

Matrix model to predict specific optical rotations of acyclic chiral molecules

Hua-Jie Zhu,^{a,*} Jie Ren^a and Charles U. Pittman Jr.^b

^a*Organic Synthesis and Natural Product Laboratory, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650204, Yunnan, PR China*

^b*Department of Chemistry, Mississippi State University, Mississippi State, MS 39762, USA*

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Abstract—This paper constructs a new matrix model to analyze the relationship of the stereogenic center and its substituents to the specific optical rotation. The variables used as matrix elements include (1) the substituents' comprehensive masses (**m**), (2) radii (**r**), (3) symmetries (**s**), and (4) the electronegativities (χ) of the atoms or groups which are bound to the stereogenic center. Solution of the matrix determinants was postulated to give scalar numbers proportional to the magnitudes of the specific rotations of the molecules being considered. A total of 94 example calculations were performed to predict the relative magnitude and direction of rotation at the sodium D line. Only two calculations failed to predict the correct direction of rotation and this occurred only when their optical rotation values were less than 0.01° . The B3LYP functional at the aug-cc-pVDZ basis set level was also used to compute the optical rotations of the 66 example chiral molecules whose geometries were previously obtained at the B3LYP/6-31G(d) level. The expected successful predictions for these acyclic molecules' optical rotation values did not appear. Overall, the matrix model is one approach to understand the optical rotation.

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1. Introduction

The relationship between a chiral center and its specific optical rotation has long been a very important and well-known part of stereochemistry research.^{1–5} This has been of interest since Biot discovered optical activity of turpentine, laurel, and lemon in liquids and solvents in 1815.^{1a} The first theory of optical rotation was described by Fresnel in 1824.^{1b} Many methods have been used to study this relationship, including chemical degradation of the target molecules,^{6a} total synthesis,^{6b} and physical methods such as X-ray crystallography,^{6b} circular dichroism,^{6b} NMR analysis of Mosher esters,⁷ and magnetic optical rotation.⁸ Empirical and semi-empirical methods⁹ and rules have been used in this effort. Now, ab initio quantum-mechanical calculations estimating optical rotation have been used.^{10–29} Recent advances in these approaches have been extremely encouraging. Although it is one of the oldest research areas in stereochemistry, determining the specific optical rotation is still a seminal tool for studying the configuration of the chiral molecules.

An early representative empirical method was developed by Brewster.^{9d–f} Other efforts were also explored.^{9a–c,g–i} The Brewster model predicted the optical rotation using a screw

pattern of electron polarizability. The specific rotation's magnitude is related to the refractions of the atoms and depends on different atomic/substituent's conformations. His intuitive work on rotation calculations opened a new stage at that time, and these ideas have influenced several generations of scientists.

The first use of modern Hatree–Fock (HF) calculations in optical rotations was reported by Polavarapu^{10a} in 1997, using the Rosenfeld method developed in the CADPAC program by Amos.^{10b} This took place almost 76 years after the initial construction of quantum-mechanical methods of optical rotation reported by Rosenfeld.¹¹ The first application of density-function theory (DFT) to optical rotation was reported by Yabana and Bertsch.¹² Then, static-limit optical rotation calculations were reported by Cheeseman et al. in 2000.^{13a} In 2002, Ruud and Helgaker reported the first coupled-cluster (CC) calculations of optical rotation.^{14c} In 2004, Tam et al. reported the method of optical rotation calculations at the level of coupled-cluster single doubles (CCSD) level.¹⁵ In the past decade, Wipf et al.,¹⁶ Grimme and Ahlrichs,¹⁷ Pedersen,¹⁸ Giorgio,¹⁹ Nafie,²⁰ Wiberg,^{13h–j,21} Vaccaro,²¹ Jorgensen²² and other theoretical chemists^{23–26} explored several computational approaches for use in optical rotation calculations. At the same time, some optical rotation computation programs, such as Dalton, Gaussian, Turbomole, and PSI have been developed.²⁸ These developed methods have enriched this research field.

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* Corresponding author. Tel./fax: +86 871 5216179; e-mail: hjzhu@mail.kib.ac.cn

However, all methods used so far to predict the magnitude and direction of optical rotation have had drawbacks. For example, chemical methods require some definite quantity of sample and consume much time. Single crystals are not always readily available for crystal structure determinations. The newer quantum-mechanical approaches are useful and have a fundamental basis in physics. Most of the successful examples in optical rotation computations were relatively rigid compounds. Acyclic chiral flexible compounds have not been as thoroughly investigated as cyclic compounds, due to the large numbers of conformations that need to be investigated for acyclic chiral molecules. Importantly, as stated in Crawford's review, 'in spite of these advances, it is not yet understood what level of theory is necessary to obtain 'the right answer for the right reason' for optical rotation, and many of successes rely implicitly on fortuitous cancellation of errors (e.g., limited basis sets, lack of explicit solvation, vibrational averaging, etc.)'.²⁹ It seems clear that chemists have a long way to go to find an absolutely rigorous physical explanation that can be quantitatively exploited to accurately calculate optical rotation.

Other methods may exist to explain the optical rotation phenomenon and compute its magnitudes and direction. Thus, it would be valuable to develop an easily understandable mathematical model, which can be directly perceived and intuitively understood by most experimental chemists. An effective model that attributes and predicts both the magnitude and direction of the specific optical rotation of chiral molecules is needed. We now propose a different type of qualitative model, which has significant potential for further development.

Our mathematical model can predict the sign and relative magnitudes for non-ring chiral molecules. This method assumes that the geometries of the chiral molecules are correct (actual) structures. These structures can, in principle, be predicted by quantum methods, such as HF or DFT approaches using different basis sets, by simply using typical bond angles or lengths or by experimental methods (e.g., X-ray crystal structure, etc.). Characteristics of the different substituents bound to a stereogenic center within the molecule were selected. The *comprehensive mass* for each of four substituents is used instead of the whole molecular weight, which was used in the computations of optical rotation in quantum theory. The *radius* of the substituent, whose values change with the substituents' conformations, is a new variable. *Electronegativity*, which is related to a group's polarizability, was selected. The *symmetry number*, related to the group's asymmetry, was the final characteristic selected (see Section 4 for details of all four concepts here). In this matrix model, *comprehensive mass*, *radius*, and *electronegativity* can each be computed by quantum theory if desired or their values can be based on experiments. The *symmetry number* is a completely new variable.

This model incorporates tangible characteristics of each substituent surrounding a stereogenic center in order to predict the direction and magnitude of that molecule's specific rotation. Molecules with two or more chiral centers were also used in optical rotation computations, so this model is not limited to molecules with only a single stereogenic center. Each molecular conformation can independently contribute

to the specific rotation, and each existing conformation and its population must be included in any prediction. Quantum mechanical calculations can be incorporated into the overall matrix model to calculate conformational energies (hence populations) and other molecular features. Alternatively, experimental values can be used if available. Finally, standard bond length, angles, and other properties can be incorporated in a less rigorous but useful approach to employ this model.

2. Matrix model

The specific rotation is a dynamic three-dimensional characteristic. Its magnitude and direction change with wavelength, temperature, solvent and so on. Quantum-mechanical theory relates optical rotation to a molecular parameter $\beta(\nu)$, where β equals $(1/3)\text{Tr}[\beta_{\alpha,\beta}]$ and $\beta_{\alpha\beta(\nu)}$ is the frequency-dependent electronic dipole-magnetic polarizability tensor.^{3a,e,32} Computations of $\beta_{\alpha,\beta}$ at the HF level of theory were introduced by Amos for the static limit ($\nu=0$)^{10b} and by Helgaker for any frequency ν .^{14a} This method can simply be described as follows:

$$[\alpha]_{\nu} = \frac{28,800\pi^2 N_A \nu^2}{c^2 M} \gamma_{s,\nu} [\beta(\nu)]_0$$

where N_A is Avogadro's number, M is the molecular weight, c is the light speed in vacuum, γ is the correction from solvent, which is either neglected ($\gamma=1$) or approximated by equation: $\gamma=(n^2+2)/3$. Thus, the value of $[\alpha]_{\nu}$ depends upon the magnitude of the tensor of β .

Quantum methods, such as TD-DFT,¹² CC2,^{13–15} or other methods^{16–21} have been developed. These methods can compute the absolute values of chiral molecule's optical rotation and many successes have been achieved in optical rotation computations. The chiral molecules used in these calculations have been relatively rigid. When many conformations exist in flexible and acyclic compounds, the computation time will become very large using DFT or especially CCSD methods.

DFT calculations, which are also reported in this paper, are used as a standard for comparison with results obtained using the matrix model. Our results show that this matrix method is worthy of future development. These DFT computations, including geometry optimizations at the B3LYP/6-31G(d) level, required continuous use of five processors for almost one month in a workstation. The conformations were found first for each chiral molecule and were then used to obtain the corresponding optical rotations. Details are summarized in [Supplementary data](#).

Brewster's model uses refractivity. Quantum mechanical theories use molecular mass, frequency of light, and a specific molecular conformation. All the factors (matrix elements), which influence the optical rotation values used in the matrix model, are separated into two parts: internal factors and external factors. Internal factors are independent of each other. Examples include molecular weight, electronegativities, and the geometries of different conformations. External factors are those that can be changed by the conditions used in optical

rotation experimental measurements. Examples include the solution concentration, the wavelength of light, and the temperature. All external factors affect the magnitude of the internal factors or states. Thus, they affect the optical rotations. For example, a temperature rise would change the conformational populations in solution. This new population distribution would result in the change of the radii of the substituents. This, in turn, would cause the optical rotation value to change. Concentration of chiral molecules in solution greatly affects the optical rotation. Thus, a model must treat the entire molecule as a whole.

The properties defining the entire molecule can be obtained from its calculated or experimental structure. Although less rigorous, one could use structural approximations from classical bond length and angles. We represent each molecular factor (e.g., element) in four parts (four substituents at the stereogenic center), which are then recombined (reconstructed) when put together in the matrix model (2-D model rather than a 1-D equation). A scalar optical rotation value can be produced by solving this model. Solving the matrix's determinant provides this reconstruction of the optical rotation as a scalar value.

A typical flexible chiral molecule has four different groups that can rotate freely in space. Each of the four groups' masses could be obtained and the other characteristics could be also obtained. The most difficult problem in previous methods is the complete determination of all the different conformations, their relative populations and the individual contributions of each conformation in predicting optical rotations. Each different conformation has a different radii, defined in the model as an effective radii. Therefore, by computing the effective radii of each of the substituents over the existing conformational populations, radii use would be a logical substitute for conformations. Obviously, this portion of the matrix model could be constructed from conformations and their relative energies calculated by quantum mechanics.

A model based on the mathematics deduction here could provide the solutions to this question. The concepts of radii and comprehensive mass can serve to describe and account for the different conformations when the traditional chemistry data are used. The optical rotation values were computed for 94 chiral molecules using this matrix model method. Then 66 molecules of this same series were subjected to DFT calculations to obtain their predicted optical rotations for comparison.

The model incorporates characteristics of any molecule into a matrix where the molecular characteristics are elements of that matrix. The elements are defined relative to an axis system in which the molecule's three-dimensional structure is placed. Any number of elements can, in principle, be used; we chose only four. After defining and quantifying each element, they were incorporated into the matrix in order to construct the relationship of the elements to the specific rotation within the molecule. The scalar number $\det(D)$ obtained by calculating the matrix determinant is postulated to be proportional to the specific rotation.

The weighting factors for each of the matrix elements are the four coefficients a_1 – a_4 (where $a_1 \neq a_2 \neq a_3 \neq a_4$). Each

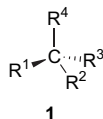
coefficient describes the different contribution of the matrix element to the optical rotations and therefore, each will have different value with varying unit (e.g., the unit of a_1 is the contribution per one carbon atomic weight to the entire molecular optical rotation). However, their values are unknown at present. By defining the formula $[\alpha]_D = k_0 \det(D)$, the model illustrates why the direction of rotation reverses when any two substituents on the stereogenic carbon exchange their positions and it shows why a molecule's rotation value is zero when any two groups are the same. Furthermore, dividing the experimental value of $[\alpha]_D$ by the value of the matrix determinant, $\det(D)$, gives the value of k_0 .

The value of k_0 must represent all the external effects (influences other than those stemming from the molecule's structure) on the magnitude of rotation. These include temperature, solvent, wavelength of the polarized light and other factors. Therefore, the value of k_0 should be approximately constant for a series of chiral molecules when the temperature, solvent, and light wavelength used to determine the specific rotation are fixed. The direction of rotation is predicted by the sign of the calculated $\det(D)$. Moreover, if the model is a reasonable approach, then the magnitude and direction of the specific rotation of other molecules should be predicted from the calculated values of their $\det(D)$ after obtaining the value of k_0 from an initial series of molecules. One measure of this model's success is how close to a single constant the calculated values of k_0 are when the calculated values of $\det(D)$ are divided into the experimental values of $[\alpha]_D$ for a series of chiral molecules with different structures. The degree of structural variation between the series of molecules used to define k_0 and the range of molecules, where the calculated value of $\det(D)$ gives a good estimate of the specific rotation's magnitude, is another measure of the model's success.

While this method is completely general, the input values may be based on quantum-mechanical calculations or classical values. It is necessary to understand the errors, which will be encountered where quantum effects are neglected. The interaction time of a photon passing through a molecule is very short (about 5×10^{-18} s, 0.005 fs, if this molecule has a 15 Å diameter or 1×10^{-18} s for a diameter of 3 Å length). The movement of a whole molecule in solution is very slow (e.g., 0.2 cm/s), so the velocity uncertainty of 2-butanol, for example, is 13% of the 0.2 cm/s if specifying the atom's position in the molecule to 0.05 cm. Compared with the behavior of entire molecule in solution, the uncertainty of an atom's velocity within a molecule, Δv , is about 10^5 cm/s, which is almost the same as that of atom's vibration speed when specifying the atom's position in the molecule to 10^{-8} cm. Quantum effects on atoms should be considered. The mass and size of an electron are much smaller than those of an atom, and its velocity is faster than an atom's. The quantum effects on an electron should also be considered. Thus, a new model should consider two factors: (1) the entire molecule's behavior in solution; and (2) the position of the atoms in a molecule, namely, the different conformations. Since quantum effects from factor (1) are not big, the variables of quantum mechanics could be replaced by other variables. In the matrix model, these are the comprehensive mass and radius of the substituents (see the next part). Only these contributions from factor (2) need to be carefully

investigated. The atomic positions in a molecule (different conformations) can be investigated using quantum theory. Different molecular conformations, in this model, reflect the various magnitudes of the comprehensive masses and radii (these terms are carefully defined in Section 3: Discussion of the substituent's elements). These quantities finally influence the magnitude and direction of different optical rotations.

A typical flexible chiral molecule, **1**, was selected, which contains one stereogenic center to illustrate the deduction of the matrix model step by step as shown below. However, this method can be extended to molecules with two or more stereogenic centers, stereogenic ring systems, and chiral compounds, which do not have one or more stereogenic centers, such as allenes, in computations of optical rotations (see dual-stereogenic-center molecule, found near the end section of this paper).



The major factors that affect the specific optical rotation of **1** include

1. The comprehensive mass (**m**) of the substituents (depend on conformations, details in Section 4.1). The value of (**m**) changes with different conformations.
2. The radius (**r**) of the substituents (depends on conformations; details in Section 4.2).
3. The electronegativity (**χ**) of the atom connected with stereogenic center.
4. The symmetry (**s**) of the substituents. A new factor which has never been considered in previous methods.
5. The solvent and temperature.
6. The concentration (**c**) of the solution.
7. The wavelength (**λ**) of the light used to determine specific rotation value.
8. The hybridization (**h**) of the atom constituting the stereogenic center and that of the atoms directly or indirectly attached to the stereogenic center atoms.

Each of these factors could effect the specific optical rotation. This model considers the external factors, such as the solvent, temperature, and the wavelength of light, and internal factors of a chiral molecule. External factors are those, which can be changed by artificial actions, such as the concentration of solution, the wavelength, and temperatures employed. The molecular (internal) factors such as comprehensive mass and electronegativities are independent. The hybridization, for example, is related to the comprehensive mass and radii (see Section 4). In the list of factors above, four major internal factors were identified and used after an independent analysis. These four independent internal factors were *comprehensive mass*, *radius*, *electronegativity* and *symmetry number*. Their contribution to the optical rotation can be written as a set of functions f_1 , f_2 , f_3 , and f_4 . The bracket is the mathematical symbol illustrating that these functions are linked closely by belonging to the same group.

$$\begin{cases} f_1 = a_1\mathbf{m}_1 + a_2\mathbf{r}_1 + a_3\chi_1 + a_4\mathbf{s}_1 \\ f_2 = a_1\mathbf{m}_2 + a_2\mathbf{r}_2 + a_3\chi_2 + a_4\mathbf{s}_2 \\ f_3 = a_1\mathbf{m}_3 + a_2\mathbf{r}_3 + a_3\chi_3 + a_4\mathbf{s}_3 \\ f_4 = a_1\mathbf{m}_4 + a_2\mathbf{r}_4 + a_3\chi_4 + a_4\mathbf{s}_4 \end{cases}$$

Here a_1 – a_4 (where $a_1 \neq a_2 \neq a_3 \neq a_4$) are weighting factors for each of the matrix element, which represent the magnitudes of effects exerted by the mass, radius, electronegativity, and symmetry of the substituents, respectively, on the functions f_1 – f_4 . Each coefficient's value is different and constant but their values are unknown at the present time.

When photons of light with a frequency (ν) interact with each of four substituents of the chiral molecule (one conformation), the function F_1 is generated:

$$F_1 = f(\nu) \begin{bmatrix} f_1 \\ f_2 \\ f_3 \\ f_4 \end{bmatrix} \quad (1)$$

This matrix function expresses the interaction of the photons with the four characteristics (elements) of all four substituents simultaneously (one conformation). Similarly, the functions, F_2 , for the specific solvent employed, F_3 , for the temperature, and others could be written in the same form as Eq. 1.

$$F_2 = f(s) \begin{bmatrix} f_1 \\ f_2 \\ f_3 \\ f_4 \end{bmatrix} \quad \text{and} \quad F_3 = f(t) \begin{bmatrix} f_1 \\ f_2 \\ f_3 \\ f_4 \end{bmatrix}$$

The overall function which describes the interaction of light with the chiral molecule for this conformation can then be described as \mathbf{F}_{coni}

$$\mathbf{F}_{\text{coni}} = F_1 + F_2 + F_3 + \dots$$

where

$$\mathbf{F}_{\text{coni}} = f(\nu) \begin{bmatrix} f_1 \\ f_2 \\ f_3 \\ f_4 \end{bmatrix} + f(s) \begin{bmatrix} f_1 \\ f_2 \\ f_3 \\ f_4 \end{bmatrix} + f(t) \begin{bmatrix} f_1 \\ f_2 \\ f_3 \\ f_4 \end{bmatrix} + \dots \quad (2)$$

The functions of solvent and temperature on the optical rotation are unknown, and the function $f(\nu)$ can be fixed. Thus, the formula would have the following form:

$$[\alpha]_{\lambda} \propto f(\nu) \propto \frac{\lambda_{\text{ns}}^2}{\lambda^2 - \lambda_{\text{ns}}^2}$$

Here λ and λ_{ns} are the wavelengths when the unperturbed energies are in ground and excited states, respectively.

If solvent, temperature, and other determined conditions are fixed, the functions $f(s)$ and $f(t)$ and others will be constant. Eq. 2 becomes

$$\mathbf{F}_{\text{coni}} = \frac{k_v \lambda_{\text{ns}}^2}{\lambda^2 - \lambda_{\text{ns}}^2} \begin{bmatrix} f_1 \\ f_2 \\ f_3 \\ f_4 \end{bmatrix} + k_s \begin{bmatrix} f_1 \\ f_2 \\ f_3 \\ f_4 \end{bmatrix} + k_t \begin{bmatrix} f_1 \\ f_2 \\ f_3 \\ f_4 \end{bmatrix} + \dots \quad (3)$$

where k_v , k_s , and k_t are constants.

Each conformation has a specific energy and the population of that conformation versus those of all molecules in the sample is determined by the Boltzmann distribution. The optical rotation of each specific conformation must be multiplied by the fraction of molecules in those respective conformations. The sum over all the conformations gives the net optical rotation, \mathbf{F} .

$$\mathbf{F} = \sum (\mathbf{F}_{\text{coni}}) \left(\frac{Q_i}{\sum Q} \right)$$

Here $Q_i = k \exp(-\Delta G_i/RT)$, Q_i is the amount of the i th conformation, k and R are constants, ΔG_i is the difference between i th conformation's free energy and the lowest conformational free energy. Thus, theoretically, other elements could also be added into Eq. 4 to determine the specific studies.

In this manuscript, the effects from the outside factors, such as solvent, temperature or light are not studied. These external factors were fixed. When the frequency of light is kept constant (e.g., at the sodium D line) and other external factors (temperature, solvent) are constants, the overall function \mathbf{F}_{coni} for this selected conformation becomes

$$\mathbf{F}_{\text{coni}} = (k_1 + k_2 + k_3 + \dots) \begin{bmatrix} \mathbf{m}_1 & \mathbf{r}_1 & \boldsymbol{\chi}_1 & \mathbf{s}_1 \\ \mathbf{m}_2 & \mathbf{r}_2 & \boldsymbol{\chi}_2 & \mathbf{s}_2 \\ \mathbf{m}_3 & \mathbf{r}_3 & \boldsymbol{\chi}_3 & \mathbf{s}_3 \\ \mathbf{m}_4 & \mathbf{r}_4 & \boldsymbol{\chi}_4 & \mathbf{s}_4 \end{bmatrix} \begin{bmatrix} a_1 \\ a_2 \\ a_3 \\ a_4 \end{bmatrix} \quad (4)$$

where $k_1=f(v)$, $k_2=f(s)$, $k_3=f(t)$. Therefore, the expression for \mathbf{F}_{coni} becomes

$$\mathbf{F}_{\text{coni}} = k \begin{bmatrix} \mathbf{m}_1 & \mathbf{r}_1 & \boldsymbol{\chi}_1 & \mathbf{s}_1 \\ \mathbf{m}_2 & \mathbf{r}_2 & \boldsymbol{\chi}_2 & \mathbf{s}_2 \\ \mathbf{m}_3 & \mathbf{r}_3 & \boldsymbol{\chi}_3 & \mathbf{s}_3 \\ \mathbf{m}_4 & \mathbf{r}_4 & \boldsymbol{\chi}_4 & \mathbf{s}_4 \end{bmatrix} \begin{bmatrix} a_1 \\ a_2 \\ a_3 \\ a_4 \end{bmatrix} \quad (5)$$

where k is the sum of all the constants (e.g., $k_1+k_2+k_3+\dots$). The total contribution \mathbf{F} from all conformations can be written in the form of Boltzmann distribution.

$$\mathbf{F} = \sum (\mathbf{F}_{\text{coni}}) \left(\frac{Q_i}{\sum Q} \right)$$

Eq. 5 shows that the contributions of all the factors to the optical rotation of one conformation contain three parts: (1) external factor contributions: $f(v)$, $f(s)$, $f(t)$..., (2) the

center matrix which combines only the specific internal molecular characteristics, and (3) the matrix on the right (the coefficient matrix) which presents the magnitudes of the contributions of the different weighting factors to the optical rotation. The values for a_1 , a_2 , a_3 , and a_4 cannot yet be obtained. This coefficient matrix should be positive. When all of the outside factors are held constant, Eq. 3 can then be transformed to Eq. 5.

Now, function \mathbf{F} , which expresses the various effects of both internal and external factors on the optical rotation's magnitude and direction of this selected conformation, has been obtained. This function \mathbf{F} contains all the information needed, including three contributions: (1) external factors' contributions; (2) the molecule's characteristic contributions and (3) the weighting factors' contributions. However, \mathbf{F} contains a matrix within the function, so it is not a scalar number. Thus, we define $[\alpha]=|\mathbf{F}|$. Also, the sodium D line is used to obtain the optical rotation. Then, one conformation has

$$[\alpha]_{D_i} = k \times a_1 \times a_2 \times a_3 \times a_4 \times \det(D_i) = k_0 \times \det(D_i) \quad (6)$$

where

$$\det(D_i) = \begin{vmatrix} \mathbf{m}_1 & \mathbf{r}_1 & \boldsymbol{\chi}_1 & \mathbf{s}_1 \\ \mathbf{m}_2 & \mathbf{r}_2 & \boldsymbol{\chi}_2 & \mathbf{s}_2 \\ \mathbf{m}_3 & \mathbf{r}_3 & \boldsymbol{\chi}_3 & \mathbf{s}_3 \\ \mathbf{m}_4 & \mathbf{r}_4 & \boldsymbol{\chi}_4 & \mathbf{s}_4 \end{vmatrix} \quad (7)$$

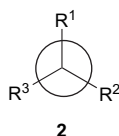
The different conformations of chiral molecule have different energies. Thus, the final observed optical rotation must employ the Boltzmann distribution of all these conformations.

$$\det(D) = \sum (\det(D_i)) \left(\frac{Q_i}{\sum Q} \right)$$

It is impossible to get a_1 , a_2 , a_3 , and a_4 and k values at this point. Therefore, there is no absolute value to $[\alpha]$. However, it is useful to obtain the relative values by computing $\det(D)$ since $\det(D)$ is characteristic of that molecule and proportional to the optical rotation values when the outside factors are kept constant. Herein, we will carefully analyze the magnitude of $\det(D)$. These values represent relative optical rotation values, which are different from those obtained by quantum chemistry methods.

Input values to this general matrix model could be computed by quantum calculations or employ classical bond lengths and angles. All such input data have their own errors. Thus, we will apply standard structural data from handbooks for the computation of $\det(D)$ and then test this model by comparing these computed $\det(D)$ data with experimental results. The DFT method (B3LYP/aug-cc-pVDZ//B3LYP/6-31G*) has proved useful and economic in computations of chiral rigid compounds. Therefore, this DFT method was also used as a comparison standard to evaluate the matrix model. Furthermore, chiral molecules' optical rotations obtained by matrix were compared with experimental results.

Obviously, $\det(D)$ represents the molecule's characteristics in this matrix model. It has nothing to do with external factors, such as the solution concentration, the wavelength of light, the temperature, etc. Substituent R^4 of the chiral molecule **1** is defined as the smallest group in the determinant. The definition for the biggest or smallest groups in a chiral molecule is exactly the same as those used to define (*R*) or (*S*) absolute configurations. In a Newman structure, **2**, R^4 is the circle to the rear and R^1 , R^2 , R^3 , and R^4 are the four different substituents bound to the stereogenic carbon of **1**.



The values for the elements of R^4 , the smallest group, are first introduced into the bottom line of the determinant. Then, the corresponding values for the elements of the other *R* groups are introduced into the determinant, from the top down, in the order with which these *R* groups appear in the clockwise direction in the Newman structure. This determinant, $\det(D)$, is written as shown in Eq. 7. The calculated $\det(D)$ value may be either positive or negative, indicating the direction of the specific rotation.

Alternatively, the values of the elements of the largest substituent can be introduced into the first line in the determinant. Then the corresponding values for the other substituents' elements are added as the second, third, and bottom lines, respectively. This determinant is designated $\det(D_0)$. Then, a positive sign (+) is selected for $[\alpha]_D$ when the direction of a rotational arrow, drawn from R^1 to R^2 to R^3 , is clockwise while looking down the bond from the stereogenic atom to the R^4 group, in accordance with the general and widely used empirical rule. When this arrow is counterclockwise, the negative sign (–) is selected.

$$[\alpha]_D = (\pm)k_0\det(D_0) \quad (8)$$

The result of this procedure (Eq. 8) will be the same as that of using $\det(D)$ (Eq. 7). This result can also be deduced from the Newman structure **2** by transposition of lines in $\det(D)$ to $\det(D_0)$. First, $\det(D)$ is written according to the clockwise direction of the groups R^1 , R^2 , and R^3 . Then the rows of the determinant are transposed until the elements of the highest priority substituent are on the first line, and those of the

second and third highest priority groups are on the second and third lines, respectively. A new determinant $\det(D')$ is obtained after this rearrangement. Thus, $\det(D')$ equals $\det(D_0)$.

There are six possible relationships among the sizes of substituents, R^1 , R^2 , and R^3 . The two possible results for each of these six cases are listed in Table 1 together with the transpositions employed in $\det(D)$. The empirical rule here has been well explained by this model directly.

The chiral molecule can also be placed in a three-dimensional coordinate system with the chiral center at the origin and the smallest group, R^4 , along the *Z*-axis. The groups R^1 , R^2 , R^3 , and R^4 , which are considered to be *perfect point masses* (e.g., single atoms) have the corresponding coordinates: $C_1(x_1, y_1, z_1)$, $C_2(x_2, y_2, z_2)$, $C_3(x_3, y_3, z_3)$, and $C_4(x_4, y_4, z_4)$. Next, three new determinants, $\det(D_x)$, $\det(D_y)$, and $\det(D_z)$ are formed by projecting the matrix elements from $\det(D)$ onto the *X*, *Y*, and *Z*-axes. From the projected values, $\det(D_x)$, $\det(D_y)$, and $\det(D_z)$ are obtained. Since substituent R^4 is located at the origin ($x_4=y_4=0$), all the projected values for the elements of R^4 on the *X* and *Y* axes are zero. This implies that the contributions to the optical rotation can also be represented with $\det(D_z)$, the determinant of the elements of substituents R^1 , R^2 , R^3 , and R^4 , which is projected on the *Z*-axis. Obviously, when there are four different atoms connected to the stereogenic center, this molecule does not have a standard tetrahedron's geometry. Thus, $\det(D_z)$ can accurately reflect the characteristics of molecular optical rotation (see Section 5). However, if the four connected groups are complex substituents, the use of $\det(D_z)$ may result in bigger errors than for $\det(D)$ due to the second processing of data.

3. Discussion of the substituent's elements

When two or more of the substituents are identical, the corresponding values of *r*, *m*, χ , and *s* will be the same. Then the value of $\det(D)$ must be equal to zero. In this case, the molecule has no dissymmetry. Hence its specific rotation is zero.

$$\det(D) = \begin{vmatrix} \mathbf{m}_1 & \mathbf{r}_1 & \boldsymbol{\chi}_1 & \mathbf{s}_1 \\ \mathbf{m}_2 & \mathbf{r}_2 & \boldsymbol{\chi}_2 & \mathbf{s}_2 \\ \mathbf{m}_3 & \mathbf{r}_3 & \boldsymbol{\chi}_3 & \mathbf{s}_3 \\ \mathbf{m}_4 & \mathbf{r}_4 & \boldsymbol{\chi}_4 & \mathbf{s}_4 \end{vmatrix} = 0$$

Table 1. The six cases possible from the rearrangement of $\det(D)$

Six cases	Newman projection arrow directions	$[\alpha]_D = \pm k_0 \det(D_0)$	Transposition in $\det(D)$ employed	$[\alpha]_D = k_0 \det(D)^a$
$R^1 > R^2 > R^3$	Clockwise	$k_0 \det(D_0)$	No transposition	$k_0 \det(D')$
$R^1 > R^3 > R^2$	Counterclockwise	$-k_0 \det(D_0)$	L1 and L3 ^b	$-k_0 \det(D')$
$R^2 > R^1 > R^3$	Counterclockwise	$-k_0 \det(D_0)$	L1 and L2	$-k_0 \det(D')$
$R^2 > R^3 > R^1$	Clockwise	$k_0 \det(D_0)$	L1 and L2, then new L1 and L3	$k_0 \det(D')$
$R^3 > R^1 > R^2$	Clockwise	$k_0 \det(D_0)$	L1 and L3, then new L1 and L2	$k_0 \det(D')$
$R^3 > R^2 > R^1$	Counterclockwise	$-k_0 \det(D_0)$	L1 and L3	$-k_0 \det(D')$

^a $\det(D) = \det(D')$ in the three cases where $R^1 > R^2 > R^3$, $R^2 > R^3 > R^1$, and $R^3 > R^1 > R^2$; $\det(D) = -\det(D')$ in the three cases where $R^1 > R^3 > R^2$, $R^2 > R^1 > R^3$, and $R^3 > R^2 > R^1$; $\det(D') = \det(D_0)$.

^b Here L1, L2 and L3 mean the first, second, and third lines in the determinant $\det(D)$, respectively.

When the positions of any two substituents (e.g., R^1 and R^2) are changed, then the following determinant results.

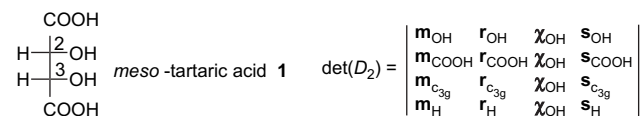
$$\det(D') = \begin{vmatrix} \mathbf{m}_2 & \mathbf{r}_2 & \chi_2 & \mathbf{s}_2 \\ \mathbf{m}_1 & \mathbf{r}_1 & \chi_1 & \mathbf{s}_1 \\ \mathbf{m}_3 & \mathbf{r}_3 & \chi_3 & \mathbf{s}_3 \\ \mathbf{m}_4 & \mathbf{r}_4 & \chi_4 & \mathbf{s}_4 \end{vmatrix} = - \begin{vmatrix} \mathbf{m}_1 & \mathbf{r}_1 & \chi_1 & \mathbf{s}_1 \\ \mathbf{m}_2 & \mathbf{r}_2 & \chi_2 & \mathbf{s}_2 \\ \mathbf{m}_3 & \mathbf{r}_3 & \chi_3 & \mathbf{s}_3 \\ \mathbf{m}_4 & \mathbf{r}_4 & \chi_4 & \mathbf{s}_4 \end{vmatrix} \\ = -\det(D)$$

The specific rotation's direction is now reversed. Thus, in a racemate, the specific rotation will be zero.

When a molecule has two or more stereogenic carbons, the $\det(D_i)$ values of each different stereogenic center would be calculated. If a compound has n stereogenic centers, then its net optical rotation will be the sum of each stereogenic center:

$$\det(D_1) + \det(D_2) + \dots + \det(D_n) = \sum \det(D_i)$$

A positive or negative value of $\det(D)$ designates the direction of rotation for that specific configuration. In a molecule with multiple stereogenic centers, the positive or negative value of the sum of all $\det(D_i)$ determines the direction of rotation. For *meso* compounds, such as *meso*-tartaric acid, $\det(D_2)$ and $\det(D_3)$ for stereogenic carbons C2 and C3 are given below, respectively, where c_{2g} represents the substituent $C^2H(OH)CO_2H$ and c_{3g} represents the substituent $C^3H(OH)CO_2H$ in these expressions. This $\det(D_2)$ is written using the clockwise order of $-OH$, $-c_{3g}$, and $-CO_2H$, as shown below.



We can write $\det(D_3)$ in the same way. Since the values of \mathbf{m} , \mathbf{r} , \mathbf{s} , and χ are the same for c_{2g} and c_{3g} , $\det(D_3)$ can be written as illustrated below

$$\det(D_3) = \begin{vmatrix} \mathbf{m}_{OH} & \mathbf{r}_{OH} & \chi_{OH} & \mathbf{s}_{OH} \\ \mathbf{m}_{c_{2g}} & \mathbf{r}_{c_{2g}} & \chi_{c_{2g}} & \mathbf{s}_{c_{2g}} \\ \mathbf{m}_{COOH} & \mathbf{r}_{COOH} & \chi_{COOH} & \mathbf{s}_{COOH} \\ \mathbf{m}_H & \mathbf{r}_H & \chi_H & \mathbf{s}_H \end{vmatrix} \\ = - \begin{vmatrix} \mathbf{m}_{OH} & \mathbf{r}_{OH} & \chi_{OH} & \mathbf{s}_{OH} \\ \mathbf{m}_{COOH} & \mathbf{r}_{COOH} & \chi_{COOH} & \mathbf{s}_{COOH} \\ \mathbf{m}_{c_{2g}} & \mathbf{r}_{c_{2g}} & \chi_{c_{2g}} & \mathbf{s}_{c_{2g}} \\ \mathbf{m}_H & \mathbf{r}_H & \chi_H & \mathbf{s}_H \end{vmatrix} \\ = - \begin{vmatrix} \mathbf{m}_{OH} & \mathbf{r}_{OH} & \chi_{OH} & \mathbf{s}_{OH} \\ \mathbf{m}_{COOH} & \mathbf{r}_{COOH} & \chi_{COOH} & \mathbf{s}_{COOH} \\ \mathbf{m}_{c_{3g}} & \mathbf{r}_{c_{3g}} & \chi_{c_{3g}} & \mathbf{s}_{c_{3g}} \\ \mathbf{m}_H & \mathbf{r}_H & \chi_H & \mathbf{s}_H \end{vmatrix} = -\det(D_2)$$

Therefore

$$\sum \det(D_i) = \det(D_2) + \det(D_3) = 0$$

and the specific rotation of *meso*-tartaric acid is zero.

As the bond angles bend, the values of the groups R^1 , R^2 , and R^3 along the Z -axis change. Thus, the determinant $\det(D_2)$ changes when R^1 , R^2 , R^3 , and R^4 are considered to be perfect point masses. That means the magnitude of optical rotation for a chiral molecule would change when the bond angles about the stereogenic atom changes.

There is little difference in electronegativity or symmetry from group to group when all four R groups are linear aliphatic functions with similar group lengths. In such cases, the magnitude of optical rotation will be small, and in some cases too small to be readily measured.

4. Sample calculations

Matrix theory is a general method in mathematics, widely used in many research areas when different variables are used. It is a useful tool for scientists to dissolve different academic problems although, in many cases, the linkage between the matrix theory and the target studied is not clear.

After setting up the matrix model for optical rotation, it is critical to provide accurate values for the variables (elements) to compute optical rotation. If the variables cannot have suitable magnitudes, no matter how reasonable the deduction is, this model will fail. Therefore, to reasonably quantitate the variables and let the four variables work well in matrix model become an arduous and important task. These definitions for the four variables and their magnitude computations are described below.

4.1. Comprehensive mass \mathbf{m}

The use of mass has a long history in the optical rotation computations.^{1c,d,6a} Atoms in different positions within the substituents have different degrees of contribution to the specific rotation. If the atom is directly connected to the stereogenic center, its coefficient is b_1 . Coefficients of the other atoms, which are further removed are b_2 , b_3 , and so on. Thus, the comprehensive mass of the substituent group becomes

$$\mathbf{m} = b_1 \mathbf{m}_1 + \sum b_2 \mathbf{m}_2 + \sum b_3 \mathbf{m}_3 + \sum b_4 \mathbf{m}_4 + \dots$$

Here, \mathbf{m}_1 is the mass of atom 1, which is directly connected to the stereogenic center and \mathbf{m}_2 is the mass of atom 2, which is directly bound to atom 1. Since more than one atom can be bonded to atom 1, the summation term is used to indicate that the contributions of all these atoms must be included. This is also true for each of the substituent atoms, which are one step further removed from the stereogenic center. The term b_1 is the coefficient for \mathbf{m}_1 , b_2 is the coefficient for \mathbf{m}_2 and b_n is the coefficient for \mathbf{m}_n .

As mentioned earlier, quantum effects on atoms' positions within the molecule (different conformations) should be considered. Quantum effects would affect the substituent's conformation. This causes the changes in comprehensive masses (\mathbf{m}) and radii (\mathbf{r}). Thus, the comprehensive mass and radius values could be evaluated by quantum mechanics (HF or DFT methods). In this paper, we have used the standard data for computations of $\det(D)$ and then test this model by

comparing these computed $\det(D)$ data with experimental results. Furthermore, two examples to show the effect of different conformations on $\det(D)$ values are presented in the subsection ‘The effect of the radius of the substituent on the optical rotation’ found in the discussion section.

The method to compute the comprehensive masses and radii is described below.

The calculation of each b_i value is now shown for the *n*-propyl group as a simple example (see Fig. 1). In this model, the coefficients of the masses are related to reciprocal volume. The values of b_i are defined as being proportional to the reciprocal of the volume swept out by that specific mass. Atoms attached further from the stereogenic center sweep out larger net volumes about that stereogenic center. Hence, the value of b_i will decrease if an atom is far from the stereogenic center since the reciprocal of the volume decreases. As can be seen in Figure 1, C1 (Fig. 1) is directly bonded to the stereogenic atom. C1 is at the center of the sphere.

The average unit volume of the C1 atom is

$$\begin{aligned} 1/v_1 &= 1/(4\pi r_1^3/3) = 1 \times 3/(4 \times 3.14 \times 0.77^3) \\ &= 0.5232 \text{ (\AA}^{-3}\text{)} \end{aligned}$$

where r_1 is the radius of an sp^3 -hybridized carbon.

C2 and C3 also sweep out volumes around the C1 center during rotations of both the C1 to stereogenic atom bond and the C1–C2 bonds. Their average unit volumes can be calculated, respectively, as above.

$$1/v_2 = 1/(4\pi r_2^3/3), \quad r_2 = 1.54 \text{ (\AA}^{-3}\text{)}$$

$$1/v_2 = 0.06538 \text{ (\AA}^{-3}\text{)}$$

and $1/v_3 = 1/(4\pi r_3^3/3)$, where $r_3 = (1.54^2 + 1.54^2 - 2 \times 1.54 \times 1.54 \times \cos 109) / 2 = 2.51$

$$1/v_3 = 0.01516 \text{ (\AA}^{-3}\text{)}$$

Here, r_3 is distance AC in Figure 1.

The b_i values are defined as being proportional to the respective calculated reciprocal volumes, $1/v_i$.

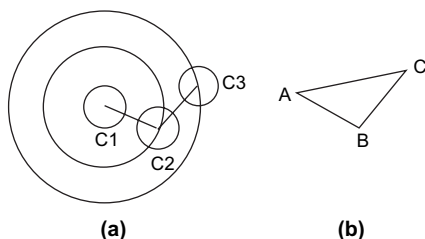


Figure 1. *n*-Propyl model used for the calculation of its b_i value. Plot b is the simplified geometry for calculating the distance from C1 to C3.

$$\begin{aligned} b_1:b_2:b_3 &= v_1^{-1}:v_2^{-1}:v_3^{-1} = 0.5232:0.06538:0.01516 \\ &= 1:0.125:0.029 \end{aligned}$$

Therefore, the mass contributions of C2 and C3 to the specific rotation are 0.125 and 0.029 times that of C1, respectively. This calculation for a carbon bonded to C3 (e.g., C4) results in a value of b_4 , which is only 0.008 that of b_1 . Different elements have different values of b_i and the same elements will have different b_i values when they are in different states of hybridization (see Section 2). The values of b_i also change with different conformations. A few example b_i values are calculated and listed in Table 2. For example, the comprehensive mass of the CO₂H group is estimated, as shown below, keeping in mind the two oxygen atoms (C=O, C–OH) have to be treated separately.

$$\mathbf{m} = 12 \times 1 + 0.156 \times 16 \times 2 + 0.114 \times 16 = 18.7$$

Some comprehensive masses of simple groups, calculated in the simple manner described above, are summarized in Table 3. There are many ways that the reciprocal volumes for any given function can be determined. Whatever method is selected, that procedure should be applied consistently to each molecule considered.

4.2. Radius *r*

The radius is defined, herein, as the smallest contact radius of the substituent when that substituent is in a stable conformation. We use the traditional method to obtain their magnitudes. The substituent's *r* value can be estimated by its geometry or it can be set equal to its Van der Waal's radius. Some example cases are now discussed.

- (1) The methyl group's *r* value is taken as that group's Van der Waal's radius (e.g., 2.0 Å).³⁰ The *r* radius of an ethyl group is also its group Van der Waal's radius. This is approximated as the distance from the center of the ethyl group's carbon–carbon single bond to a methyl hydrogen plus an additional 0.8 Å.³¹ For other alkyl groups, the Van der Waal's radii may be estimated by the distance for the group's center of mass to the outer hydrogen plus 0.8 Å.
- (2) The Van der Waal's radii of simple aromatic rings, such as phenyl or furan rings are approximated as 1.7 Å.
- (3) If a heavy atom is linked to one or two light atoms, such as in –OH and –NH₂, the radius used in this manuscript is simply regarded as the large atom's Van der Waal's radius. For complex substituents, the value of *r* could be calculated by its actual geometry. The radii for selected substituents were calculated and summarized in Table 2.

Table 2. Sample b_i values calculated for substituents ($b_1=1.0$)

Substituent	b_i	Substituent	b_i
–CH ₂ CH ₂ CH ₃	C–C: $b_2=0.125$, $b_3=0.029$	–CH ₃	C–H: $b_2=0.33$
–Phenyl	$b_2=0.125$, $b_3=0.024$, $b_4=0.0156$	–C(sp ³)–C=C–	$b_2=0.024$, $b_3=0.0135$
–CO ₂ H	C=O: $b_2=0.156$, C–O: $b_2=0.114$	–C(sp ³)–O–C(sp ³)	$b_2=0.162$, $b_3=0.033$
–C(sp ³)–N<	$b_2=0.144$ for N	–C(sp ³)–OH	$b_2=0.166$
–C(sp ²)=N–	$b_2=0.137$ for N	–C(sp ³)–S–	$b_2=0.077$

Table 3. Values of **m**, **r** and **s** for some selected substituents

R	m	r (Å)	χ	s	R	m	r (Å)	χ	s
–CH ₃	13.0	2.0	2.5	0.44	–NH ₃ ⁺	15.0	1.5	3.8	0.44
–C ₂ H ₅	13.6	2.2	2.5	0	–CO ₂ H	18.7	1.7	2.7	0
– <i>n</i> -Pr	14.0	2.2	2.5	0	–CO ₂ Me	19.2	2.7	2.8	0
– <i>n</i> -Bu	14.1	2.2	2.5	0	–CONH ₂	18.5	1.6	2.7	0
– <i>n</i> -C ₅ H ₁₁	14.2	2.9	2.5	0	2-Furyl	18.1	1.7	2.7	0
<i>c</i> -C ₆ H ₁₂	16.4	2.4	2.5	0	–Ph	18.9	1.7	2.7	0.25
– <i>i</i> -Pr	15.6	2.3	2.5	0	4-Cl–Ph	19.0	1.8	2.7	0.25
–CMe ₃	16.9	2.8	2.5	0.44	4-Me–Ph	18.9	1.7	2.7	0
– <i>i</i> -Bu	14.9	2.0	2.5	0	2-Br–Ph	20.1	1.95	2.7	0
–OH	16.3	1.4	3.5	0	1-Naphthyl	20.0	1.7	2.7	0
–OMe	17.3	2.3	3.5	0	2-Naphthyl	19.2	1.7	2.7	0
–OAc	19.9	2.9	3.5	0	3-Pyridyl	18.8	1.7	2.7	0–0.25
–NH ₂	14.7	1.5	3.0	0	4-Pyridyl	19.0	1.7	2.7	0.25
–C≡C	16.5	1.5	3.0	0.25	PhCH ₂ =CH–	15.7	2.0	2.8	0
–NCO	17.7	1.5	3.5	0	PhCH ₂ CH ₂ –	14.7	3.6	2.5	0
–CN	17.8	1.45	3.2	0.25	–H ₂ PO ₃	45.9	2.4	2.1	0
–CH ₂ Cl	15.6	1.8	2.5	0	–I	127	2.5	2.5	1
–CH ₂ OH	15.2	2.1	2.6	0	–Br	80.0	1.95	2.8	1
–CH ₂ Br	17.7	1.95	2.5	0	–Cl	35.5	1.8	3.0	1
–CH ₂ CN	18.1	2.9	2.5	0	–F	19.0	1.35	4.0	1
–NHMe	15.6	2.2	3.0	0	–H	1.0	1.2	2.1	1
–NMe ₂	16.6	2.3	3.0	0	–D	2.0	1.2	2.1	1

The effect of solvent on each substituent is different. Furthermore, the radius of a specific group can change in a different solvent. Chiral molecules, with very small rotation values, may undergo a change in the direction of rotation from positive to negative (or the reverse) due to small changes in the value of substituent radii. Nevertheless, most chiral compounds have large enough specific rotation values that these small errors are negligible. Thus, it is possible to use either the calculated radii or Van der Waals radii in this matrix model. Polar compounds can have strong intermolecular interactions with each other as their concentration increases, which may induce small changes in the values of substituents' radii. Thus, the direction of the specific rotation may change if the original value of the rotation was close to zero. In the matrix model, the effects of the solvent, temperature and concentration are mostly due to changes in the size of the substituents in solution. Holding solvent and temperature as constant, eliminates these effects when predicting specific rotations for a series of molecules.

The predictions of this matrix model are very sensitive to the geometries employed. Ideally, exact experimental geometries of rigid molecules should be used when they are available. The most difficult aspect of our model involves conformationally flexible molecules, where each conformation that contributes some fraction of that molecule's population. Each conformation contributes to the net optical rotation. It would be ideal to establish the exact geometry and the precise fraction present for each conformation. This is a major task and this will be essential in further work to apply this model to increasingly complex molecules in the future. For now, we have employed simple geometric models to illustrate the method.

4.3. Electronegativity χ

The effect of electronegativity on the specific rotation is large. In the matrix model, Pauling electronegativities are used throughout unless stated otherwise. Atom or group electronegativity³² has been used. When the stereogenic

atom is carbon, carbon's electronegativity value is used directly. When the stereogenic atom is not carbon, the calculated $\det(D)$ should be multiplied by the ratio χ_c/χ_y , where χ_c is carbon's electronegativity and χ_y is the stereogenic atom's electronegativity.

4.4. Symmetry **s**

The symmetry factor, **s**, represents the space group operation that is widely used to analyze the molecular structure and chirality. Early studies used the term 'atomic asymmetry' to calculate and understand optical rotation.^{6a,b} Herein we quantitate this term, symmetry, and use these values in our model. If one substituent has the highest symmetry operation number *N*, and this symmetric axis passes through the atom which is connected to the stereogenic atom, then the symmetry factor for that substituent is

$$s = [(N - 1)/N]^2$$

Values of **s** for selected substituents are listed in Table 3.

This model needs a chiral molecule having at least one symmetric group for its optical rotation computation, such as a single atom, H, Cl, or a group, e.g., –CH₃, –Ph, –CCl₃. If there is no symmetric group connected to the stereogenic center in a chiral molecule, this model would predict its optical rotation values as zero. For example, 5-ethyl,5-propylundecane and some glycerides,^{9c,f,k,l} have asymmetric centers. However, their optical rotation values are zero. An example may exist in which a chiral molecule has no symmetric group connected to the stereogenic center has a definite optical rotation value. Therefore, one should be careful to use this model to predict these chiral molecules' optical rotations.

Calculations of the specific rotation of 90 example compounds, in which specific interactions among the four substituents (cross products) are not considered, were carried out by determining the values of the four factors, **m**, **r**, χ ,

and *s*, for these substituents. These values were put into $\det(D)$. After determining the value of $\det(D)$ for each example molecule, the value of k_0 was obtained by dividing the experimental value of the specific rotation, $[\alpha]_D$, of the optically pure enantiomer by the value of $\det(D)$.³³ If the matrix model represents a reasonable method to predict the magnitude and direction of specific rotation, then the value of k_0 should be approximately constant when obtained for different chiral compounds with similar structure in the same solvent (and at the same temperature and light wavelength). This would demonstrate that the value of $\det(D)$ was proportional to the magnitude of the specific rotation. The deviation of such k_0 values represents a measure of how well the model works. This premise is tested in Table 4 where the calculated values of $\det(D)$, the experimental values of specific rotation (using the sodium D line), the solvent and the calculated k_0 values of 90 molecules are summarized.

5. Results and discussion

5.1. Calculated k_0 values in same series of compounds

Experimental optical rotations were obtained on eight alcohols (**1–8**) (Table 4) and the values of $\det(D)$ were calculated. The values of k_0 were determined from the calculated values of $\det(D)$ and the experimental values of $[\alpha]_D$. These values (0.59, 0.87, 0.40, 0.35, 0.48, 0.78, 0.64, and 0.76, where the average value is 0.61) are remarkably similar considering the many assumptions used in the model, the use of only four elements (substituent characteristics) and noticing that all the experimental $[\alpha]_D$ values were reported by different research groups. The k_0 values of compounds **20–23** measured in methanol are 6.60, 5.73, 5.20, and 6.04, respectively. The measured rotation of **20** is almost the same in EtOH as in MeOH. Thus, the k_0 values of compounds **16–19** (4.64,

Table 4. Calculated values of $\det(D)$, experimental and computed $[\alpha]_D$ values (by DFT methods) of specific rotation and the values of k_0 from $[\alpha]_D/\det(D)$ for ninety example molecules³⁴

Molecule no.	Structure	$\det(D)$	$[M]/k_0$	$[\alpha]_D$ (determined)	k_0	$[\alpha]_D$ (DFT) ^a	Ref.
1		+16.16	+11.96	+9.57 (neat)	0.59	+53.1	33a
2		+14.98	+13.18	+13 (neat)	0.87	+70.5	33b
3		-12.10	-10.55	-4.9 (neat)	0.40	+44.5	33c
4		-27.18	-31.53	-9.5 (neat)	0.35	—	33d
5		-11.57	-14.81	-5.6 (neat)	0.48	+55.85	33e
6		-31.43	-47.15	-24.6 (neat)	0.78	-11.7	33f
7		+31.23	+51.22	+20 (neat)	0.64	+77.9	33g
8		-14.46	-14.75	-11 (neat)	0.77	-9.03	33h
9		+3.13	+3.19	+8.14 (neat)	2.60	-22.61	33i

(continued)

Table 4. (continued)

Molecule no.	Structure	det(<i>D</i>)	[<i>M</i>]/ <i>k</i> ₀	[α] _D (determined)	<i>k</i> ₀	[α] _D (DFT) ^a	Ref.
10		+4.95	+5.74	+10.25 (neat, <i>l</i> =0.5)	2.07	+13.8	33j
11		−4.36	−5.58	−23.7 (neat, <i>l</i> =1)	5.44	+ 54.14	33k
12		−11.02	−8.04	−7.5 (neat)	0.68	−55.5	33l
13		−8.17	−10.31	−4.0 (neat)	0.49	+13.0	33m
14		+13.81	+20.30	+10.5 (neat)	0.49	−51.4	33n
15		+11.87	+14.36	+38 (neat)	3.12	+74.8	33o
16		+8.19	+14.09	+38 (EtOH)	4.64	+22.2	33p
17		+4.97	+8.15	+24.7 (EtOH) 92% ee	5.40	+2.2	33q
18		+5.28	+7.13	+35 (EtOH)	6.63	−29.3	33r
19		+10.55	+18.15	+78 (EtOH)	7.39	+69.5	33s
20		−8.81	−15.06	−55 (EtOH) −59 (MeOH)	6.24 6.60	−118.7	33t
21		−7.01	−9.46	−40.2 (MeOH)	5.73	−130.2	33u
22		−8.27	−16.46	−43 (MeOH)	5.20	—	33v

(continued)

Table 4. (continued)

Molecule no.	Structure	det(<i>D</i>)	[<i>M</i>]/ <i>k</i> ₀	[α] _D (determined)	<i>k</i> ₀	[α] _D (DFT) ^a	Ref.
23		+8.31	+12.38	+50.2 (MeOH)	6.04	+68.7	33v,w
24		+5.98	+8.49	+8.1 (CHCl ₃)	1.45	−6.36	33x
25		−32.16	−43.74	−45.6 (CHCl ₃)	1.42	−105.5	33y
26		−18.96	−23.89	−17.9 (CHCl ₃)	0.94	−86.0	33z
27		−5.14	−8.33	−5.94 (HCl ₃)	1.16	—	33aa
28		−31.41	−47.12	−45.2 (PhH) −48.6 (CHCl ₃)	1.44 1.55	—	33ab
29		+7.06	+9.39	+42 (CHCl ₃)	5.95	+0.6	33ac
30		+8.81	+14.76	+39 (CHCl ₃)	4.43	+51.8	33ad
31		+9.28	+13.64	+39 (CHCl ₃)	4.20	+72.1	33ae
32		+30.64	+50.25	+25.9 (PhH)	0.85	+64.5	33af
33		+15.41	+18.80	+43.1 (<i>c</i> -C ₅ H ₁₀)	2.80	+130.7	33ag
34		−16.52	−25.85	−48 (<i>c</i> -C ₆ H ₁₂)	2.90	−82.2	33ah
35		+5.90	+14.63	+35 (<i>c</i> -C ₆ H ₁₂)	5.93	—	33ai
36		−29.53	−37.21	−22.38 (ether)	0.76	—	33aj





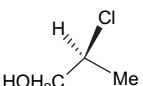
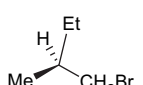
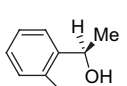
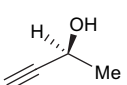
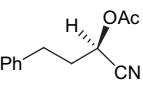
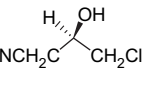
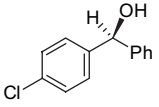
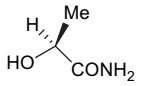
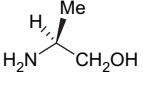
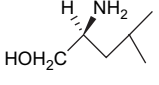
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Table 4. (continued)

Molecule no.	Structure	det(<i>D</i>)	$[M]/k_0$	$[\alpha]_D$ (determined)	k_0	$[\alpha]_D$ (DFT) ^a	Ref.
37		-18.58	-18.21	-15.4 (ether) -9.1 57% (ee) (dioxane)	1.45 0.86	-109.5	33aj
38		+7.69	+12.76	+149 (EtOH)	19.4	+106.3	33ak
39		+20.16	+35.68	+8.0 (CHCl3)	0.40	+7.6	33al
40		+8.21	+7.59	+38.9 +33.8 (neat)	4.7 4.1	+24.0	33am, 21d
41		+8.06	+8.58	+43.2	5.3	+26.8	33am
42		+12.64	+10.49	+30.7 +36.3	2.43 2.9	+23.6	33am 21d
43		+11.79	+11.44	+50.5	4.28	+34.4	33am
44		+11.57	+12.84	+45.9	3.97	—	33am
45		+6.57	+8.80	+27.6	4.20	+52.4	33am
46		+6.18	+9.15	+25.6	4.14	+25.4	33am
47		+6.08	+9.84	+24.1	3.96	—	33am
48		+14.67	+20.09	+26.3	1.8	+23.5	33am
49		+14.73	+22.24	+41.7	2.8	+21.3	33am

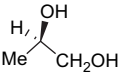
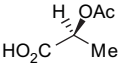
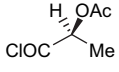
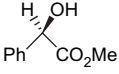
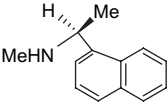
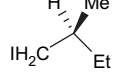
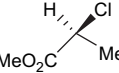
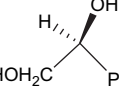
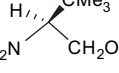
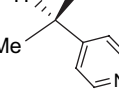
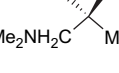
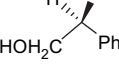
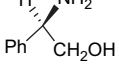
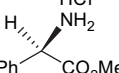
(continued)

Table 4. (continued)

Molecule no.	Structure	det(<i>D</i>)	[<i>M</i>]/ <i>k</i> ₀	[α] _D (determined)	<i>k</i> ₀	[α] _D (DFT) ^a	Ref.
50		−0.65	−1.11	+0.0035	−0.05	—	33am
51		+0.93	+1.02	+0.0068	0.07	—	33am
52		−0.21	−0.124	+0.0095	−0.45	—	33am
53		+1.86	+1.73	+1.58 (<i>c</i> -C ₅ H ₁₀)	0.85	—	33am
54		+16.24	+15.34	+17.5 (neat)	1.08	+11.4	33an
55		+3.36	+5.04	+4.5 (CHCl ₃)	1.34	+6.8	33ao
56		+6.27	+12.54	+54 (CHCl ₃)	8.61	+135.6	33ap
57		−14.79	−10.20	−45 (neat)	3.04	−105.9	33aq
58		+14.34	+23.39	+44.0 (CHCl ₃)	3.07	—	33ar
59		+8.24	+9.85	+11 (neat)	1.33	−38.5	33as
60		+2.80	+6.12	+16.0 (CHCl ₃)	5.71	—	33at
61		−7.95	−7.08	−20.5 (H ₂ O)	2.58	—	33au
62		+6.56	+4.92	+18 (neat)	2.74	—	33av
63		+0.82	+3.98	+4.0 (EtOH)	4.88	—	33aw

(continued)

Table 4. (continued)

Molecule no.	Structure	det(<i>D</i>)	[<i>M</i>]/ <i>k</i> ₀	[α] _D (determined)	<i>k</i> ₀	[α] _D (DFT) ^a	Ref.
64		−10.26	−7.80	−15 (neat)	1.46	+58.6	33ax
65		−8.52	−11.25	−51 (CHCl ₃)	5.99	−27.7	33ay
66		−7.80	−8.97	−31 (CHCl ₃)	3.97	−58.3	33az
67		−35.69	−59.25	−144 (CHCl ₃)	4.03	−187.7	33aaa
68		−9.79	−17.55	−89.0 (EtOH)	9.1	−126.7	33aab
69		+1.75	+3.50	+5.7 (neat)	3.26	—	33aac
70		−2.47	−3.01	−26 (neat)	10.5	−104.6	33aad
71		−25.86	−35.71	−69 (CHCl ₃)	2.67	+107.1	33aae
72		+9.78	+11.44	+37 (CHCl ₃)	3.78	+11.0	33aaf
73		+15.71	+19.32	+55 (CHCl ₃)	3.50	+122.1	33aag
74		+21.82	+22.47	+27.0 (neat)	1.24	−144.4	33aah
75		−6.18	−8.40	−17 (neat)	2.75	+13.3	33aai
76		−17.53	−24.01	−31.7 (HCl)	1.81	—	33aaj
77		−28.29	−46.67	−118 (H ₂ O)	4.08	—	33aaj, aak

(continued)

Table 4. (continued)

Molecule no.	Structure	det(<i>D</i>)	[<i>M</i>]/ <i>k</i> ₀	[α] _D (determined)	<i>k</i> ₀	[α] _D (DFT) ^a	Ref.
78		-7.81	-8.04	-8.0 (MeOH)	1.02	—	33aal
79		+2.19	+3.94	+16 (neat)	7.03	-24.3	33aam
80		+0.92 (<i>s</i> _{NH₃⁺} =0.44, χ _{NH₃⁺} =3.70) +2.8 (<i>s</i> _{NH₃⁺} =0.44, χ _{NH₃⁺} =3.80) +5.7 (<i>s</i> _{NH₂} =0, χ _{NH₂} =3.5)	+1.39 +4.22 +8.60	+23 (1 <i>N</i> HCl)	25.0 8.21 4.03	-20.0	33aan
81		+2.06 (<i>s</i> _{dopl} =0.25) ^b +6.37 (<i>s</i> _{dopl} =0.0)	+4.14 +2.80	+61 (EtOH)	29.6 9.57	+6.7	33aao
82		-6.0 (<i>r</i> _{PhCO} =2.0) -23.8 (<i>r</i> _{PhCO} =2.6)	-12.72 -50.65	-115 (acetone)	19.2 4.8	-96.2	33aap
83		-53.48 (<i>s</i> _{NH₂} =0) -54.51 (<i>s</i> _{NH₃⁺} =0.44)	-59.36	-4.8 (H ₂ O)	0.090 0.088	+29.5	33aaq
84		-96.02 (<i>s</i> _{NH₂} =0) -96.67 (<i>s</i> _{NH₂} =0.44)	-120.0	-16.5 (1 <i>N</i> NaOH)	0.17 0.17	+24.8	33aar
85		-259.5	-188.5	-25.0 (NaOH)	0.16	—	33aas
86		-7.61 × 2 = -15.32	-13.70	-13 (neat)	0.85	-40.7	33aat
87		+7.27 × 2 = 14.54	+21.81	+12.4 (H ₂ O)	0.57	—	33aau
88		-13.86 × 2 = -27.72	-28.83	-40.4 (CHCl ₃)	1.45	-41.5	33aav
89		det(<i>D</i> ₁)=-21.37 det(<i>D</i> ₂)=+9.5 Σdet(<i>D</i>)=-11.87	-19.58	-34.0 (H ₂ O)	2.86	-44.2	33aaw

(continued)

Table 4. (continued)

Molecule no.	Structure	det(<i>D</i>)	[<i>M</i>]/ <i>k</i> ₀	[α] _D (determined)	<i>k</i> ₀	[α] _D (DFT) ^a	Ref.
90	 (1 <i>S</i> ,2 <i>S</i>)	det(<i>D</i> ₁)=+21.37 det(<i>D</i> ₂)=+9.5 Σdet(<i>D</i>)=+30.87	+50.93	+ 61.0 (H ₂ O)	1.98	—	33aax

^a The DFT method used in these predictions first established all the specific conformations of each molecule at the B3LYP/6-31G(d) level and then employed the B3LYP/aug-cc-pVDZ level to compute the optical rotation.

^b dkpl=2,5-dione-pyrrolyl (in no. **81**).

5.40, 6.63, and 7.39) are in good agreement. Using the experimental rotations for compounds **12–14**, measured neat, the calculated det(*D*) values resulted in small variations in *k*₀. The calculated det(*D*) values for **33** and **34** led to *k*₀ values 2.80 and 2.90 in the essentially identical solvating media of cyclopentane and cyclohexane. The experimental rotations of alcohols **24–28** and 1,3-diol **89** were obtained in CHCl₃. Their corresponding *k*₀ values upon applying the matrix model are 1.45, 1.42, 0.94, 1.16, 1.55, and 1.45 (average=1.33), respectively. Again these values are close. Cyanohydrins **29–31** and **43–44** also gave tightly grouped *k*₀ values (5.95–4.20 and 4.28–3.97). When the small nitrile group of **30** is directly replaced with the phenyl ring in compound **60**, the *k*₀ value only changes from 4.43 to 5.71 despite this radical structure change. This change is of the same range as the *k*₀ variation within the series **29–31**. The *k*₀ values for the structurally similar series **45–47** are very close to 4.1 (4.20, 4.14, and 3.96). The compounds, **65–67** have different functional groups (acid, acid chloride, ester, phenyl), yet their *k*₀ values are 5.99, 3.97, and 4.03 in chloroform.

The directions of rotation were predicted incorrectly in only two of **90** compounds in Table 4. This occurred for **50** and **52** where the experimental rotation values were extremely small (both less than 0.01°). Taken together, these results suggest that this matrix model holds significant promise for predicting the magnitude and direction of specific rotations.

Aminoalcohols **63** and **72** have same (*S*)-configuration and differ only in the structure of the butyl group attached to the stereogenic center (2-methylpropyl vs *tert*-butyl). The calculated det(*D*) for (*S*)-**63** is +0.82. In contrast, the value of det(*D*) for (*S*)-**72** is +10.02, almost 12 times larger than that of (*S*)-**63**. The experimental values of [α]_D for (*S*)-**63** is 4.0° while that for (*S*)-**72** is +37° in ethanol, some nine times greater than (*S*)-**63**.

As mentioned above, when a group of molecules have large differences in structure, the resulting *k*₀ values can vary even when their rotations were determined under the same conditions. For example, the *k*₀ values of compounds **8–11** change from 0.71 to 2.60, 4.14 and 5.44, respectively. Molecules with both H and D atoms bound to the same stereogenic center are known to exhibit small specific rotation values. In accord with this observation, the matrix model predicted small values for the four compounds **50–53**, which have varied structures. The *k*₀ values here are quite similar also (see **50–53** in Table 4).

The B3LYP/aug-cc-pVDZ level DFT method was also used to compute the optical rotation for a total of 65 chiral molecules after all conformations for each of them were first obtained at the B3LYP/6-31G(d) level.³⁸ They are also summarized in Table 4 for easy comparison to experimental values and matrix model predictions. When a chiral molecule has many conformations, only the conformations, whose relative energies are between 0 and 3.0 kcal/mol above the most stable conformation were used in further optical rotation calculations (e.g., 17 conformations of the 35 total conformations were used in the optical rotation calculations of chiral molecule number 17). The conformations with relative energies of 3.0 kcal/mol higher than the most stable one, have very low populations that can be neglected. The predictions of the optical rotation values for acyclic compounds (stereogenic centers are not in rings) at this DFT theoretical level were not as good as those for relatively rigid cyclic compounds (chiral centers are located in rings). The major reason may be that (1) more conformations need to be investigated in computations of optical rotation for these acyclic chiral compounds, and (2) also the computational level may not be high enough to obtain the more accurate geometries. For example, calculated optical rotation values of 2-chlorobutane and 2-cyanobutane were 24.0° and 23.6°, respectively, at the B3LYP/aug-cc-pVDZ//B3LYP/6-31G(d) level (see Supplementary data for details). These values became 32.6° and 33.8° at the B3LYP/aug-cc-pVDZ//MP2/6-311+G(d) level of theory, respectively.^{21d} The latter values are close to the experimental results, which are +33.8°^{21d} or 38.0°^{33am} for 2-chlorobutane and 30.0°^{33am} or 36.3°^{21d} for 2-cyanobutane, respectively. More accurate conformational geometries improve the accuracy of predicted optical rotations. However, the computations of optical rotation at the B3LYP/aug-cc-pVDZ//MP2/6-311+G(d) level of theory are not economic when an acyclic chiral molecule has many conformations that need to be investigated.

5.2. The det(*D*) of L-cysteine and its disulfide dimer

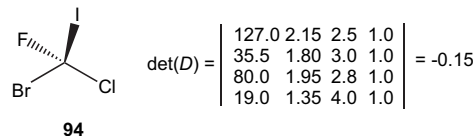
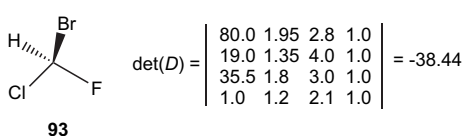
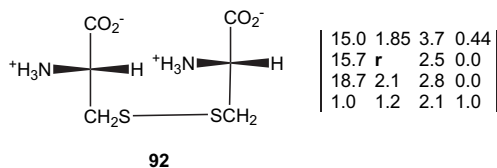
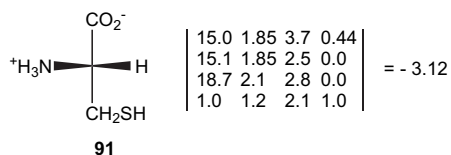
The complexity increases when two or more substituents in the same chiral molecule interact with each other. For example, the experimental optical rotations of L-cysteine and its disulfide dimer have long puzzled chemists. It represents a model system of some interest. L-cysteine hydrochloride, **91**, exhibits an experimentally measured specific rotation, [α]_D, of +6.5 in 2 N HCl while its dimer hydrochloride, **92**, exhibits a rotation of –217.8 in 1 N HCl.³⁵ While one might naively expect the dimer to have a specific rotation

Table 5. The effect of the radius of r , $-\text{CH}_2\text{SSCH}_2\text{CH}^+(\text{NH}_3)\text{COOH}$, on the value of $\det(D)$ using two values of electronegativity (χ) for NH_3^+

r	$\det(D)$ of 92 when $\chi=3.7$	$\det(D)$ of 92 when $\chi=3.8$
3.0	-14.46	-18.37
4.0	-25.80	-31.39
5.0	-36.94	-44.40
6.0	-48.09	-57.41
7.0	-60.51	-70.43
8.0	-71.65	-83.44

with about twice the magnitude and same direction as that of L-cysteine, the dimer **92** actually exhibits a rotation 33 times greater in magnitude and in the opposite direction. Calculation of specific rotation via the matrix model leads to $\det(D)$ values of -1.85 and -2.39 for L-cysteine hydrochloride, **91** ($k_0=-3.51$ and -2.72) using electronegativity values (χ) of 3.7^{36} and 3.8^{37} for NH_3^+ , respectively, and of 2.8 for COO^- .³⁶

The values of $\det(D)$ for dimer **92** are listed in Table 5 as a function of the radius, r , using both $\chi=3.7$ and 3.8 for $-\text{NH}_3^+$. It is not easy to determine the radius of the large substituent ($-\text{CH}_2\text{SSCH}_2\text{NH}(\text{NH}_3)\text{COO}^-$) due to the large number of conformations possible, many of which would have similar energies and be populated at ambient temperature. Therefore, a series of r values were used in the calculations to illustrate the response of $\det(D)$ as radius increases. Since, the measured specific rotation is for the hydrochloride salt, **92**, the amino group must be replaced by $-\text{NH}_3^+$. Hence the value of $\det(D)$ for **92** depends on the electronegativity values used for $-\text{NH}_3^+$. It will also require the use of the different symmetry exhibited by sp^3 hybridized $-\text{NH}_3^+$ ($s=0.44$) versus $-\text{NH}_2$ ($s=0.0$). Values of $\det(D)$ were calculated for **92** using $-\text{NH}_3^+$ electronegativity values of both 3.7 and 3.8 , where r was assigned values of $3-8$. The corresponding values of $\det(D_1)$ are listed in Table 5. Clearly, both electronegativity and r values have large effects on $\det(D)$. The magnitude increased with increase in both χ and r . Using the k_0 values of -3.51 and -2.72 (obtained for **91**) to calculate $\det(D)$ from the experimental $[\alpha]_D$ value of -217.8 gives values of 62.1 and 80.4 , respectively. This suggests that $-\text{CH}_2\text{SSCH}(\text{N}^+\text{H}_3)\text{COOH}$ has a radius of about $7.2-7.7$ Å in solution. This seems reasonable in view of expected change–change repulsions between the two $-\text{NH}_3^+$ groups.



5.3. The $\det(D)$ of bromochlorofluoromethane and (S)-bromochlorofluoroiodomethane

Bromochlorofluoromethane, **93**, is an interesting model molecule containing highly electronegative fluorine. It has been studied for many years.³⁹ Its direction of rotation versus configuration has been defined. (S)-**93** has a small positive value: $+1.78^\circ \pm 0.18$ (in cyclohexane) at 100% ee.^{10e} Our initial matrix calculation, using standard tetrahedral geometry, predicts the (S)-configuration of this chiral molecule will have a sizeable negative value for rotation (e.g., $\det(D)=-38.4$), unlike the small positive experimental value. However, steric repulsions exist among the halogen atoms and an appreciable electrostatic attraction between the F and H atoms deforms the true molecular geometry away from 109.5° angles. This will cause the initial matrix calculation, which used all 109.5° bond angles to be in error and overestimate both the value of $\det(D)$ and the optical rotation. On the other hand, (S)-bromochlorofluoroiodomethane, **94**, with only repulsive interactions among its substituents (unlike **93**) is predicted to have a small optical rotation value with a negative sign (e.g., $\det(D)=-0.15$).

The initial matrix model calculation on **93** pointed out the need to use more realistic geometries. The geometries of molecules **93** and **94** were both optimized using the AM1 method. The distortion from a perfect tetrahedral geometry is significant for **93** where $\angle \text{HCF}=109.6$; $\angle \text{HCCI}=106.4$ and $\angle \text{HCB r}=105.6$. The calculated $\det(D_z)$ for the AM1-optimized (S)-**93** geometry is $+3.93$. The $\det(D_z)$ for AM1-optimized (S)-**94** becomes -0.66 . Therefore, the matrix model when using a more correct geometry correctly predicts that (S)-(+)-**93** has a small rotation value when realistic geometries are used. The optical rotation of (S)-**94** is predicted to be about -0.3° if its optical rotation is measured under similar conditions to that of (S)-**93**. However, this predicted value has not yet been verified by experiments.

5.4. The effects of symmetry and electronegativity on the specific optical rotation

In N-protonated-2-aminoalcohol **80**, the effects of the electronegativity and symmetry on the calculated optical rotations are observed. When the electronegativity of the nitrogen atom is changed from 3.7 to 3.8 , the $\det(D)$ varies from 0.92 to 2.80 . When the amine group's symmetry

changes from 0.00 to 0.44 for the protonated amine and the electronegativity changes from 3.0 ($-\text{NH}_2$) to 3.8 ($-\text{NH}_3^+$), the $\det(D)$ value varies from +2.06 to +5.70. The effects are sharp in this example. Compound **83** is another example in which the state of the amine function must be considered. Compound **83** can exist as the amino phosphonic acid or as the *N*-protonated zwitterion. In the zwitterion, the electronegativity of *N* is changed from 3.0 to 3.8, and the symmetry changes from 0 ($-\text{NH}_2$) to 0.44 ($-\text{NH}_3^+$). Although the variables have big changes in matrix model, the changes of $\det(D)$ value of **83** are very small (originally from -53.48 to -54.51) in the zwitterion. Obviously, a same variable will play different roles in different chiral molecules.

The lone pair of electrons on an α,β -unsaturated imide nitrogen are conjugated and the function is planar. An example is no. **81**. If the planar conformation is deformed to non-planar conformations, the values of $\det(D)$ will change. The $\det(D)$ value is very sensitive to the amount of deformation. The $\det(D)$ is +2.06 when the imide is planar, but this changes to +6.37 when the nitrogen out of plane deformation is only 0.5° . Larger the radius is, smaller the computed $\det(D)$ will be, e.g., if $r=1.8$, $\det(D)=6.17$ and $r=2.1$, $\det(D)=5.55$. See Figure 2.

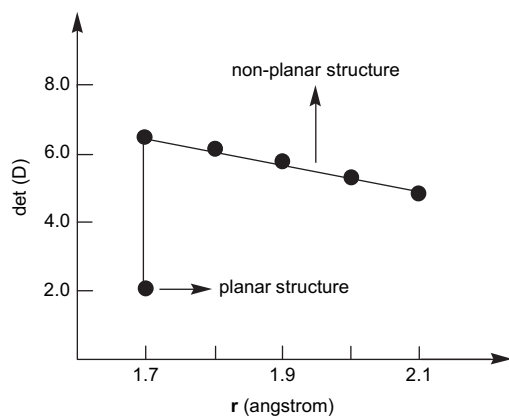


Figure 2. The computed $\det(D)$ changed when the planar conformation changes to non-planar conformation.

5.5. The effect of the radius of the substituent on the optical rotation

In **82**, a radius of 2.0 \AA was used for the $\text{PhC}=\text{O}$ substituent in this calculation. If the radius increases to 2.2 \AA , the $\det(D)$ value decreases from -6.0 to -23.89 . This is a very large change. How large an effect changing the radius has on the optical rotation depends very specifically on the molecule's structure. Each factor's effect on the optical rotation must be specifically determined for each molecular structure, as previously mentioned above.

5.6. Dual-stereogenic-center molecules

Four dual-chiral-center molecules (molecules **87–90**) were examined. Ephedrine **89** and pseudoephedrine **90** are diastereomers, differing only in the absolute configuration at C-1. (1*R*,2*S*)-(–) Ephedrine, **89**, exhibits a $\det(D_1)$ value of -21.37 and $\det(D_2)$ is $+9.50$. Therefore, the $\det(D)$ sum

is -11.87 . For the enantiomers, (1*R*,2*R*)-**90** and (1*S*,2*S*)-**90**, the sums of the $\det(D)$ values for each stereogenic center are as follows:

(1*R*,2*R*)-pseudoephedrine, **90**

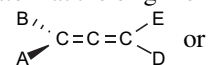
$$\sum \det(D) = (-21.37) + (-9.50) = -30.87;$$

(1*S*,2*S*)-pseudoephedrine, **90**

$$\sum \det(D) = 21.37 + 9.50 = 30.87.$$

The predicted absolute optical rotation values of (1*R*,2*R*)-**90** or (1*S*,2*S*)-**90** should be about 2.6 times larger than those of (1*R*,2*S*) or (1*S*,2*R*)-**89**. These calculated relative values approximate the observed rotation values of -34° for the HCl salt of (1*R*,2*S*)-(–) ephedrine, **89**, and $+61^\circ$ for the HCl salt of (1*S*,2*S*)-pseudoephedrine, **90**, both obtained in water. Experimentally, the rotation of **90** is 1.8 times larger than **89**.

The matrix method could be extended to molecules with two or more stereogenic centers, ring-structured stereogenic molecules and chiral compounds, which do not have one or more stereogenic centers, such as dissymmetric allenes or substituted biphenyls with restricted rotation. The examples of molecules with two stereogenic centers are summarized in Table 4 (see **86–90**). The same principles can be used to compute the optical rotation for ring-structured chiral molecules. Predicting rotations for allenes requires defining the elements in a way that does not reference everything to specific atoms that are adjacent to the atom at the origin of

the coordinate system. For example,  or substituted biphenyls with restricted rotation would be put into a 3-D coordinate system. The key point is that the groups A, B, D, and E would be in four quadrants of the coordinate system, which is selected. Upon separating the molecule into four parts, the parameters (elements) selected would then be appropriately defined. For example, the center of mass of C–D (or C–A, C–B or C–E) might be used as a distance parameter. Actually a large variety of terms to include \mathbf{x} , \mathbf{s} , \mathbf{m} and \mathbf{r} can be designed to be used as elements. The center carbon of allenes could be the geometric center (origin) of an axis system. Looking down the $\text{C}=\text{C}=\text{C}$ axis puts A, B, D, and E into different quadrants. However, that effort will be discussed in a future extension of the model.

6. Summary

The matrix model is in its infancy. Many improvements can be explored in the future. Accurate molecular geometries can be used, which have either been determined experimentally or accurately calculated using quantum mechanical or molecular mechanics methods. As substituents become increasingly large, the question of which conformations and their fractional populations must be accurately addressed in order to get proper optical rotation values. The accuracy of the experimental rotation values cited herein from the literature is not known. Some shortcomings of the current matrix model calculations exist. For example, the effects of light, solvent or temperature on the optical rotation

were not yet investigated. However, the results obtained so far using this matrix approach are encouraging. This suggests that further development of this model should be pursued.

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Supplementary data

Matrix model computational and the DFT computational results are available. Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2006.12.061

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