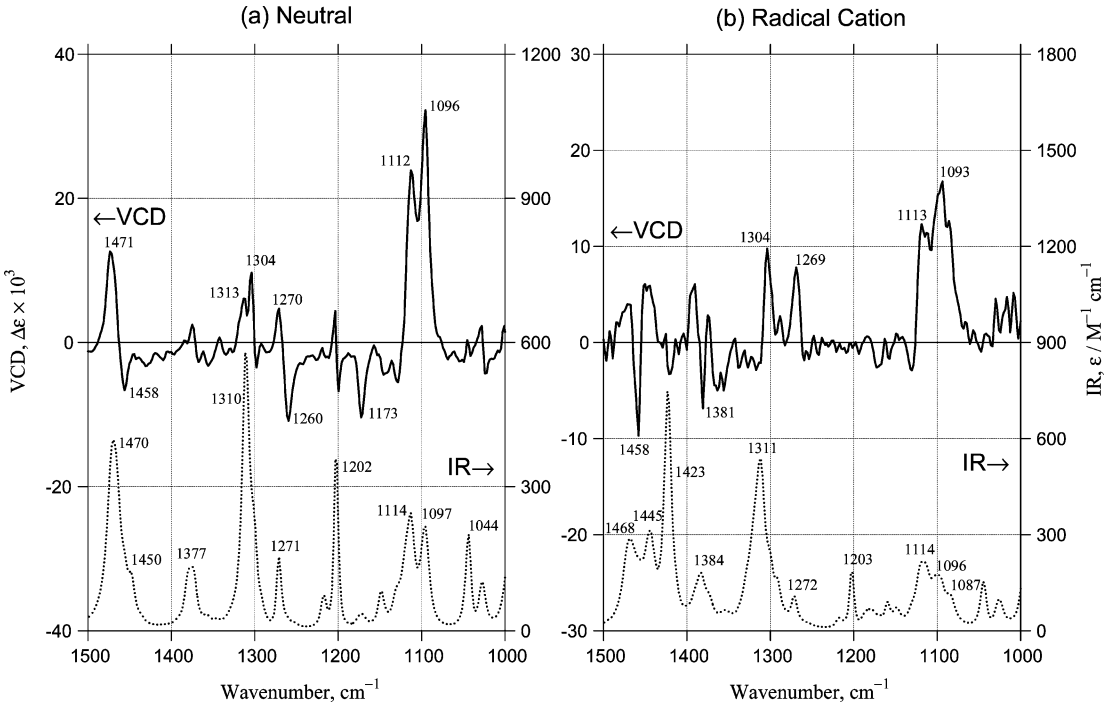



**Figure 3.** VCD and IR spectra of (a) neutral **2b** (0.22 M) and (b) radical cation **2b**$^{\bullet+}$ (0.22 M) in dichloromethane-$d_2$ at ambient temperature.

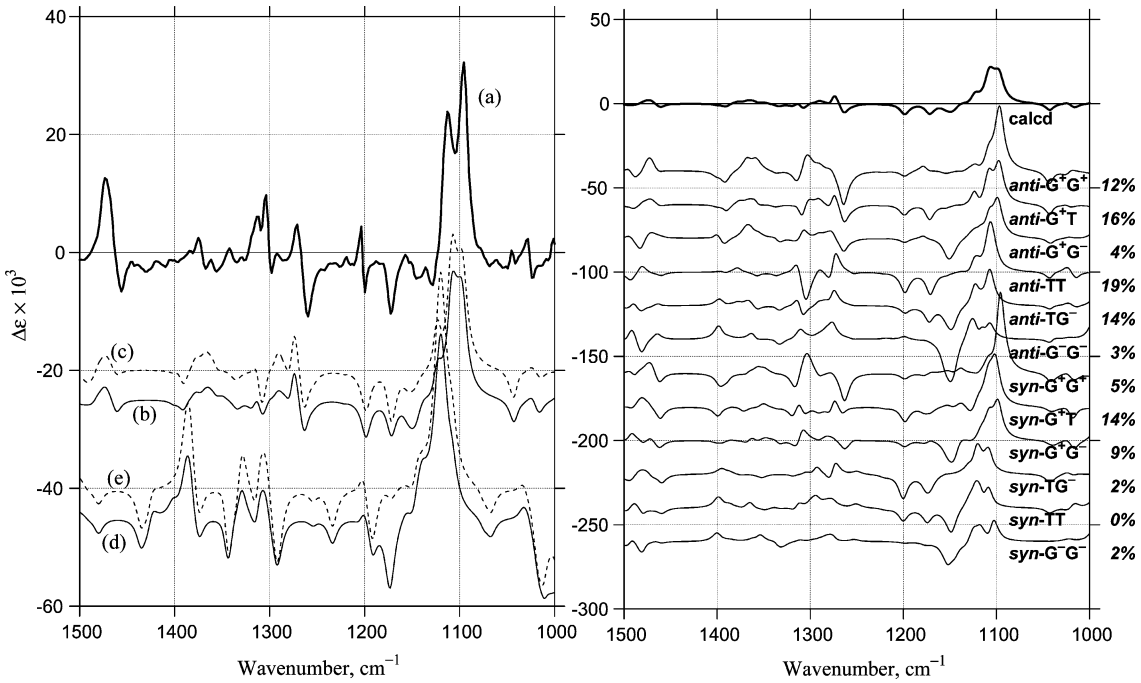



**Figure 4.** Experimental and calculated VCD spectra of **2b**. Left: (a) observed; (b) DFT simulation using all 12 conformers; (c) DFT simulation using 5 major conformers; (d) HF simulation using all conformers; (e) HF simulation using 3 conformers. Right: a breakdown of the DFT-simulated spectrum b into each conformer with relative contribution. *Y*-axis of the calculated spectra is shifted for clarity.

using purge gas ($N_2$) in a closed $BaF_2$ cell, a short exposure to the air (upon transfer of the sample to the cell) and continuous IR irradiation (during the VCD measurement) did not appreciably damage the sample. However, prolonged exposures to air or IR may lead to decomposition of the radical cation to give the corresponding benzoquinone derivative[51] and other unidentified byproducts during the spectrum accumulation (see Figure S4 in Supporting Information for detail). Hence, we chose the $SbCl_6^-$, rather than the $BF_4^-$, salt for greater stability and used the VCD data obtained in the initial 3-h accumulation. If the sample preparation was done very carefully (fully air-protected), the VCD spectrum obtained did not change for up to 5−6 h under the conditions employed. The VCD and IR spectra of **2b**$^{\bullet+}$ thus obtained are shown in Figure 3b.

Calculations of the IR and VCD frequencies and intensities were also performed for all 12 conformations and optimized independently for the relevant conformations of radical cation **2b**$^{\bullet+}$ at both HF and DFT levels as for the neutral species (Figures 5 and 6). As anticipated, the HF-level calculations led to significant deviations from the experimental IR and VCD spectra, while the DFT calculations gave satisfactory results. Again, the DFT-calculated frequencies and intensities for each conformation do not immediately agree with the experimental values, especially for the VCD spectrum. However, the Boltz-

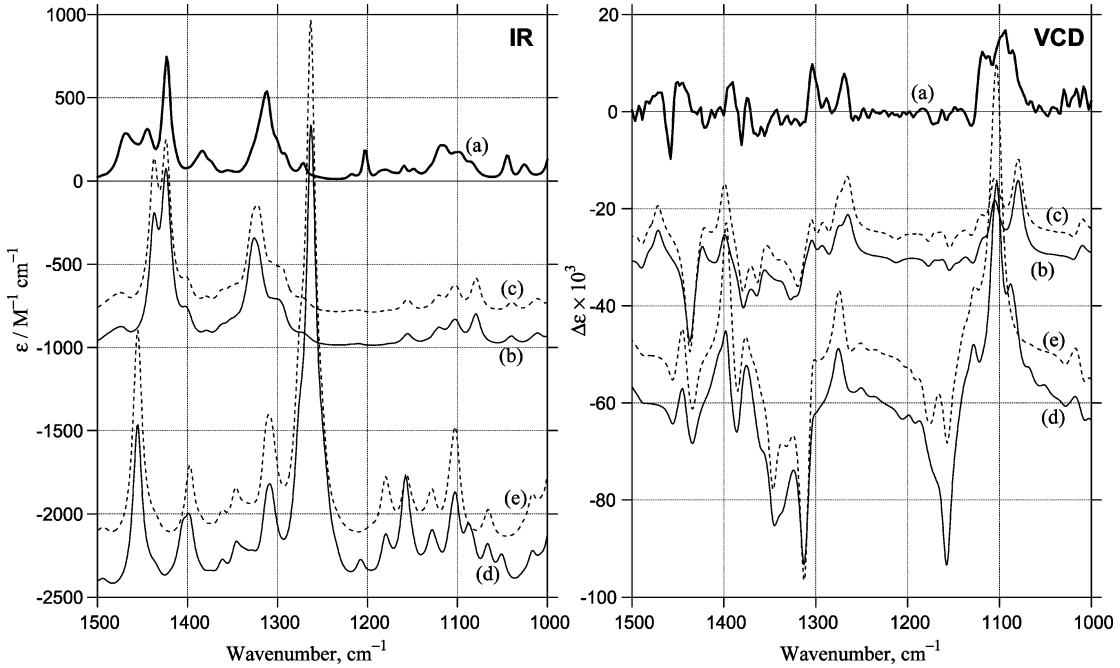



**Figure 5.** Experimental and calculated IR (left) and VCD (right) spectra of **2b**$^{\bullet+}$. (a) Observed; (b) DFT simulation using all 12 conformers; (c) DFT simulation using 4 selected conformers; (d) HF simulation using all conformers; (e) HF simulation using 4 conformers. *Y*-axis of the calculated spectra is shifted for clarity.

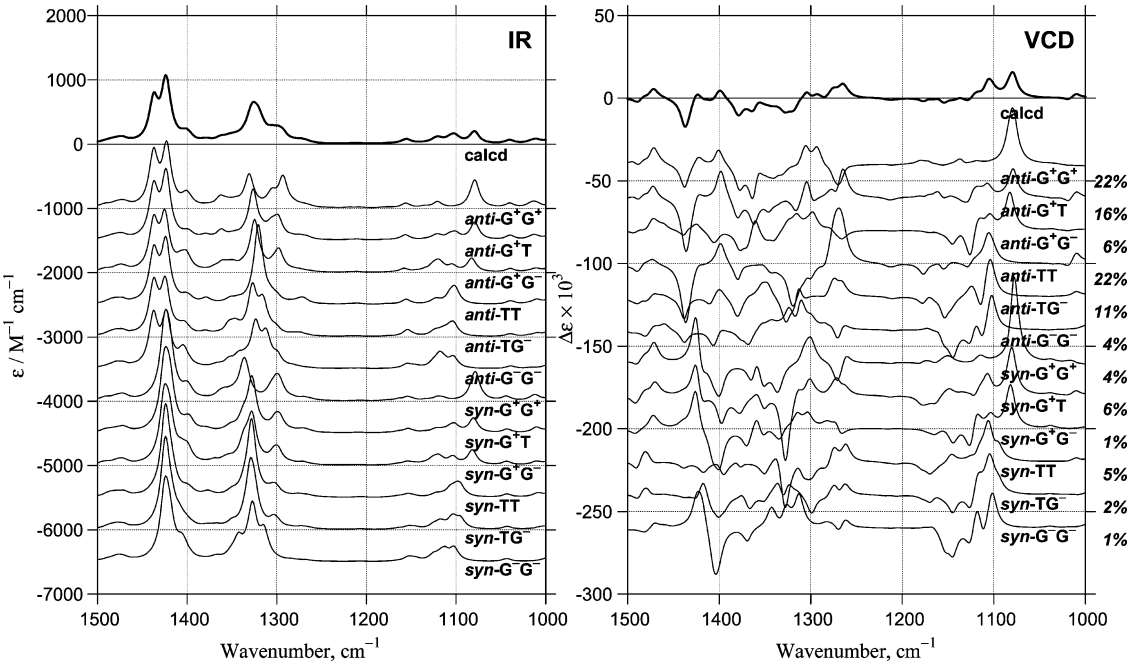



**Figure 6.** Calculated IR (left) and VCD (right) spectra of **2b**$^{\bullet+}$. The DFT-calculated IR and VCD profiles of each conformer and the relative contribution estimated from the Gibbs free energies are shown. *Y*-axis of the calculated spectra is shifted for clarity.

mann statistics and the Gibbs free energies as determined by the high-level energy calculations with a relatively large basis set (6-31G(d)) allow the population determination of the 12 conformers (See Table S2 in Supporting Information), and if the relative distribution of these conformers is taken into account, the calculated IR and VCD spectra of the radical cation **2b**$^{\bullet+}$ are in excellent agreement the experimental ones, as shown in Figure 5b.

Although the iodometric titration of the radical cation sample indicated a purity of >95%, the observed IR and VCD spectra of the solution of **2b**$^{\bullet+}$ appear to contain some neutral species. For instance, the IR peaks at 1468 and 1203 cm$^{-1}$, both of which are seen in the spectrum of **2b**$^{\bullet+}$ solution (Figure 3, right), do not match to any of the calculated peaks of **2b**$^{\bullet+}$ but are found in the observed spectrum of neutral **2b**, indicating possible contamination by the neutral species, especially at the later stages of the data accumulation. Thus, the slight differences between the simulated and observed VCD and IR intensities may partly originate from a small amount of **2b**$^{\bullet+}$ formed during sample preparation or spectral measurement.

The population-weighted theoretical spectra of neutral **2b** and radical cation **2b**$^{\bullet+}$ are in good agreement with the experimental spectra obtained in dichloromethane-$d_2$ under inert conditions. It is noted that the DFT calculations nicely simulate the VCD spectra of not only the neutral but also the radical cationic species by using the calculated energies and populations of all

12 possible conformations. The anti-*T*,*T* is the most stable conformation for neutral **2b**, as was the case with (*R*)-2-butanol,[43] while the anti-$G^+$,$G^+$ and anti-*T*,*T* are almost comparable in energy and equally populated for radical cation $\mathbf{2b}^{\bullet+}$. This chiroptical approach, combining the theoretical prediction with the experimental verification, provides us with a versatile and powerful tool for conveniently and reliably analyzing a complex conformer mixture and even an experimentally difficult-to-access unstable species.

## Conclusion

The only electronic CD spectrum reported for a radical cation of α-tocopherol acetate has turned out to be incorrect and is thought to arise from an artifact, because our own examinations under the reported conditions gave the oppositely signed (positive) Cotton effect for the $d_0-d_2$ transition with a much lower $\Delta\epsilon$ value. This was made possible by employing a vitamin E analogue with a low oxidation potential ($E_{1/2}$) and SET oxidants such as $NO^+$ and antimony derivatives, which eliminates the possible contamination by side products such as the arenium ion. Thus, the first reliable ECD spectra of radical cations were obtained by quantitatively oxidizing chirally modified, sterically hindered hydroquinone ethers with triethyloxonium hexachloroantimonate or nitrosonium tetrafluoroborate. These first CD spectral observations revealed that the CE and the *g* factor of the radical cations of vitamin E derivatives and chiral hydroquinone ether are relatively small and comparable to those of the relevant neutral species.

Vibrational CD spectroscopy, associated with ab initio calculations, can be used as a standard protocol for analyzing (and even predicting) the configuration, conformation and conformer population of chiral radical cations such as $\mathbf{2b}^{\bullet+}$. Low-level optimizations at the HF/3-21G* level do not appear to be useful, while DFT calculations provide satisfactory agreements of the VCD and IR spectra with the experimental ones both for neutral and radical cationic species. Despite the limited number of successful examples presented here, it is clear that the use of chiral probes in ECD and VCD spectral studies combined with the (rather economical) theoretical DFT calculation at 6-31G(d)-level optimization allows us to elucidate the structural details of a variety of chemically and biologically important radical cations in solution, which is complimentary or even superior to the X-ray crystallographic structure obtained in the solid state.

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**Supporting Information Available:** General experimental details, full tables of ab initio calculations, electrochemical analysis of **2b**, observed and calculated IR spectra of **2b**, time dependence of the VCD spectra of the radical cation, and VCD and IR spectra of relevant reference compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(36) All calculations in Table 2 were performed for the ($G^+$, $G^+$) conformations with respect to the 2-methypropyl groups. This is indeed not complete, however, because other conformations such as (T, T) may be energetically much more favorable in some cases. For instance, the anti ($G^+$, $G^+$) conformer is most stable for **2b** and **2b**$^{\bullet+}$ at B3LYP/6-311+G-(2d, p)//HF/3-21G* level calculations, while the most stable conformer of **2b**$^{\bullet+}$ is the anti (T, T) conformation at the B3LYP/6-311+G(2d, p)//B3LYP/6-31G(d) level. Accordingly, in Table 2, we can only roughly estimate the relative energetical preference of anti and syn forms. This phenomenon is further examined in Table 3 for the compound **2b**.

(37) We have prepared similar derivatives using achiral 2-butanol. From GC analysis, the meso form and dl pairs were obtained in ca. 1:1 and appeared separately in the GC chromatogram. In use of (*S*)-2-butanol, such epimers were not observed, and a single stereoisomer was detected by GC. This indicates that the stereoretention was not occurring during the Mitsunobu coupling reaction.

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