Optical Rotation of Noncovalent Aggregates

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Spontaneous molecular assembly is a fundamental biological phenomenon.[1] Specific noncovalent association via hydrogen-bonding has been studied using a variety of experimental and theoretical approaches.[2] Here, we demonstrate that the observed $[\alpha]_D$ for a self-associating chiral species is a composite of the response of the monomeric solute and its self-assembled dimer. Accordingly, polarimetry in conjunction with theoretical $[\alpha]_D$ calculation can be used as a quantitative probe of intermolecular binding and assembly.

It has been known for some time that the nonlinear concentration dependence of $[\alpha]_D$ in mixtures of two enantiomers can be attributed to the association of chiral species in solution, referred to as the *Horeau effect*.[3] More recently, polarimetry was used to estimate dimerization equilibrium constants.[4] These studies suggested that hydrogen-bonded complexes, with their unique optical rotatory response, provide discrete contributions to the measured optical rotation of species with a propensity to self-assemble. Since it is possible to predict $[\alpha]_D$ theoretically,[5,10a] the change in $[\alpha]_D$ upon assembly should also be predictable.

As a proof-of-principle, we have explored the self-association of (R)-(−)-pantolactone (**I**), because the K_{eq} of dimerization in CCl_4 is known (8.9 ± 0.6 M^{-1}),[6] the monomer structure is relatively rigid, and the mode of interaction through alcohol/carbonyl intermolecular H-bonding is well precedented and directional (Scheme 1).

Since monomer and dimer species are believed to dominate in CCl_4,[6] the $[\alpha]_D$ of this two-component system can be expressed as

$$[\alpha]_D^{\text{equilibrium}} = \chi_I^2[\alpha_I] + \chi_{II}^2[\alpha_{II}] \tag{1}$$

where χ_I is the mole fraction of monomer species in solution, χ_{II} is the mole fraction of dimer species in solution, and $[\alpha_I]$ and $[\alpha_{II}]$ are the respective specific rotations of the two equilibrium species. Using the experimental value of K_{eq}, the mole fractions χ_I and χ_{II} can be calculated for any given solute concentration. The species-specific responses $[\alpha_I]$ and $[\alpha_{II}]$ can be determined theoretically.

Molecular modeling of monomer (**I**) and dimer (**II**) structures, and of their thermally accessible conformers, was performed using a Monte Carlo conformational analysis with the MM3* force-field in MacroModel 7.0,[7] similar to previous studies performed by our group.[5c−f] For consistency, these geometries were further optimized in a quantum mechanical framework using density functional theory with the SVP basis set and the B3-LYP hybrid correlation-exchange functional in Turbomole 5.6.[8a,d,e] The $[\alpha_I]$ and $[\alpha_{II}]$ values were calculated using gauge-invariant atomic orbitals[9] with Dunning's correlation-consistent valence double-ζ (aug-cc-pVDZ) basis set in the time-dependent density functional theory (TD-DFT) response formalism implemented in Turbomole.[10a,b] Both the geometry optimizations and TD-DFT molecular response properties were

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Scheme 1. Monomer/Dimer Equilibrium of Pantolactone[6]
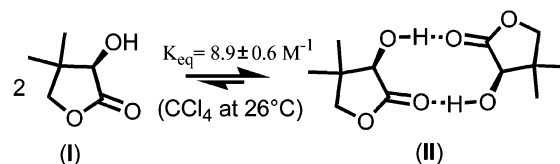
computed using the Conductor-Like Screening Model (COSMO),[8e] with the carbon tetrachloride dielectric constant equal to 2.23.[8a]

The calculated Boltzmann weighted specific rotation of the monomer is $[\alpha_I] = -1$ (two unique thermally accessible conformers were found, Figure 1), and a Boltzmann weighted dimer specific rotation $[\alpha_{II}] = -203$ (four unique thermally accessible conformers were found, Figure 1) was computed on the basis of DFT energies with the aug-cc-pVDZ basis using the CCl_4 dielectric solvation parameters in COSMO. In this context, van't Hoff's optical superposition principle is clearly invalid,[11] presumably because of the strong interactions between stereocenters mediated by the hydrogen bonds. The structural rigidity of the monomeric units, and the specific location of the hydrogen bonding acceptor (C=O) and donor (O−H) in direct contact with the stereogenic centers lead to chiral assemblies with nonadditive chiroptical properties. Both halves of the dimer must be included in the electronic structure analysis to obtain meaningful rotation values. However, calculated values of $[\alpha_I]$ and $[\alpha_{II}]$ together with the known K_{eq} allow the prediction of the concentration dependence of $[\alpha]_D$.

To compare our theoretical predictions with experiment, we measured the concentration-dependent $[\alpha]_D$ of (R)-pantolactone **I** over the concentration range of its solubility in CCl_4 (1−40 mM). The concentration-dependent $[\alpha]_D$ of a monomer−dimer equilibrium can thus be determined using the computed $[\alpha_I]$, $[\alpha_{II}]$, c, and K_{eq}. The experimental data, the computed concentration-dependent $[\alpha]_D$ calculated using eq 1, where mole fractions are determined on the basis of the experimental $K_{eq} = 8.9 \pm 0.6$ M^{-1},[6] and the species-specific $[\alpha]_D$ values with all conformations used in this study are shown in Figure 1. The level of theory used in this study typically has an error of 20−30 deg/(dm/(g/mL)),[10c] and accordingly the experimental data are well within the expected error range (the shaded area in Figure 1). The $[\alpha]_D$ values measured at lower concentrations (i.e., below 8 mM) may vary to some extent due to instrument noise. Despite the variations in $[\alpha]_D$ at lower concentrations, Figure 1 clearly demonstrates the good agreement between theoretical and experimental concentration-dependent analyses and reconfirms the monomer−dimer model proposed by Nakao and co-workers, which was based on NMR and IR studies.[6] For the first time, the $[\alpha]_D$ of self-aggregating species and the concentration-dependent $[\alpha]_D$ values could successfully be predicted. In addition, these studies suggest that at a concentration below 5 mM, positive and negative contributions of equilibrating species to $[\alpha]_D$ may cancel and result in $[\alpha]_D = 0$ (i.e., the solution becomes cryptochiral), despite the presence of a single enantiomer.
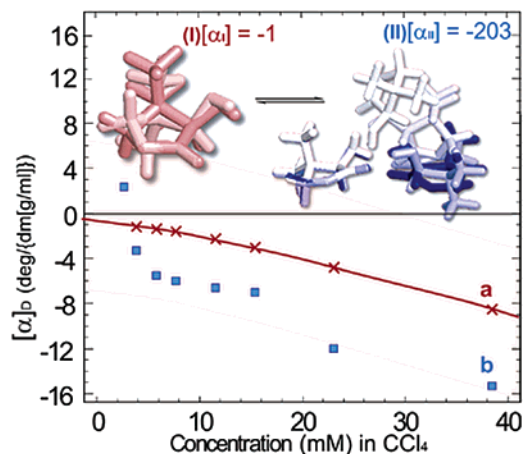
Figure 1. (Top) Superimposed structures of thermally accessible monomeric (**I**) and dimeric (**II**) species with their respective thermally averaged $[\alpha]_D$ values. (a) $[\alpha]_D$ values computed via eq **1** with ± 7 error (shaded) based on theoretically obtained $[\alpha_I]$ $[\alpha_{II}]$ with the experimental $K_{eq} = 8.9 \pm 0.6 M^{-1}$.[6] (b) Experimental $[\alpha]_D$ values at 26 °C.
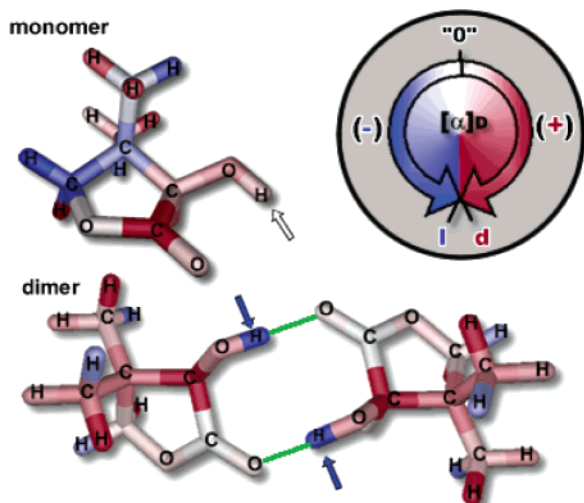

Figure 2. Boltzmann weighted atomic maps of monomer and dimer species superimposed on minimum energy conformers of **I** and **II**, with color legend for sign and magnitude of atomic contribution to $[\alpha]_D$.

In addition to experimental and theoretical concentration studies, we computed the atomic contributions to $[\alpha]_D$ for both monomer and dimer geometries (Figure 2).[12] The Boltzmann weighted atomic map of $[\alpha]_D$ contributions for the dimer reveals a large negative contribution at the hydroxyl (OH) hydrogen, associated with the hydrogen bond, which is not present in the monomer. These changes are independent of the geometry of the monomeric subunit and are observed when the interacting units are brought into proximity with each other to form the aggregated species.

Our work demonstrates that the computational prediction of $[\alpha]_D$ values of a concentration-dependent noncovalent aggregate is feasible. For self-associating chiral species with interacting stereogenic centers, the observed $[\alpha]_D$ value reflects the equilibrium distribution of the two-component system. The agreement between experiment and theory in relation to the observed $[\alpha]_D$ is quanti-

tatively consistent with the monomer−dimer equilibrium. This study confirms that (i) aggregated species can have greatly altered $[\alpha]_D$ values compared to the monomeric component, (ii) $[\alpha]_D$ can be used as a quantitative probe of molecular aggregation, and (iii) the concentration-dependent optical rotatory response of several interconverting species can be accurately described using modern theoretical methods.

Supporting Information Available: Experimental details for concentration-dependent measurements, derivations of $[\alpha]_D$ of dimerization, DFT geometries, and a table of relative energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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