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Effect of Substituents and Conformations on the Optical Rotations of Cyclic Oxides and Related Compounds. Relationship between the Anomeric Effect and Optical Rotation[1]

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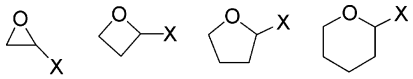

Specific rotations with X = F,Cl,CN,CCH

The effect of substituents on the specific rotation of substituted cyclic oxides (X = F, Cl, CN, and HCC) and related compounds was studied via geometry optimization at the B3LYP/6-311+G** level followed by calculations of the specific rotation with B3LYP/aug-cc-pVDZ and, when practical, also with B3LYP/aug-cc-pVTZ. In some cases chiral samples were prepared so that the calculated specific rotations could be compared with experimental data. With most compounds there was only a minor effect of the basis set on the specific rotations. With the oxiranes and oxetanes, the chloro derivative gave a different behavior than the other substituents, but all substituents behaved in the same fashion with *trans*-2-methyl-1-X-cyclopropanes. Therefore the unusual behavior of chlorooxirane probably results from an interaction between oxygen and chlorine rather than being due to the presence of a three-membered ring. Chlorine is also an unusual substituent for the tetrahydrofurans. The effect of conformation on the calculated specific rotations was examined with the axial and equatorial 2-substituted tetrahydropyrans, where the anomeric effect is operative with the axial substituent, and also the 3-substituted tetrahydropyrans that would not be subject to the anomeric effect. The unusual effect of chlorine was seen only when it is antiperiplanar with respect to the oxygen.

Introduction

Chirality has become of increased interest because of the realization that the two enantiomers of a given drug may often have different physiological effects.[2] As a result, there have been major efforts to develop enantioselective synthetic methods[3] and to relate the configuration of a given enantiomer to that of the receptor site of an enzyme or other biologically active substrate.[4] This requires knowledge of the absolute configuration and, although specialized X-ray crystallographic tools can be used to directly obtain the configuration of a given enantiomer,[5] this is not a routine solution. Rather experimental methods that depend on X-ray[6] or NMR[7] studies of a diastereomer formed with a compound having a known configuration are generally more useful, but their application requires complexing agents that bond selectively to the molecule of interest. More recently, the ability to directly calculate the sign and magnitude of the specific rotation of a given enantiomer with reasonable accuracy has provided another tool,[8] especially when the calculated and experimental values are compared over a range of wavelengths.[9]

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FIGURE 1. Interaction between electric (linear) and magnetic (circular) transition dipoles leading to a helix that can interact distinctly with the two circularly polarized components comprising plane polarized light.

There are medium effects on the optical rotation[10] and they can be studied by Cavity Ring-Down Polarimetry (CRDP), which allows us to measure the intrinsic optical activity exhibited by a vapor-phase sample.[11]

The optical activity of a compound, usually expressed as the specific rotation [α], is, in a fashion similar to NMR chemical shifts, derived from quantities that are directed along three orthogonal axes. For optical rotation, these terms are designated as β and are derived from the following:[12]

$$\beta_{xx} = -\frac{2}{\hbar}\sum_{n\neq 0}^{\infty} \mathrm{Im}\frac{\mu_x^n m_x^n}{\omega_n{}^2 - \omega^2} \qquad (1)$$

where μ_x^n is the electric transition moment on going from the ground state to a given excited state, *n*, along the *x* direction and is directly related to the intensity of an electronic transition. The second term, m_x^n, is the corresponding magnetic transition moment that is directly related to the paramagnetic chemical shift found in NMR experiments.[13] The terms ω and ω_n are the frequency of the light used in observing the rotation and the frequency of the transition to the excited state, *n*. The sum is taken over all of the exited states and the three Cartesian directions. The specific rotation is calculated by averaging over all orientations as follows

$$[\alpha] = c\omega^2\left(\frac{\beta_{xx} + \beta_{yy} + \beta_{zz}}{3}\right)$$

where *c* is a constant.

The magnetic dipole transition moment m_x is an inherently circular term and can have either a clockwise or a counterclockwise nature. The product of μ_x, which is a linear term, with m_x, which is circular, gives a helical interaction term (Figure 1) with either a clockwise or a counterclockwise sense. This effectively helical transition moment can interact with the two circularly polarized components of the incident light in a distinct fashion. Achiral molecules in their minimum energy conformation will give a zero value for all of the terms in the above summation.

Modern programs for calculating specific rotations have become capable of predicting the sign and magnitude of the specific rotation in most cases.[8] Here, linear response theory is usually used to bypass the calculation of excited states. It also is possible to calculate the individual terms with respect to the excited states in the above summation and we have done so for several compounds, including the substituted oxiranes discussed below.[14] It was found, for most molecules, that the summation converges slowly and often requires the inclusion of over 1000 excited states. This and related observations indicate that the peripheral electron density is primarily responsible for the observed specific rotation.[14] It should not be surprising since for a nonresonant interaction the incident light wave should have its principle interaction with the outer electrons of the molecule.

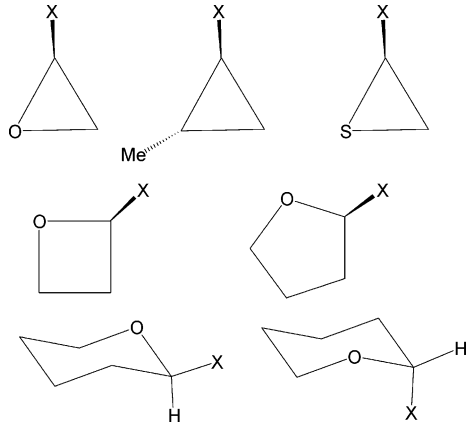

FIGURE 2. Standard configurations of the molecules giving negative C−O−C−X, C−C(Me)−C−X, and O−C−C−X torsion angles.

Previously, we have examined substituent effects for 2-substituted butanes[15] and 3-substituted-1-butenes[16] where X = F, Cl, CN, and HCC. These substituents were chosen since they have a range of electrical effects and do not contribute any conformational flexibility. Here, we found that the effect of conformation on the specific rotation was very large, and that it was mainly determined by the C−C−C−C torsion angle, whereas the substituent had a smaller effect.

We have also examined 2-methyloxirane in some detail and in the gas phase the specific rotation was found to change sign on going from 633 to 355 nm.[10] This observation of a zero crossing led to high-level theoretical calculations that first found no change in sign.[17] However, more comprehensive studies have suggested that vibrational effects associated with the methyl group are responsible for the sign change.[17] As a result, we are preparing some substituted oxiranes that have less conformational flexibility so that we can determine their specific rotations at different wavelengths. At the same time, we have carried out calculations of the expected specific rotations for these and other related heterocyclic compounds shown in Figure 2. The results of the calculations are given below. In all cases, the structures were calculated at the B3LYP/6-311+G** level, and the specific rotations were calculated at the B3LYP/aug-cc-pVDZ level and where practical also at B3LYP/aug-cc-pVTZ level. The latter basis set is over twice as large as the former and requires much more computer time. These levels of theory commonly have been used in calculating specific rotations,[18]

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TABLE 1. Calculated B3LYP/aug-cc-pVTZ Specific Rotations for Substituted Oxiranes

	X = F (*S*)	X = Cl (*S*)	X = CN (*R*)	X = CCH (*R*)
633 nm	11.2	−74.4	80.4	114.3
589 nm	13.3	−87.1	95.7	136.6
578 nm	14.0	−90.8	100.2	143.2
546 nm	16.1	−103.0	115.4	165.7
436 nm	29.6	−172.5	210.2	309.2
365 nm	50.9	−266.9	360.4	548.8
355 nm	55.8	−286.7	394.0	606.1
250 nm	235.9	−80.5	1726.1	3447.3
τ,[a] deg	−110.3	−113.3	−111.2	−112.0
r(C−X)	1.370	1.789	1.448	1.440
μ, D	2.511	2.435	3.895	2.003

[a] C−O−C−X torsion angle.

and their accuracy has been estimated to be around 25° dm^{-1} $(g/mL)^{-1}$ by Stephens and co-workers.[18] In many cases they have been found to fairly well reproduce the observed gas-phase specific rotations.[19]

It may seem strange that one basis set is used for geometry optimizations and another is used for specific rotation calculations. We have found that 6-311+G** gives more satisfactory calculated structures than aug-cc-pVDZ,[20] but that the latter is more satisfactory than the former for specific rotation calculations because it includes diffuse p-functions at hydrogens that sometimes have a marked effect on the calculated values.[21]

The calculations were carried out for the wavelengths that can be observed by using our liquid-phase polarimeter (589, 578, 546, 436, and 365 nm) and also for 633 and 355 nm that are available with our gas-phase polarimeter.[11] Little experimental data are available for the rotations of the compounds in this report, and we have obtained additional information.

Results and Discussion

Oxiranes and Oxetanes. We have continued our study of chiral oxiranes by examining compounds having F, Cl, C≡N, and C≡CH as substituents. These groups are convenient in that they will not lead to additional conformations, but they also have quite different electrical characteristics. The results of the calculations are given in Table 1 that includes the bond lengths to the substituents, the C−O−C−X torsion angles, and the dipole moments. The effect of wavelength on the specific rotation is shown in Figure 3. The arrangement of the molecule is shown in Figure 2 and leads to negative values of the indicated torsion angle. With X = F and Cl, this corresponds to the *S* conformation, whereas with X = CN or CCH, it corresponds to the *R* conformation. The aug-cc-pVDZ calculated rotations were essentially the same as those using the larger basis set.[22]

To see if the calculated specific rotations agree with experimental measurement, (*S*)-(−)-cyanooxiranre was prepared by a kinetic resolution with use of Jacobsen's chiral (salen)-Co^{111} complex.[23] The percent ee was 5.6 ± 0.2, which is quite

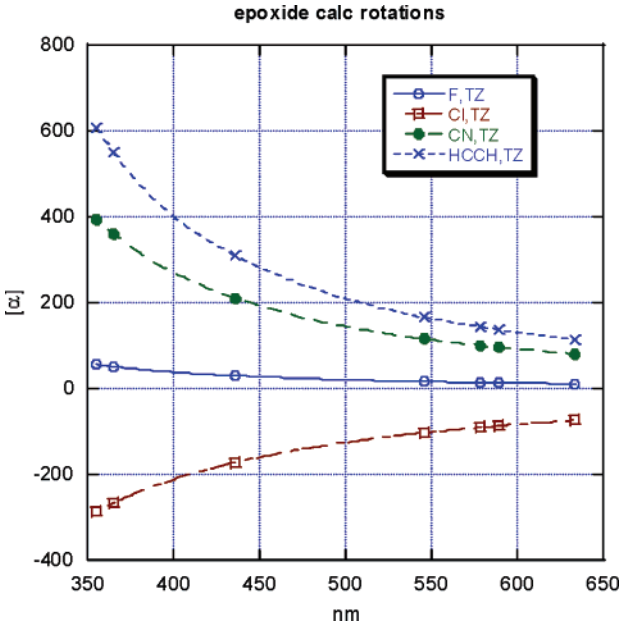

FIGURE 3. Effect of wavelength on the calculated specific rotations of substituted oxiranes.

low for this type of reaction. However, other methods that were tried, such as reactions with chiral amines, were less successful. When corrected to 100% ee we obtained the following for the neat liquid (d = 1.067 g/mL): 589 nm, 99 ± 4; 578 nm, 104 ± 4; 546 nm, 119 ± 4; 436 nm, 214 ± 8; and 365 nm, 353 ± 13. These values are in very good agreement with the calculations. Jacobsen et al.[23] reported the preparation of (*R*)-1-(*tert*-butyldimethylsilyl)-3,4-epoxy-1-butyne with ee of 99.4% via a kinetic resolution. The TBS protecting group could be removed by treatment with tetrabutylammonium fluoride in THF, but because of the similarity in properties between 3,4-epoxy-1-butene and THF, it has not as yet been possible to prepare a pure sample of the epoxide. We do not expect to be able to prepare a chiral sample of chlorooxirane, but fluorooxirane has been prepared in quite low yield via a procedure that could lead to a chiral sample.[24] Efforts to increase the scale of this preparation have not as yet been successful. An attempt at preparing these chiral epoxides continues.

The notable feature of Figure 3 is that whereas decreasing wavelengths leads to increased specific rotations with most substituents, the chlorine leads to the opposite change. In view of the different behavior of 2-chlorooxirane, the specific rotations were calculated for two wavelengths by using the length gauge at the CCSD/aug-cc-pVDZ level for each of the four compounds. The CCSD level of theory usually is quite successful in reproducing experimental results[12] and it is practical to carry out a set of these calculations in the present case because of the small size of the compounds. The results are given in Table 2. The difference between Cl and CN or CCH as the substituent found at the B3LYP level is confirmed by these calculations. The B3LYP and CCSD results are in quite good agreement for 2-chlorooxirane, but the agreement becomes less satisfactory with X = CN or CCH. With 2-fluorooxirane, B3LYP and CCSD predict small rotations with opposite signs. The difference is probably within the intrinsic uncertainty of the calculations.

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TABLE 2. CCSD/aug-cc-pVDZ Calculated Specific Rotations

	X = F	X = Cl	X = CN	X = CCH
589 nm	−11.3	−94.2	67.3	93.3
365 nm	−24.6	−279.2	243.8	351.2

TABLE 3. Calculated B3LYP/aug-cc-pVTZ Specific Rotations for Substituted *trans*-2-Methylcyclopropanes

	X = F (*S*)	X = Cl (*S*)	X = CN (*S*)	X = CCH (*S*)
633 nm	33.0	69.8	118.6	136.8
589 nm	38.4	80.9	138.5	159.3
578 nm	39.9	84.1	144.3	165.8
546 nm	45.1	94.6	163.3	187.1
436 nm	72.9	157.0	270.0	302.9
365 nm	107.0	212.3	408.3	439.3
355 nm	113.6	223.2	436.9	463.9
250 nm	182.6	106.3	981.6	−137.9
τ,[a] deg	−107.8	−109.4	−108.6	−109.2
r(C−X)	1.386	1.789	1.441	1.436
μ, D	2.086	2.239	4.658	1.070

[a] C−O−C−X torsion angle.

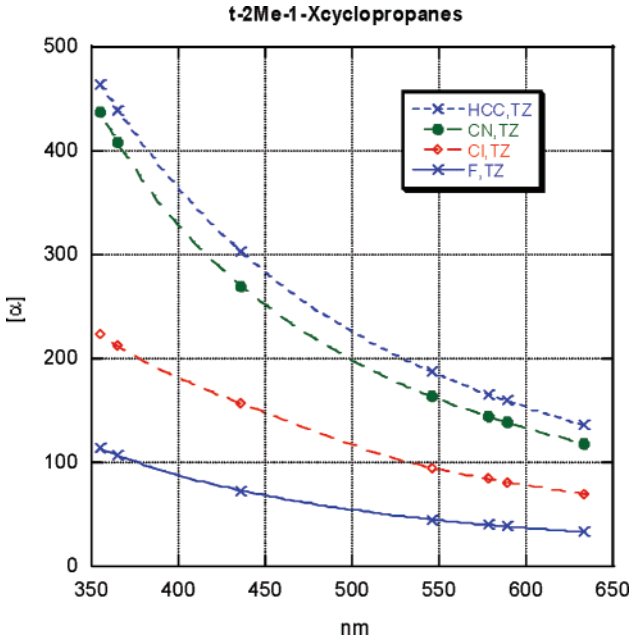

FIGURE 4. Effect of wavelength on the specific rotations of substituted cyclopropanes.

Is the effect of chlorine due to being attached to a three-membered ring, or is it associated with the oxygen in the ring? The first part of this question can be answered by examining the corresponding *trans*-1-methyl-2-X-cyclopropanes. Table 3 and Figure 4 show the results of the calculations and here, all of the substituents give the same type of change in specific rotation with decreasing wavelengths. It might be noted that the maximum rotation of (*S*)-(+)-*trans*-2-methylcyclopropyl cyanide has been found to be $[\alpha]_D$ 150 ± 4,[25] and the calculated value is in good agreement with this experimental observation.

It is reasonable to conclude from these data that the effect of chlorine on the specific rotation of chlorooxirane is not due to the three-membered ring, but rather is probably associated with an interaction between the oxygen and the chlorine. Such interactions are well-known and are referred to as anomeric effects[26] where an electron-withdrawing substituent antiperiplanar to an atom with a lone pair leads to energetic stabilization and the bond to the substituent is found to have an increased length. This results from the donation of electron density from the electron-rich lone pair to the σ^* orbital of the C−X bond. The C−Cl bond lengths in the larger ring cyclic ethers (see below) are considerably larger than a normal C−Cl bond and they show a similar change in rotation compared to other substituents.

TABLE 4. Calculated B3LYP/aug-cc-pVTZ Specific Rotations for Substituted Oxetanes

	X = F (*S*)	X = Cl (*S*)	X = CN (*R*)	X = CCH (*R*)
633 nm	27.1	−54.1	139.9	192.9
589 nm	32.6	−63.0	167.0	231.4
578 nm	34.2	−65.5	175.1	242.9
546 nm	39.9	−73.5	202.3	282.1
436 nm	76.7	−116.0	375.1	537.6
365 nm	139.1	−164.6	659.5	982.7
355 nm	154.0	−173.5	726.8	1092.0
250 nm	778.4	−232.6	3816.3	7522.3
τ,[a] deg	−112.1	−109.6	−119.6	−125.9
r(C−X)	1.393	1.843	1.466	1.454
μ, D	3.125	3.300	4.635	2.217

[a] C−O−C−X torsion angle.

We have tried to identify the source of the difference between chlorine and the other substituents using a sum-over-states approach (eq 1). No single or small group of excited states was primarily responsible for the difference.[14] The origin of the chlorine effect continues to be studied.

The observations for the oxiranes led to the question of whether or not the effect of substituents would be the same in larger rings. Oxetane is essentially planar[27] and the structural calculations find the substituted oxetanes to also be essentially planar. Table 4 shows the results of the calculations and they are also shown in Figure 5.

The changes in specific rotations with wavelength are similar to those found with the oxiranes, with fluorine giving a small increase with decreasing wavelengths, chlorine giving a decrease, and CN and CCH giving relatively large increases with decreasing wavelength. It seems clear that the difference between chlorine and the other substituents in this case is a result of an interaction with the oxygen. The increase in the C−Cl bond length is in accord with this conclusion. Unfortunately, the above oxetanes have not been obtained in chiral form and so we cannot compare experimental and computational data for these compounds.

Tetrahydrofurans. The oxetanes are essentially planar, and so the orientation of the substituents with respect to the ring is essentially the same as that for the oxiranes. The tetrahydrofuran ring is more flexible, and may lead to pseudoaxial and pseudoequatorial positions for the substituents. The four substituents that were examined adopted the pseudoaxial conformations. The results of the calculations for these compounds are recorded in Table 5 and Figure 6.

Here, again, fluorine and chlorine have opposite effects on the specific rotation. However, unlike the oxiranes and oxetanes, the cyano and ethynyl substituents also lead to a decrease in specific rotation with decreasing wavelength. It is worth noting

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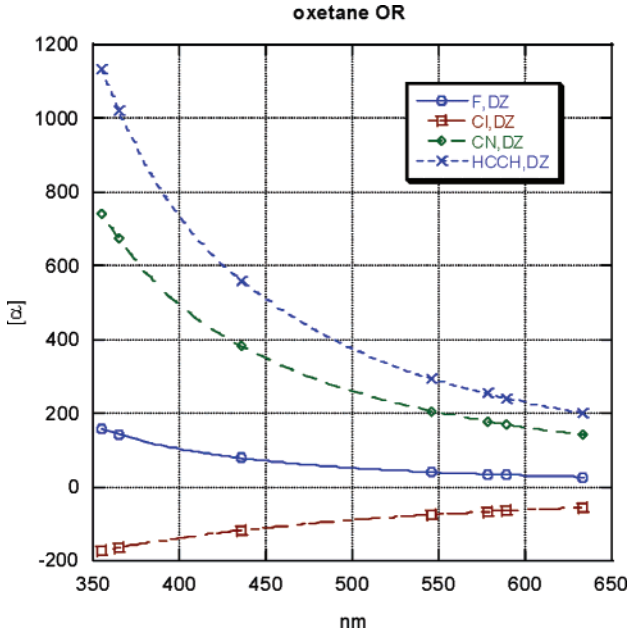

FIGURE 5. Effect of wavelength on the specific rotations of substituted oxetanes.

TABLE 5. Calculated B3LYP/aug-cc-pVDZ Specific Rotations for Substituted Tetrahydrofurans

	X = F (*S*)	X = Cl (*S*)	X = CN (*R*)	X = CCH (*R*)
633 nm	93.5	−296.4	−108.6	−115.7
589 nm	109.1	−348.6	−126.8	−134.9
578 nm	113.7	−363.9	−132.1	−140.4
546 nm	128.7	−414.9	−149.6	−158.7
436 nm	212.9	−714.3	−247.9	−260.0
365 nm	324.5	−1145.3	−378.4	−388.7
355 nm	347.5	−1239.1	−405.4	−414.2
250 nm	903.3	−4151.4	−1087.4	−772.3
τ,[a] deg	−87.6	−90.4	−97.5	−97.5
r(C−X)	1.418	1.890	1.481	1.471
μ, D	2.969	3.356	4.491	2.071

[a] C−O−C−X torsion angle.

that the C−O−C−X torsion angles for the tetrahydrofurans are considerably larger than those for the smaller rings and it is known from other studies that small changes in the torsion angle can lead to large changes in specific rotation.[15,16]

The specific rotation of (*R*)-(−)-2-cyanotetrahydrofuran has been reported[28] to be −28.7° (corrected to 100% ee), which is markedly different than the calculated value. There are several possible explanations for the difference: (1) the calculations are markedly in error, (2) the reported rotation is in error, or (3) there is another structure that must be considered.

Although with X = F or Cl the anomeric effect can lead to a strong preference for a pseudoaxial conformation, it is possible with X = CN or CCH that there is a pseudoequatorial conformer with the opposite sign of rotation and a low enough energy to be significantly populated. This possibility was examined for the cyano derivative by scanning the torsional angle profile from 175° to 80° in 5° intervals, optimizing all of the other structural variables for each step. The calculated relative energies are shown in Figure 7. The observed specific rotation was obtained by using chloroform as the solvent with a dielectric constant of

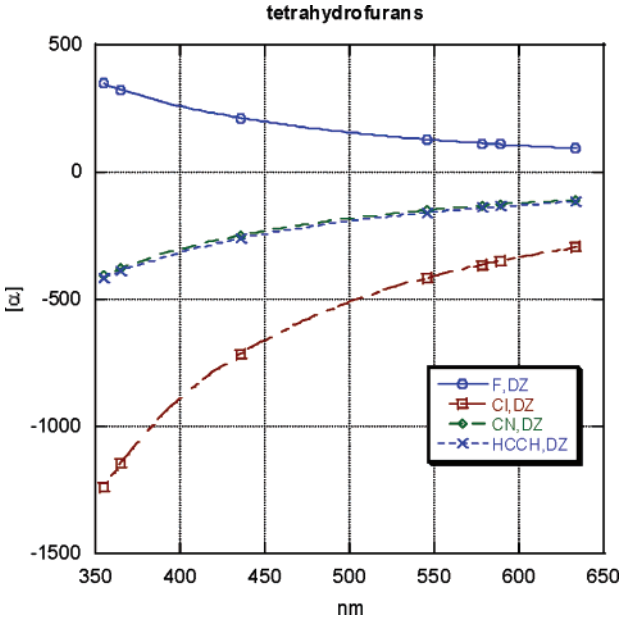

FIGURE 6. Effect of wavelength on the specific rotations of substituted tetrahydrofurans.

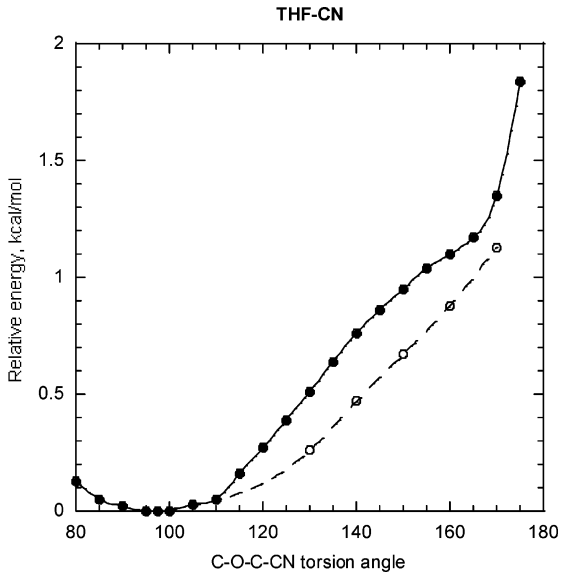

FIGURE 7. Effect of the C−O−C−CN torsion angle on the relative energy for 2-cyanotetrahydrofuran. The closed circles give the B3LYP/6-311+G** data, and the open circles give the corresponding data corrected for the solvent effect calculated by using the IPCM model and a dielectric constant of 4.9.

4.9. The effect of this solvent on the relative energies was estimated by using the IPCM solvation model[29] and these values are shown in the figure as open circles. It is also possible that MP2 may lead to a somewhat different change in energy on rotating about the C−O−C−CN torsion angle. This was explored at the MP2/6-311+G** level and there is little difference between the B3LYP and MP2 relative energies.

Although there is a small shoulder at ∼160°, there is clearly no minimum corresponding to a pseudoequatorial form. There is a significant decrease in dipole moment with decreasing

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TABLE 6. Calculated B3LYP/aug-cc-pVDZ Specific Rotations for 2-Substituted Tetrahydropyrans

	X = F (*S*)	X = Cl (*S*)	X = CN (*R*)	X = CCH (*R*)
		(a) axial		
633 nm	−76.3	−299.1	−72.1	−37.5
589 nm	−89.3	−352.3	−84.0	−44.4
578 nm	−93.0	−368.0	−87.4	−46.6
546 nm	−105.5	−430.1	−98.7	−53.5
436 nm	−176.1	−729.5	−161.3	−96.7
365 nm	−271.6	−1183.5	−241.2	−165.8
355 nm	−291.6	−1283.6	−257.5	−908.9
250 nm	−817.9	−4611.	−607.4	−908.9
τ,[a] deg	−68.0	−72.2	−68.4	−68.5
r(C−X)	1.420	1.891	1.484	1.473
μ, D	2.423	2.984	3.868	1.687
		(b) equatorial		
633 nm	15.0	12.8	38.4	37.5
589 nm	17.9	15.0	43.4	44.5
578 nm	18.7	15.7	47.4	46.6
546 nm	21.6	18.0	54.3	53.5
436 nm	39.4	31.4	96.3	96.7
365 nm	68.3	51.4	160.6	165.8
355 nm	75.0	55.9	175.2	182.0
250 nm	365.8	192.7	725.4	908.9
τ,[a] deg	178.8	176.2	176.3	175.7
r(C−X)	1.382	1.812	1.468	1.461
μ, D	3.554	3.661	5.418	2.038

[a] C−O−C−X torsion angle.

torsion angle, and when corrected for the solvent, the results indicate that the calculated specific rotation must take into account the low-energy species that will have a different specific rotation than the lowest energy 97° conformer. At τ = 150°, the calculated specific rotation at 589 nm is −44.2, not sufficiently different to explain the difference between experiment and theory.

A chiral sample of (*R*)-(−)-2-cyanotetrahydrofuran was obtained by using a different set of reactions than previously reported (see the Experimental Section), and its specific rotation determined in chloroform and corrected for the percent ee was found to be $[\alpha]_D$ −37.4. This is somewhat larger than previously reported, but still much smaller than the calculated specific rotation. It was possible to measure the rotation in the gas phase, finding −25.7 ± 10.1 at 633 nm and −131.0 ± 15.2 at 355 nm.

The B3LYP/aug-cc-pVDZ calculations could lead to an incorrect value of the specific rotation. Therefore, it was also calculated at the CCSD/aug-cc-pVDZ level to find $[\alpha]_D$ −101.9. This is smaller than the B3LYP value, but still larger than the experimental rotation. Figure 7 makes it clear that we must take the slightly higher energy conformers into account, since at τ = 130° the relative energy has only increased by 0.5 kcal/mol in the gas phase, and only 0.3 kcal/mol in chloroform solution. It is not clear how this might best be done and we are working on the problem. It might be noted that for 2-cyanotetrahydropyran (see below), which has two well-defined conformers, the calculated specific rotation is in good agreement with the experimentally determined value.

Substituted Tetrahydropyrans. In the above examples, the substituents in the equilibrium conformation adopted a pseudo-axial position. The tetrahydropyrans have a sufficiently large ring inversion barrier[30] so that axial and equatorial forms have separate existence, although rapidly interconverting. Here,

(30) Lambert, J. B.; Mixan, C. E.; Johnson, D. H. *J. Am. Chem. Soc.* **1973**, *95*, 4634.

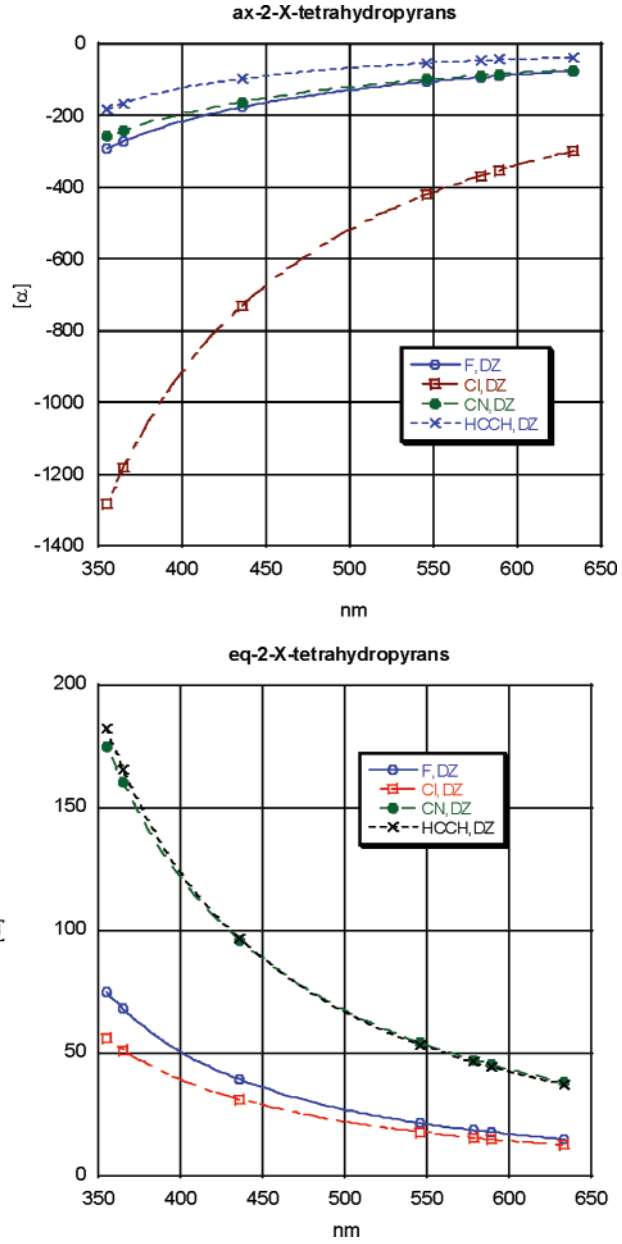

FIGURE 8. Effect of wavelength on the calculated specific rotations of 2-substituted tetrahydropyrans (upper plot, axial substituents; lower plot, equatorial).

TABLE 7. Properties of Axial and Equatorial Conformers of Substituted Tetrahydropyrans Calculated at the B3LYP/6-311+G Level**

	F		Cl		CN		HCC	
	E_{rel}	m	E_{rel}	m	E_{rel}	m	E_{rel}	m
ax-2	0.00	2.423	0.00	2.984	2.13	3.868	1.84	1.687
eq-2	2.96	3.557	3.73	3.661	2.82	5.416	1.91	2.038
ax-3	7.57	2.965	4.98	3.141	1.18	4.921	1.70	1.885
eq-3	12.88	2.103	3.34	2.265	0.00	3.946	0.00	1.456

we begin by examining 2-substituted tetrahydropyrans with substituents in both the axial and equatorial positions. The axial substituents may lead to an anomeric effect, but this is not possible with the equatorial substituents. The calculated specific rotations, along with the O−C−C−X torsion angles,

TABLE 8. Calculated B3LYP/aug-cc-pVDZ Specific Rotations for 3-Substituted Tetrahydropyrans

	X = F (*S*)	X = Cl (*S*)	X = CN (*R*)	X = CCH (*R*)
		(a) axial		
633 nm	−6.8	−73.4	−73.2	−98.6
589 nm	−7.7	−86.6	−85.7	−115.7
578 nm	−7.9	−90.4	−89.3	−120.7
546 nm	−8.6	−103.3	−101.3	−137.3
436 nm	−11.5	−180.5	−169.4	−233.8
365 nm	−11.7	−297.1	−261.3	−369.9
355 nm	−11.2	−323.5	−280.4	−399.2
250 nm	62.0	−1428.	−740.4	−1313.1
τ,[a] deg	−69.9	−71.6	−69.2	−69.6
r(C−X)	1.412	1.837	1.466	1.463
μ D	2.965	3.141	4.921	1.885
		(b) equatorial		
633 nm	−8.3	−21.1	9.8	15.5
589 nm	−9.6	−25.2	11.6	18.5
578 nm	−9.9	−26.4	12.2	19.5
546 nm	−11.1	−30.5	14.0	22.5
436 nm	−16.8	−57.0	25.0	43.0
365 nm	−21.3	−100.6	42.5	78.9
355 nm	−21.6	−110.9	46.6	87.8
250 nm	112.2	−546.6	247.5	668.2
τ,[a] deg	177.6	180.0	179.4	179.3
r(C−X)	1.410	1.828	1.461	1.459
μ, D	2.108	2.265	3.946	1.456

[a] C−O−C−X torsion angle.

bond lengths to the substituents, and the dipole moments are given in Table 6, and the specific rotations are also shown in Figure 8.

The difference in C−X bond lengths between the axial and equatorial conformers is quite large with chlorine (0.079 Å), somewhat smaller with fluorine (0.039 Å), and much smaller with CN and CCH (0.016 and 0.012 Å, respectively). This is just what is expected from the operation of the anomeric effect. However, in contrast to the oxiranes and oxetanes, all of the axial substituents give specific rotations with negative signs. The equatorial substituents, on the other hand, give uniformly positive specific rotations. The chlorine substituent again has the largest effect on the specific rotation when in the axial position.

The specific rotation of (*R*)-(−)-2-cyanotetrahydropyran has been reported to be −36.2. However, this cannot be directly compared with the calculated rotations in Table 5 because the two conformers can be populated. In addition, the specific rotation was measured in chloroform with a dielectric constant of 4.9. Since there is a difference in dipole moment between the axial and equatorial conformers, there will be a solvent effect that preferentially stabilizes the equatorial form. The gas-phase relative energies of the axial and equatorial conformers are given in Table 7. Unlike the compounds with X = F or Cl, the difference in energy of the conformers is only about 0.7 kcal/mol indicating that both conformers will be significantly populated. To obtain a good estimate of the relative free energies, G3 calculations[31] were carried out, and the axial form had the lower free energy (1.02 kcal/mol). The solvent effect on the relative free energies in the neat liquid phase was estimated by using a reaction field model. Assuming the dielectric constant of the compound will be on the order of 10, an SCIPCM[29] calculation suggested a solvent stabilization of 0.56 kcal/mol for the equatorial form relative to axial. Therefore,

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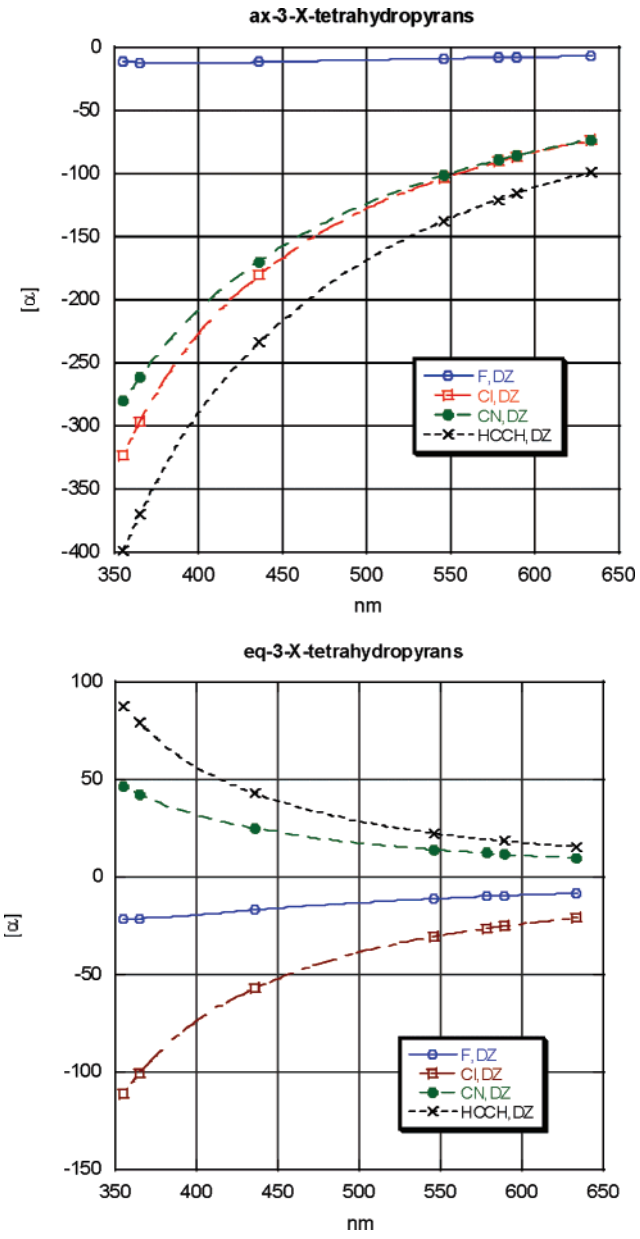

FIGURE 9. Effect of wavelength on the calculated specific rotations of 3-substituted tetrahydropyrans (upper plot, axial; lower plot, equatorial).

the net difference in energy for the liquid phase is estimated to be about 0.46 kcal/mol, leading to 68% axial and 32% equatorial. This gives an estimated $[\alpha]_D$ of −43, which is in satisfactory agreement with the experimental value considering the uncertainties in the relative energies. This compound will receive further experimental study including a redetermination of the maximum specific rotation, as well as measurement of the specific rotation in the gas phase and in several solvents.

3-Substituted Tetrahydropyrans. To further examine the results of the anomeric effect in the tetrahydropyrans, it is necessary to have information on a related series in which the anomeric effect is absent. Therefore, we have studied the 3-substituted tetrahydropyrans. The calculated specific rotations, torsion angles, bond lengths, and dipole moments are given in Table 8, and the specific rotations are shown in Figure 9. As expected, the difference in bond lengths between axial and equatorial substituents is much smaller than that found with the

TABLE 9. Calculated B3LYP/aug-cc-pVTZ Specific Rotations for Substituted Thiiranes

	X = F (*R*)	X = Cl (*S*)	X = CN (*R*)	X = CCH (*R*)
633 nm	−44.5	−41.7	−48.9	−69.2
589 nm	−51.8	−45.1	−55.3	−77.6
578 nm	−53.9	−45.8	−57.0	−79.8
546 nm	−60.8	−47.2	−62.2	−86.0
436 nm	−98.2	−18.7	−70.5	−79.7
365 nm	−144.1	198.1	32.6	178.7
355 nm	−153.3	288.6	87.2	309.9
250 nm	2288.	−1794.	−5103.	−12846.
τ,[a] deg	−110.0	−111.4	−111.8	−112.8
r(C−X)	1.372	1.786	1.440	1.434
μ, D	2.190	2.056	3.812	1.758

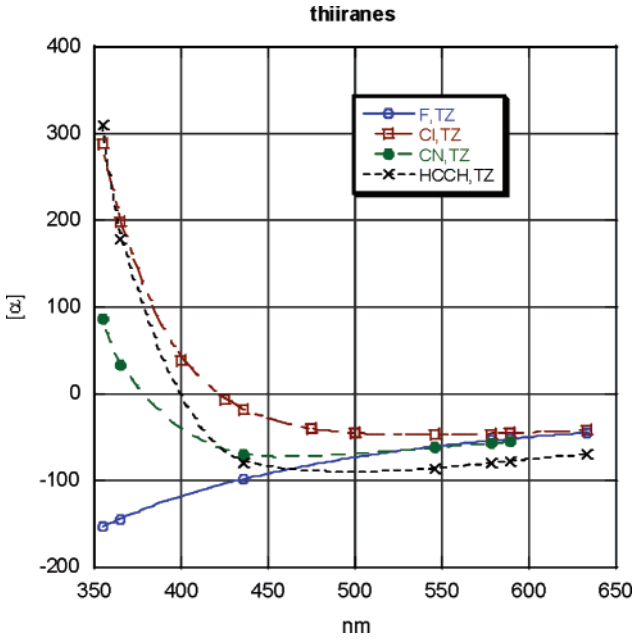

FIGURE 10. Calculated specific rotations for substituted thiiranes.

2-substituted compounds (0.010 Å for Cl, less than 0.002 Å for the others).

A comparison of Figure 8 for the axial 2-substituted tetrahydropyran with Figure 9 for the axial 3-substituted compound shows marked differences. Whereas in the former case the change in specific rotation with wavelength was relatively small for X = CN or HCC, it becomes large for the latter. The change for X = Cl is large for both compounds, but much larger for the 2-substitued compound than for the 3-substituted one. The torsional angles are about the same for the two sets of compounds and so the difference can reasonably be attributed to an interaction between the ring oxygen and the substituent with the 2-substituted series.

A comparison of the corresponding equatorial substituted compounds finds the CN and HCC substituted compounds having similar behavior, with the fluorine substituent giving a relatively small effect. The main difference is found with the chlorine substituent where a small increase in specific rotation with decreasing wavelength is found with the 2-substituted compound and a decrease with the 3-substituted. However, the changes are quite small in comparison to that of axial of 2-chlorotetrahydropyran.

It may be a coincidence, but Figure 9 for the equatorial substituents resembles Figures 3 and 4 for the oxiranes and oxetanes. However, the range of specific rotations is considerably smaller in Figure 9 than for the other figures.

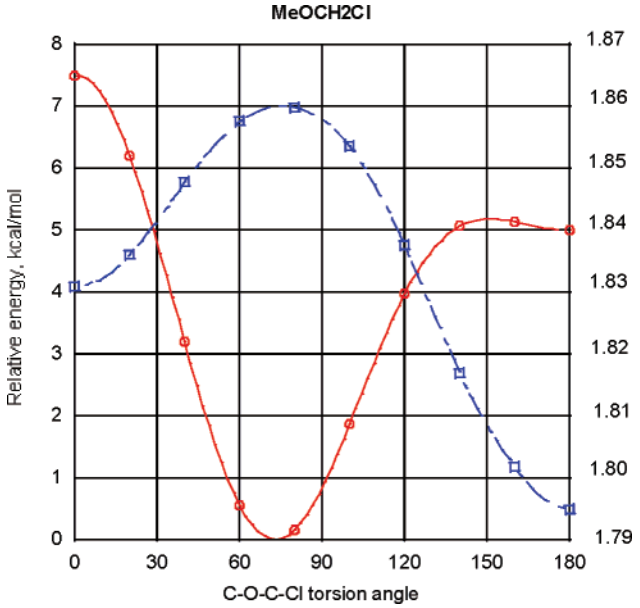

FIGURE 11. Effect of the C−O−C−X torsional angle on the relative energies (left scale, red) and C−Cl bond lengths (right scale, blue) for methoxymethyl chloride.

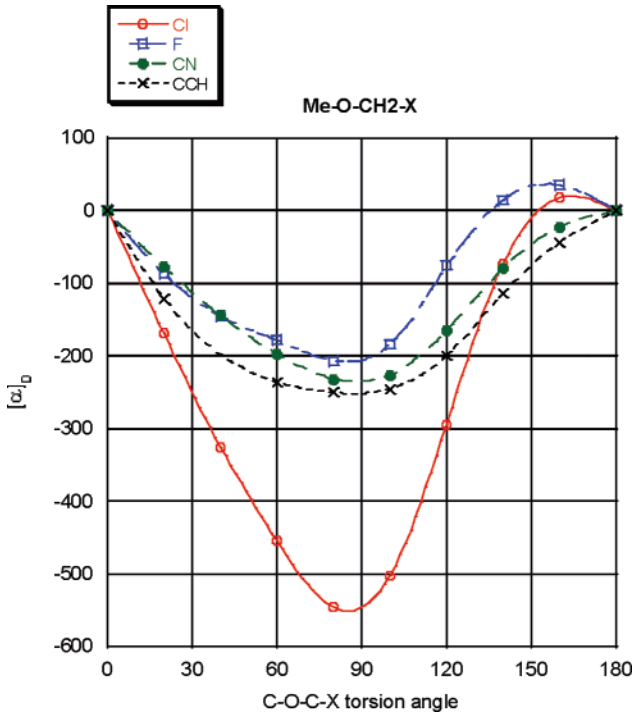

FIGURE 12. Effect of the C−O−C−X torsion angle on the calculated specific rotation of methoxymethyl derivatives at 589 nm.

Thiirnes. The results presented above clearly indicate an interaction between a ring oxygen and the substituents that affect the calculated specific rotations. It was then of interest to examine the effect of another element, sulfur, that has a lower ionization potential, but less of a tendency to give an anomeric effect. The results of calculations for substituted thiiranes are shown in Table 9 and Figure 10. Unlike the oxiranes, there is a significant difference between the rotations calculated with aug-cc-pVDZ and aug-cc-pVTZ. Further, whereas the oxiranes had positive specific rotations, except for X = Cl, the thiiranes

have negative specific rotations from 633 to 436 nm for all of the substituents. At shorter wavelengths, there is often a change in sign of rotation, as might be expected since thiirane has its electronic transitions[32] at considerably lower energy than that for oxiranes.

Conformational Effect on the Specific Rotation. The compounds studied above had C−O−C−X torsional angles either close to −100° or ∼180°. What changes might be found with other torsion angles? As a simple model we have chosen the methoxymethyl halides. Here, the compound will, of course, be achiral when planar. But, any deviation from planarity will lead to chirality, and the changes with changing torsion angle might be informative. Figure 11 shows the changes in energy and bond length for methoxymethyl chloride. The other substituents give similar plots, but with much smaller changes in bond lengths (0.035 Å for F, 0.012 Å for CN, and 0.010 Å for HCC). The effect of substituents on the specific rotation was calculated by using B3LYP/aug-cc-pVTZ and the results for 589 nm are shown in Figure 12.

Again, chlorine is the unique substituent that leads to much larger changes in specific rotation than found with the other substituents. The origin of the chlorine effect continues to be studied.

Summary. A study of a series of cyclic oxides substituted by F, Cl, CN, and CCH revealed a wide variety of optical rotatory dispersion effects. Chlorine was the more unusual substituent and this appeared to result from an anomeric effect involving the chlorine and the oxygen in the ring. This is most clearly seen in examining the tetahydropyrans where the anomeric effect is well established, and where an axial chlorine leads to a large effect, whereas an equatorial chlorine does not. In an effort to determine the origin of the chlorine effect, a sum-over-states calculation of the specific rotation was carried out, but no single excited state or small group of excited states had a major effect on the rotation.

This survey of substituent effects will be followed by more detailed examinations including measurements of the specific rotations in the gas phase and in a series of solvents, along with the preparation of additional chiral compounds.

Calculations. All of the B3LYP calculations were carried out with Gaussian-03[33] and the CCSD calculations were carried out with PSI3.[34]

Experimental Section

2-Cyanooxirane. The racemic compound was prepared by the reaction of sodium hypochlorite with acrylonitrile.[35] Several methods were explored for its kinetic resolution, such as the reaction with a chiral amine. The more successful method was a reaction with Jacobsen's chiral (salen)CO^{111} complex.[23] The (*R*,*R*) catalyst (653 mg, 0.015 equiv) was dissolved in 20 mL of dichloromethane in a water-jacketed 35 mL flask. Acetic acid (650 μL) was added and the solution was stirred for 40 min at room temperature. After a few minutes, the solvent was removed at 20 Torr and remaining volatile material was removed from the catalyst by using a mechanical pump with a −78 °C cold trap. Racemic cyanooxirane (5.0 g) was added to the catalyst along with 3.5 mL of isopropyl alcohol. The solution was cooled to 1 °C, 850 μL of water (0.65 equiv) was added, and the reaction was allowed to proceed for 5 days at 1 °C. The product was distilled, bp 50−52 °C at 25 Torr. Analysis with a Chiraldex B-DM (β-cyclodextrin) gc column indicated 5.6 ± 0.2% ee. The observed rotation corrected to 100% ee was $[\alpha]_D$ 99 ($l = 1$, $d = 1.067$). The NMR spectrum was identical with that of an authentic sample.

2-Cyanotetrahydrofuran. Tetrahydrofurfurylamine was resolved by using tartaric acid a previously described[36] and had $[\alpha]_D$ −13.9 ($l = 1$, $c = 0.044$ g/mL, methanol, 99% ee). Oxidation with sodium tungstate and hydrogen peroxide gave tetrahydrofuran-2-carboxaldehyde oxime[36] ($[\alpha]_D$ 40.1 ($l = 1$, $c = 0.042$ g/mL, methanol)), and it was dehydrated by using acetic anhydride and sodium acetate.[37] To 5.0 g of the oxime was added 0.3 g of anhydrous sodium acetate and 5 g of acetic anhydride. After the initial exothermic reaction, the solution was heated to reflux for 1 h. The cooled solution was treated with water and warmed. It was then saturated with potassium carbonate and extracted with ether. After the solution was dried over magnesium sulfate, the solvent was removed and the product was distilled, giving 3 g of 2-cyanotetrahydrofuran, bp 79−82° at 19 mm. It had $[\alpha]_D$ −30.1 ($l = 1$, 0.035 g/mL, $CHCl_3$). It was found to be 99+% pure and to have 86.8% ee via gc, using a chiral column. The specific rotation of the pure enantiomer is then $[\alpha]_D$ −34.7 ($CHCl_3$). Its NMR spectrum was identical with that of an authentic sample.

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Supporting Information Available: Specific rotations with different basis sets and calculated geometries of the compounds in this report. This material is available free of charge via the Internet at http://pubs.acs.org.

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