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ARTICLE

Wavelength Resolved Specific Optical Rotations and Homochiral Equilibria

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P. L. Polavarapu,^a and C. L. Covington^a

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The fundamental expressions governing specific optical rotations (SORs) of homochiral systems exhibiting monomer-dimer equilibria are presented. These equations are then utilized with the experimental measurements of wavelength resolved circular birefringence for (*R*)-(-)- α -Hydroxy- β , β -dimethyl- γ -butyrolactone, to determine the wavelength resolved SORs of monomer and dimer components for the first time. Density functional theory predictions on the corresponding dispersion properties of monomer and dimer are found to match with experimentally determined quantities within a factor of ~ 2 . The wavelength resolved circular birefringence in the liquid solution phase thus provides a powerful means to investigate the molecular properties involved in homochiral equilibria.

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I. Introduction

Chirality plays important roles in various branches of science. Chiroptical spectroscopy,¹ which includes circular birefringence,² circular dichroism^{3,4} and differential circular intensity Raman scattering,^{2,4} provides a powerful means to establish the predominant conformations and absolute configurations of chiral substances. Circular birefringence,⁵ manifested as optical rotation (OR, α), and its concentration normalized analogue, specific optical rotation (SOR), $[\alpha]$, and wavelength resolved extension, optical rotatory dispersion (ORD), is a sensitive probe of chirality. Advances in modern quantum chemical methods⁶ permit the prediction of wavelength resolved SORs offering a facile approach to interpret the corresponding experimentally determined quantities.

For chiral systems undergoing equilibria,⁷ detailed experimental and theoretical SOR studies are lacking in the literature. In one study,⁸ experimental OR studies at a single wavelength on systems at equilibrium were suggested to be useful for determining the equilibrium constants. But the SORs of equilibrating species and comparison to corresponding quantum chemical predictions were not addressed. In a different study,⁹ quantum chemical predictions of SOR at a single wavelength for monomer and dimer molecules were used to simulate the SOR for a system at equilibrium and the result compared to the corresponding experimental SOR measurement at that wavelength. But the adhoc equation used therein for SOR does not satisfy¹⁰ a limiting criterion (vide

infra).

These literature studies point to multiple areas that are in need of new developments for homochiral species in equilibrium: (a). fundamental equations governing the SORs remain to be established; (b). systematic experimental studies on wavelength resolved SORs for deriving the molecular properties of species involved in equilibrium are lacking; (c). The reliability of modern quantum chemical predictions of wavelength resolved SORs of equilibrating species remains to be established. The developments in these areas are reported here for the first time.

The organization of this manuscript is as follows: First, the fundamental expressions governing the SORs of systems undergoing monomer-dimer equilibria have been derived. Second, these equations are utilized with the experimentally measured concentration dependent, and wavelength resolved, circular birefringence for CCl_4 solutions of (*R*)-(-)- α -Hydroxy- β , β -dimethyl- γ -butyrolactone (also known as pantolactone), which enabled the determination of the wavelength dependent SORs of constituent monomer and dimeric species. Finally, density functional theory predictions of the corresponding molecular properties are obtained and compared to the corresponding experimentally determined quantities.

II. Results and Discussion

A. Derivation of the equation for SOR of homochiral system exhibiting monomer-dimer equilibrium

The homochiral monomer (M) - dimer (D) equilibrium of an enantiomer is represented by the expression,



with the associated equilibrium constant, K :

^aDepartment of Chemistry, Vanderbilt University, Nashville, TN 37235. Electronic Supplementary Information (ESI) available: Weighted non-linear least square fits; quantum chemical predictions in CHCl_3 solvent. Details of conformational search and Optimized structures. See DOI: 10.1039/x0xx00000x

$$K = \frac{C_d}{C_m^2}, \quad (2)$$

where, C_m and C_d are, respectively, the molar concentrations of monomer and dimer (that include all of the respective conformers) of the enantiomeric substance. The material balance requires,

$$C_o = C_m + 2C_d \quad (3)$$

where C_o is the molar concentration of the prepared enantiomer solution. The quadratic equation resulting from Eqs 2 and 3 can be solved¹¹ to determine the monomer concentration as

$$C_m = P_m C_o \quad (4)$$

where P_m is given as,

$$P_m = \frac{2}{(1 + \sqrt{1 + 8KC_o})} \quad (5)$$

Using Eq 3, the expression for C_d is obtained as,

$$C_d = P_d C_o \quad (6)$$

where P_d is given as:

$$P_d = \frac{1}{2} \frac{(-1 + \sqrt{1 + 8KC_o})}{(1 + \sqrt{1 + 8KC_o})}; \quad (7)$$

Note that P_m and P_d cannot be termed mole fractions because they do not add up to one. Instead,

$$P_m + 2P_d = 1, \quad (8)$$

and P_m and P_d are related to the mole fractions, x_m and x_d , respectively of monomer and dimer, as

$$x_m = \frac{C_m}{C_m + C_d} = \frac{P_m}{P_m + P_d} = \frac{P_m}{1 - P_d} = \frac{2P_m}{1 + P_m} \quad (9)$$

$$x_d = \frac{C_d}{C_m + C_d} = \frac{P_d}{P_m + P_d} = \frac{1 - P_m}{1 + P_m} = \frac{P_d}{1 - P_d} = \frac{2P_d}{1 + P_m} \quad (10)$$

Assuming that SORs of monomer and dimer are independent of concentrations, the observed OR, α , for a pure enantiomeric substance exhibiting homochiral monomer-dimer equilibrium, can be written as follows:

$$\alpha = [\alpha]_m c_m l + [\alpha]_d c_d l = [\alpha]_m \frac{C_m M_m}{1000} l + [\alpha]_d \frac{C_d M_d}{1000} l \quad (11)$$

where $[\alpha]_m$ and $[\alpha]_d$ are the SORs, respectively of monomer and dimer species; l is the path length of the cell used for OR measurement; c_m is the concentration of monomer in g/cc; c_d is the concentration of dimer in g/cc; M_m is the molar mass of monomer; M_d is the molar mass of dimer. Note that upper

case letter "C" is used for concentrations in mol L⁻¹ units and lower case letter "c" is used for that in g cc⁻¹ units.

Using Eqs 4 and 6 and $M_d=2M_m$, Eq 11 can be modified as:

$$\alpha = \{[\alpha]_m P_m + 2P_d [\alpha]_d\} \frac{C_o M_m}{1000} l \quad (12)$$

Writing the starting concentration, c_o , in g/cc of enantiomeric substance as,

$$c_o = \frac{C_o M_m}{1000}, \quad (13)$$

the SOR of solution,

$$[\alpha] = \frac{\alpha}{c_o l}, \quad (14)$$

becomes:

$$[\alpha] = \{[\alpha]_m P_m + (1 - P_m)[\alpha]_d\} \quad (15)$$

Eq. 15 is the fundamental expression for SOR of homochiral system exhibiting monomer-dimer equilibrium and is derived for the first time. This equation can be seen to have the correct limiting values as follows: (a). As C_o approaches zero, P_m approaches 1 (see Eq. 5), and $[\alpha]$ becomes $[\alpha]_m$. (b). As C_o approaches infinity, P_m approaches 0, and $[\alpha]$ becomes $[\alpha]_d$. (c). For the special case of $[\alpha]_m = [\alpha]_d$, monomer-dimer equilibrium should not influence the $[\alpha]$ of solution, which should then be independent of concentration C_o , as supported by Eq. (15).

B. Data and Analysis

(R)-(-)- α -Hydroxy- β,β -dimethyl- γ -butyrolactone is known to establish monomer-dimer equilibrium in CCl₄ solvent, as shown in Figure 1, with homochiral equilibrium constant of 8.9 (determined from infrared absorption spectra as a function of concentration).⁷

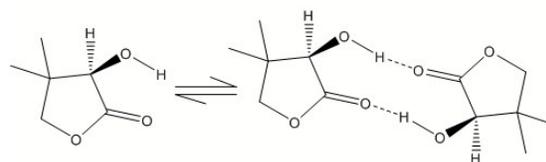


Figure 1. Monomer-dimer equilibrium in (R)-(-)- α -Hydroxy- β,β -dimethyl- γ -butyrolactone

The experimental concentration dependent, and wavelength resolved, ORs for this compound were measured in CCl₄ solvent. The measured ORs at lower concentrations and longer wavelengths have smaller magnitudes, so the relative uncertainty is lower at shorter wavelengths and higher concentrations. The measured ORs were converted to SORs by dividing with concentration (g/cc) and path length (dm) and are summarized in Table 1. These data can be used with Eq 15, along with reported K value of 8.9⁷ to determine the

wavelength resolved SORs of monomer and dimer, $[\alpha]_m$ and $[\alpha]_d$, respectively. Since the experimentally measured property is the α of solution, while the least squares fit is done for $[\alpha]$,

conc (M)	$[\alpha]_{633}$	$[\alpha]_{589}$	$[\alpha]_{546}$	$[\alpha]_{436}$	$[\alpha]_{405}$	$[\alpha]_{365}$
0.0020	-4.3	-7.2	-8.7	-14.4	-23.1	-48.1
0.0041	-3.8	-2.6	-2.8	-10.2	-22.0	-46.4
0.0060	-1.9	-5.0	-7.6	-18.2	-33.0	-59.3
0.0079	-5.0	-7.1	-8.6	-18.5	-34.5	-54.4
0.0122	-5.7	-7.8	-10.9	-27.0	-39.1	-66.4
0.0151	-6.5	-8.2	-11.6	-28.8	-39.9	-70.3
0.0229	-9.4	-11.7	-15.4	-32.5	-45.1	-76.4
0.0384	-11.7	-14.8	-19.1	-42.0	-57.4	-93.4

the concentration normalised α of solution, weighted non-linear least squares (WNLS) method¹² is required to fit the data to Eq. 15. The weights for individual SOR values were determined through error propagation using uncertainties in observed ORs, and in concentrations of solutions. In a simpler method, weights were determined assuming that relative errors in concentrations are smaller than those in ORs. Both approaches yielded identical values for $[\alpha]_m$ and $[\alpha]_d$ within their associated errors and weighted higher concentration data more than those at lower concentrations.

The WNLS fits using Kaleidagraph program¹³ are shown in Figure S1 of Supplementary Information (SI). The results obtained from the WNLS fits for $[\alpha]_m$ and $[\alpha]_d$ are summarized in Table 2 in $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$ units. This is the first determination of wavelength resolved $[\alpha]_m$ and $[\alpha]_d$ for a chiral enantiomer at homochiral equilibrium.

nm	Experiment		Predicted			
	$[\alpha]_m$	error	$[\alpha]_d$	error	$[\alpha]_m$	$[\alpha]_d$
					CAM-B3LYP/aug-cc-pVTZ	
633	-0.5	0.6	-36.0	1.6	-7.7	-109.6
589	-1.3	0.7	-43.9	1.7	-9.6	-128.4
546	-2.7	0.6	-54.6	1.7	-12.3	-152.1
436	-8.8	1.6	-112.9	4.2	-27.7	-257.8
405	-18.3	2.2	-139.9	5.9	-37.3	-310.2
365	-37.4	2.7	-212.5	7.2	-58.8	-409.5

Conformational analysis (see SI) confirmed four low energy conformations for dimer and two low energy conformations for monomer as reported in the literature⁹. These conformations are used as the starting point for further geometry optimizations and SOR calculations. These calculations were undertaken with Gaussian 09 program¹⁴ and solvents effects were included with PCM¹⁵. The populations, at B3LYP/aug-cc-pVTZ/PCM level, of two monomer conformers are 97% and 3%, while those of four dimer conformers are 91%, 5%, 2% and 2%. Thus in essence, there is only one predominant conformer each for monomer and dimer. Dispersion corrected DFT, and also a functional incorporating the non-covalent interactions, confirmed this conclusion (see SI). Boltzmann weighted SORs at CAM-B3LYP¹⁶/aug-cc-pVTZ¹⁷ level of theory using PCM are presented in Table 2. Additional calculations were also undertaken at B3LYP¹⁸/6-

311++G(2d,2p)¹⁹ level of theory using CCl_4 solvent and for the dominant dimer conformer at various levels of theory using CHCl_3 solvent. These results are provided in the SI. Difference in the influence of CCl_4 and CHCl_3 solvents is limited, as is evident from the results obtained in CCl_4 and CHCl_3 solvents at CAM-B3LYP/aug-cc-pVTZ level (see SI). The calculated SORs at CAM-B3LYP/aug-cc-pVTZ level of theory are also closest to the experimental values.

In Figure 2, the experimentally determined wavelength resolved SORs for monomer and dimeric forms of (R)-(-)- α -Hydroxy- β,β -dimethyl- γ -butyrolactone in CCl_4 are compared to those predicted at CAM-B3LYP/aug-cc-pVTZ level. The experimentally determined SOR in CCl_4 at 589 nm, for monomer and dimer are -1.3 ± 0.6 and -43.9 ± 1.7 , respectively. The corresponding predicted values at CAM-B3LYP/aug-cc-pVTZ level are -9.6 and -128.4. While any emphasis on the prediction of SORs with small magnitudes is not advised,²⁰ the magnitudes of SOR for dimer are significant and the experimental and predicted values at 589 nm differ by a factor of 3. The magnitudes of SOR at shorter wavelengths are larger, so a better assessment of experimental and calculated results can be obtained at shorter wavelengths. At 365 nm the experimental and predicted SORs for monomer differ by a factor of 1.6 and for dimer by a factor of 1.9. These differences may arise from the inadequacy of density functionals used or from vibrational contributions to SOR,²¹ which are not included in the present calculations.

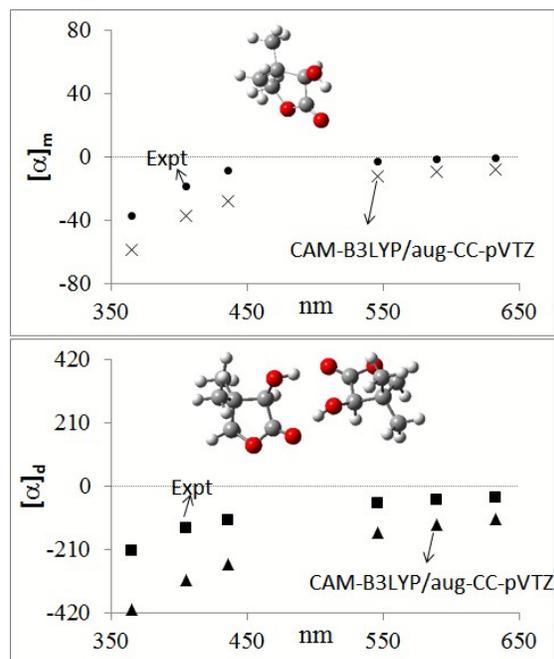


Figure 2. Comparison of experimental and CAM-B3LYP/aug-cc-pVTZ calculated wavelength resolved $[\alpha]_m$ and $[\alpha]_d$ of (R)-(-)- α -Hydroxy- β,β -dimethyl- γ -butyrolactone.

III. Experimental

ORs were measured on Autopol IV polarimeter with a stated accuracy of 0.002°. The experimental measurements of ORs for quantitative evaluations are non-trivial, since the errors in the measured ORs can arise from multiple sources.²² These errors were minimized by (a). holding the samples in a cell equipped with circulating water jacket for maintaining constant temperature (25 °C); (b). using long path length (2 dm) cell to achieve higher magnitudes of measured ORs; (c). preparing large volume (25 mL) solutions to minimize the error in volume and in the mass of weighed samples. Eight different concentrations in the range of ~0.002-0.04 M in CCl₄ were used for the OR measurements.

IV. Conclusions

The wavelength resolved SORs for monomer and dimeric forms involved in homochiral equilibrium are determined for the first time. These values are reproduced by density functional theory calculations to within a factor of ~2. This study opens up a powerful means to investigate the molecular properties involved in homochiral equilibria.

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