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Theory-Assisted Determination of Absolute Stereochemistry for Complex Natural Products via Computation of Molar Rotation Angles

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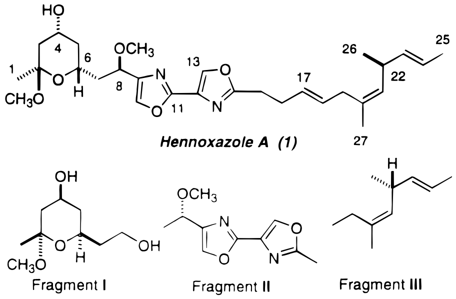
Determination of the relative and absolute stereochemistry of complex natural products currently relies on experimental techniques such as X-ray crystallography, circular dichroism,[1,2] NMR analysis of Mosher esters and related derivatives,[3] chemical degradation, and total synthesis.[4] Chemical degradation or the use of multistep total synthesis for the unambiguous assignment of the configuration of structurally novel natural products with multiple chiral centers is limited because it is time-consuming and costly. An alternative method that does not require synthetic transformations or X-ray quality crystals is clearly desirable, in particular for flexible molecules with unusual structural features that limit the applicability of NMR methods.[5] In the theory of optical activity, many empirical,[6−9] semiempirical,[10−14] classical,[15,16] and quantum mechanical[17−22] models have been developed, but not until very recently were quantitatively reliable quantum chemical computations of molar rotation angles reported.[23] Recently, ab initio calculations of molar rotation angle were performed in the zero frequency (off-resonance) approximation for small molecules with one or two chiral centers.[23] Herein, we report the first ab initio theoretical approach to assign unambiguously the configuration of a complex natural product by *calculating* molar rotation angles. Within the limits of the van't Hoff superposition principle,[6,19] the molar rotation of a natural product with weakly interacting multiple stereocenters can be calculated on the basis of the molar rotations of suitable fragments. Simple constant potential model system calculations support the principle of superposition for weakly interacting fragments.[19] Accordingly, the absolute stereochemistry of the compound can be assigned upon comparison of appropriate sums of calculated fragment rotation angles and the experimental molar rotation. Our approach divides the natural product into weakly interacting fragments, computes the molar rotations for each fragment, and sums them to obtain a composite value that is then compared to the experimental value for the natural product.

The configuration of the marine natural product hennoxazole A **(1)** was assigned previously on the basis of the total synthesis of four stereoisomers and a circular dichroism rule.[24,25] In this work, we have computed the molar rotation angles for eight different stereoisomers of hennoxazole A by combining results of independent electronic structure calculations on three fragments. Ab initio methods, in combination with molecular mechanics conformational search algorithms, were applied for the first accurate theoretical prediction of the molar rotation of a natural product. We show that the absolute stereochemistry of hennoxazole A can be correctly assigned from this series of computations and the NMR data[26] that established the relative stereochemistry of fragment **I**.



Hennoxazole A (1)

Fragment I Fragment II Fragment III

Hennoxazole A was divided into three fragments (**I**−**III**). Fragment **I** incorporates the stereocenters at carbons 2, 4, and 6, and fragment **II** has the stereocenter at C(8). Fragment **III** includes the stereocenter at C(22). The NMR spectrum of natural hennoxazole A revealed the presence of either an *all-S* or *all-R* configuration for fragment **I**. Accordingly, only two enantiomeric structures of fragment **I** were chosen with the (2*R*,4*R*,6*R*) and (2*S*,4*S*,6*S*) configurations. Similarly, enantiomeric structures of fragments **II** and **III**, with *R* and *S* configurations at the stereocenters C(8) and C(22), were selected. Low-energy geometries for these six molecules were obtained by MM2* force field optimization using the Monte Carlo conformational search algorithm implemented in Macromodel 5.5.[27] Chloroform was used as the "solvent" in the conformational search for all three fragment molecules. The fragment molar rotation angles were computed by Boltzmann weighting of angles computed for all low-energy geometries. Additional configurations were added until the Boltzmann-weighted sum converged (i.e., adding additional structures changed the computed molar rotation angle by <5%). In practice, 8−20 conformers were computed for each molecular fragment. Rotation angles were computed for at least $3.0\ \kappa T$ above the lowest energy conformer and were included in the Boltzmann sum.[41]

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Calculating the sum of molar rotation angles for fragment **III** was particularly challenging because of the relative flexibility of the skipped triene chain.[25] A total of 20 low energy conformations were used to calculate the molar rotation angle, $[M]_D$, for this fragment. Finally, the molar rotation angles for different configurations of hennoxazole A were calculated from the corresponding fragments, using

$$[M]_D = \frac{[\alpha]_D MW}{100};\ [\alpha]_D = \left(\frac{3600}{2\pi}\right)\left(\frac{\phi(\omega = \omega_D,\ \text{rad/cm})}{\text{conc (g/cm}^3)}\right) \quad (1)$$

where $[\alpha]_D$ is the specific rotation at the sodium D-line frequency in [deg(dm g/cm^3)$^{-1}$].

The expressions for the optical rotational angle, ϕ of eq 1, within the quantum mechanical framework were provided by Rosenfeld in 1928.[28]

$$\phi = 4\pi N\beta\omega^2(n^2 + 2)/3c^2 \quad (2)$$

N is the number of molecules per unit volume, n is the refractive index of the medium, c is the speed of light and β is related to the imaginary part of the electric dipole−magnetic dipole polarizability tensor $G'_{\alpha\beta}$,[29]

$$\beta = -\omega^{-1}(G'_{xx} + G'_{yy} + G'_{zz})/3 \quad (3)$$

The electric dipole−magnetic dipole polarizability tensor in a.u. can be expressed in terms of the linear response function as[30,31]

$$G'_{\alpha\beta} = -\langle\langle \mu_\alpha; m_\beta \rangle\rangle_\omega = -\sum_j Im\left[\frac{\langle n|\mu_\alpha|j\rangle\langle j|m_\beta|n\rangle}{\omega - \omega_{jn}} - \frac{\langle n|m_\beta|j\rangle\langle j|\mu_\alpha|n\rangle}{\omega + \omega_{jn}}\right] \quad (4)$$

In this expression, n and j denote the ground and excited states and $\omega_{jn} = \omega_j - \omega_n$ is the associated excitation frequency. μ_α and m_β are the electric and magnetic dipole operators, respectively. The polarizability tensor in eq 4 was calculated using the standard SCF linear response theory methods from the appropriate μ_α and m_β interaction operators.[32,33] In particular, this tensor was calculated at the frequency of the incident plane-polarized light (sodium D-line) without resorting to the Amos static field approximation.[23,34] London atomic orbitals were used to calculate the gauge origin independent $G'_{\alpha\beta}$ tensor.[35] London atomic orbitals, also referred to as gauge invariant atomic orbitals (GIAOs), are often used in ab initio calculations to compute a variety of molecular magnetic properties including nuclear shieldings,[36] magnetizabilities,[37] vibrational circular dichroism,[38] and vibrational Raman optical activity.[33] A 6-31G Gaussian basis set was used to compute the electric dipole−magnetic dipole polarizability tensor using the program Dalton.[39,40] Table 1 shows the theoretically calculated molar rotations for the three fragments in the specific enantiomeric configurations, averaged from four calculations. Calculated and observed[25] $[M]_D$ values of all eight possible stereoisomers of hennoxazole A are listed in Table 2. These values were obtained by arithmetically adding the fragment values according to the stereochemistry shown in column 2 of Table 2. The basic validity of van't Hoff's rule for hennoxazole A was demonstrated earlier.[19,25] Molar rotation angles computed for fragments **I** and **II** show little dependence on the geometry within 2−3 κT of the lowest structure. Thermal averaging of the results for fragment **III** was important in order to calculate the molar rotation angle. Our method is presently limited to molecules where the chiral centers are separated by one or more atoms,[19] although units with multiple strongly interacting chiral centers can be included in a single fragment calculation. The results in Table 2 show that these molar rotation calculations, in concert with the NMR analysis of hennoxazole A that provides the relative configuration at carbons 2, 4, and 6, unambiguously predicted the absolute stereochemistry of hennoxazole A. Within the experimental errors of both the experimentally measured and theoretically calculated molar rotations (the later defined within 2σ), only the (2*R*,4*R*,6*R*,8*R*,22*S*) stereoisomer of hennoxazole A agrees with the observed $[M]_D$. This assignment for the configuration of the natural product was indeed determined earlier by total synthesis.[24] The agreement between calculated and observed $[M]_D$ was also satisfactory for all other stereoisomers of hennoxazole A. Accordingly, we suggest that ab initio electronic structure theory can now be used as a powerful tool to assist in determining the relative and absolute stereochemistry of complex natural products. On the basis of a simple measurement of optical rotation, the number of plausible stereoisomers can be drastically reduced by molecular rotation calculations. We plan to probe the generality of this approach by further applications to complex natural products of yet undetermined stereochemistry.

Table 1. Calculated Molar Rotations for the Three Fragments in the Specific Enantiomeric Configurations, Averaged from Four Calculations

fragment	$[M]_D \pm 2\sigma$ (configuration, sign)
I	162 ± 11 (2*R*,4*R*,6*R*, −ve; 2*S*,4*S*,6*S*, +ve)
II	105 ± 22 (8*R*, +ve; 8*S*, −ve)
III	146 ± 17 (22*R*, +ve; 22*S*, −ve)

Table 2. Molar Rotations of Different Stereoisomers of Hennoxazole A Calculated from Fragment Increments According to van't Hoff's Rule[a]

hennoxazole	configuration	$[M]_D \pm 2\sigma$	obsd $[M]_D$
10	(2*S*,4*S*,6*S*,8*S*,22*R*)	+203 ± 50	+257
11	(2*S*,4*S*,6*S*,8*S*,22*S*)	−89 ± 50	−48
12	(2*S*,4*S*,6*S*,8*R*,22*S*)	+121 ± 50	+175
13	(2*S*,4*S*,6*S*,8*R*,22*R*)	+413 ± 50	+459
14	(2*R*,4*R*,6*R*,8*S*,22*R*)	−121 ± 50	(−175)[b]
15	(2*R*,4*R*,6*R*,8*S*,22*S*)	−413 ± 50	(−459)[b]
1[c]	(2*R*,4*R*,6*R*,8*R*,22*S*)	−203 ± 50	−247
16	(2*R*,4*R*,6*R*,8*R*,22)	+89 ± 50	(+48)[b]

[a] Observed molar rotations refer to data of natural or synthetic isomers. [b] Experimental molar rotation measurements for these stereoisomers are not available. Numbers in parentheses are based on the values measured for the corresponding enantiomers. [c] The natural product. Note that it can be assigned unambiguously by comparing the observed rotation angle with the eight computed values. Note, too, that all computed values correlate well with the observed rotation angles for the respective stereoisomers.

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Supporting Information Available: Figure of Macromodel structures, table of molar rotation angles, steric energies for conformational isomers, and Boltzmann averaged sum of **I**−**III** (3 pages). See any current masthead page for ordering information and Web access instructions.

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(41) Overlayed conformer structures that were generated by Macromodel for fragments **I**−**III** in both enantiomeric configurations are shown in the Supporting Information.