Exploring the Conformation Space of Cycloalkanes by Linearized Embedding

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Linearized embedding is a variant on the usual distance geometry methods for finding atomic Cartesian coordinates given constraints on interatomic distances. Instead of dealing primarily with the matrix of interatomic distances, linearized embedding concentrates on properties of the metric matrix, the matrix of inner products between pairs of vectors defining local coordinate systems within the molecule. Here, the approach is used to explore the full conformation space allowed to small cyclic alkanes, given the constraint of exact bond lengths and bond angles. Useful general tools developed along the way are expressions for rotation matrices in any number of dimensions and a generalization of spherical coordinates to any number of dimensions. Analytical results give some novel views of the conformation spaces of cyclopropane, cyclobutane, cyclopentane, and eyclohexane. A combination of numerical and analytical approaches gives the most comprehensive description to date of the cycloheptane conformation space with fixed bond lengths and angles. In this representation, the pseudorotation paths of cyclohexane and cycloheptane are closed curved lines on the surfaces of spheres.

INTRODUCTION

Suppose we want to search out the full range of conformations available to a molecule, given fixed values for bond lengths and vicinal bond angles, but certain torsion angles are allowed free rotation. In reality, of course, bond lengths and angles are stiff but somewhat flexible, and the physically important conformations are those having relatively low internal energy. For the present purposes, we simplify the problem by ignoring energetic considerations and even van der Waals contacts between atoms. For acyclic molecules under these assumptions, the full conformation space is simply the Cartesian product of all the torsion angle one-dimensional cycles (torsion angle $\tau \in [0, 2\pi]$). In fancier terminology, this is called an n-dimensional toroidal manifold, where n is the number of rotatable bonds. Such spaces, together with all sorts of energetic and geometric restrictions, are routinely explored exhaustively by computer methods developed by Marshall, Dammkohler, and coworkers.[1,2]

For cyclic molecules having rotatable bonds in the rings, the problem is qualitatively different because now typically six degrees of freedom are lost due to the ring closure constraint and the allowed conformation space is some collection of subspaces of the acyclic molecule's toroidal manifold. One approach is to allow flexible bond lengths and angles and then parameterize the conformation space such that some degrees of freedom are associated with ring puckering.[3,4] However, such a treatment does not show the restriction of conformation forced by the rigid valence geometry constraint. Precisely this problem has been solved in specific cases by analytical methods (e.g., Dress's analysis of cyclohexane[5]), and a relatively general analysis that solves specific ring closure problems by numerical methods has been given by Gō and Scheraga.[6] An extremely general numerical approach is the distance geometry EMBED algorithm,[5] which explores the conformation space by producing a random sampling of allowed conformations, specified in terms of atomic coordinates in ordinary three-dimensional Cartesian space (R^3). The algorithm applied to cyclic molecules of n atoms simply chooses an $n \times n$ matrix of random interatomic *trial distances* subject to the bond length and angle constraints and converts these to a corresponding $n \times n$ *trial metric matrix.* The trial metric matrix corresponds generally to some conformation in R^n, but the nearest rank 3 metric matrix, built up out of the three largest positive eigenvalues and corresponding eigenvectors of the trial metric matrix, can be directly converted to a set of atomic *trial coordinates* in R^3. The trial coordinates have the correct dimensionality, but they no longer obey the original geometric constraints, in general. *Refined coordinates* are found by local numerical minimization of the constraint violations as a function of atomic coordinates starting from the trial coordinates. The allowed conformation space can in principle be exhaustively explored by generating many sets of refined coordinates starting from different random trial distance matrices, but

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it is not clear when to stop, nor is there much insight gained as to the structure of the conformation space.

In this study, I explore the conformation spaces of cycloalkanes by a variation on EMBED similar to the method of linearized embedding.[7] Molecular conformation is represented primarily by a metric matrix, and analytical methods restrict the values the elements of the matrix can attain because of the fixed bond lengths, fixed bond angles, and ring closure constraints. Requiring a conformation in R^3 puts more constraints on the matrix, which can still be expressed exactly. Finally, I outline a few methods to numerically explore the full space of allowed conformations, given this analytical foundation. Of course, Cartesian coordinates and dihedral angles can be readily calculated from the solved metric matrix. This approach to searching out the conformation space for small but difficult molecules can be extremely thorough and lead to a better understanding of its structure.

METHODS

Consider only the carbon skeleton of idealized cycloalkanes. All C—C bond lengths are fixed to 1.54 Å, and all C—C—C bond angles are fixed at the perfect tetrahedral angle, 109.47122°. In everything that follows, the absolute size scale is irrelevant, so let the unit of length be the C—C bond length. Then, one can compactly describe a cyclo-n-alkane as n atoms having positions $\mathbf{P}_1, \ldots, \mathbf{P}_n \in R^3$ specified in terms of n unit vectors

$$\begin{aligned} \mathbf{P}_2 &= \mathbf{P}_1 + \mathbf{u}_1 \\ &\cdot \\ &\cdot \\ &\cdot \\ \mathbf{P}_n &= \mathbf{P}_{n-1} + \mathbf{u}_{n-1} \\ \mathbf{P}_1 &= \mathbf{P}_n + \mathbf{u}_n. \end{aligned} \tag{1}$$

(see Fig. 1). Overall translation of the molecule is irrelevant to the conformation, so we could assume $\mathbf{P}_1 = \mathbf{0}$, for example, express the positions of all the other atoms in terms of the unit vectors via eq. (1),

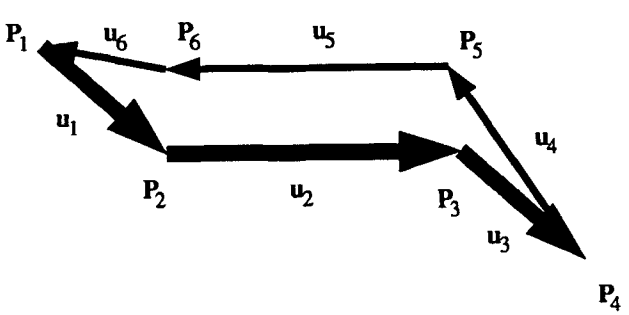

Figure 1. Representation of cyclohexane in terms of unit vectors.

and concentrate on the relations between the unit vectors. The bond length constraint is simply that

$$\mathbf{u}_i \cdot \mathbf{u}_i = 1 \qquad \forall\, i \tag{2}$$

and the bond angle constraint is

$$\mathbf{u}_i \cdot \mathbf{u}_{i+1} = \tfrac{1}{3} \qquad \forall\, i \bmod n \tag{3}$$

since the cosine of the supplement of the tetrahedral angle is exactly ⅓. Since the important constraints in the problem can be expressed so simply in terms of vector scalar products, it is natural to work in terms of the corresponding metric matrix. In general, for any set of vectors, the corresponding metric matrix has its ijth entry defined to be the scalar product of the ith and jth vectors. In this case, the target metric matrix for the molecule is the symmetric $n \times n$ matrix

$$\mathbf{T} = (t_{ij}) = \begin{pmatrix} 1 & \frac{1}{3} & t_{13} & \cdots & \frac{1}{3} \\ \frac{1}{3} & 1 & \ddots & & \\ t_{13} & \ddots & \ddots & & \\ \cdot & & & & \\ \cdot & & & & \\ \cdot & & & & \\ \frac{1}{3} & & & & \end{pmatrix}, \tag{4}$$

where the unspecified elements are restricted by at least

$$-1 \le t_{ij} \le +1. \tag{5}$$

Any particular conformation will have a metric matrix different from that of any other conformation, but our aim must always be to match this template, hence the term *target* metric matrix.

Since conformational analysis of molecules under the rigid valence geometry assumption is usually described in terms of dihedral angles, it may be helpful to illustrate the corresponding ideas in terms of metric matrices. Suppose we had only the first four atoms and hence first three unit vectors of Figure 1 as part of an acyclic chain. Then,

$$\mathbf{T} = \begin{pmatrix} 1 & \frac{1}{3} & t_{13} \\ \frac{1}{3} & 1 & \frac{1}{3} \\ t_{13} & \frac{1}{3} & 1 \end{pmatrix} \tag{6}$$

and of course $-1 \le t_{13} \le 1$. To correspond to atomic coordinates in R^n, there must be n positive eigenvalues of $\mathbf{T}$ and the rest must be zero.[5] ($\mathbf{T}$ being real and symmetric guarantees the eigenvalues will be real.) In this case, the eigenvalues are: $\lambda_1 = 1 - t_{13} \ge 0$ for $t_{13} \le 1$, $\lambda_2 = 1 + t_{13}/2 - (9t_{13}^2 + 8)^{1/2}/6 \ge 0$ for $t_{13} \ge -7/9$ and $\lambda_3 = 1 + t_{13}/2 + (9t_{13}^2 + 8)^{1/2}/6 \ge 1$ for all t_{13}. Thus,

$$-7/9 \le t_{13} \le 1 \tag{7}$$

and the lower limit corresponds to the planar *cis* conformation, where $\mathbf{T}$ has rank 2, and the upper limit is the planar *trans* conformation. Everywhere between, the conformation is nonplanar. An easier

way of locating the planar conformations is by solving the necessary condition det (**T**) = 0, which is quadratic in t_{13}. This guarantees that at least one of the three eigenvalues of **T** must be zero (i.e., its rank is no more than 2), and, as it works out, the remaining two are positive, as required. By looking at the components of $\mathbf{u}_1$ and $\mathbf{u}_3$ that are orthogonal to $\mathbf{u}_2$, it is easy to show that the dihedral angle

$$\phi = \arccos\left(\frac{1}{8} - \frac{9}{8}t_{13}\right) \tag{8}$$

with the usual convention that *cis* = 0.

For a chain of four ideal tetrahedral carbons, the full conformation space can be summarized by eq. (7). But what does the conformation space look like for a chain of five carbons? Now,

$$\mathbf{T} = \begin{pmatrix} 1 & \frac{1}{3} & t_{13} & t_{14} \\ \frac{1}{3} & 1 & \frac{1}{3} & t_{24} \\ t_{13} & \frac{1}{3} & 1 & \frac{1}{3} \\ t_{14} & t_{24} & \frac{1}{3} & 1 \end{pmatrix}, \tag{9}$$

where t_{13} and t_{24} are restricted to the usual *cis*/*trans* range and $-1 \leq t_{14} \leq 1$. To restrict the conformations to R^3, we must have det (**T**) = 0, which is quadratic in each of t_{13}, t_{24}, and t_{14}. In Figure 2, the conformation space is displayed within the $[-1, +1]$ cube of these three variables. The surface is a smooth pillow shape, with straight "seams" at the extremes of the three variables. It is important to note that the dimensionality constraint on the molecule has reduced the conformation space to a surface within the whole cube of the three parameters, and paths of conformational change (without steric hindrance) look like loops.

Now in the case of cyclic molecules, the ring closure constraint requires that

$$\sum_{i=1}^{n} \mathbf{u}_i = \mathbf{0}, \tag{10}$$

which implies that $\mathbf{u}_j \cdot \Sigma_i \mathbf{u}_i = 0$ for all j. This says that the kernel of **T** must include the vector with all unit components, $\mathbf{e} = (1, 1, \ldots, 1)^T$, i.e.,

$$\mathbf{Te} = \mathbf{0}. \tag{11}$$

The main problem in all of this is to restrict the conformations to R^3. Because any real, symmetric matrix can be expressed in terms of its (not necessarily distinct but real) eigenvalues, $\lambda_1, \ldots, \lambda_n$, and corresponding (chosen to be orthonormal) eigenvectors, $\mathbf{v}_1, \ldots, \mathbf{v}_n$, one can enforce the dimen-

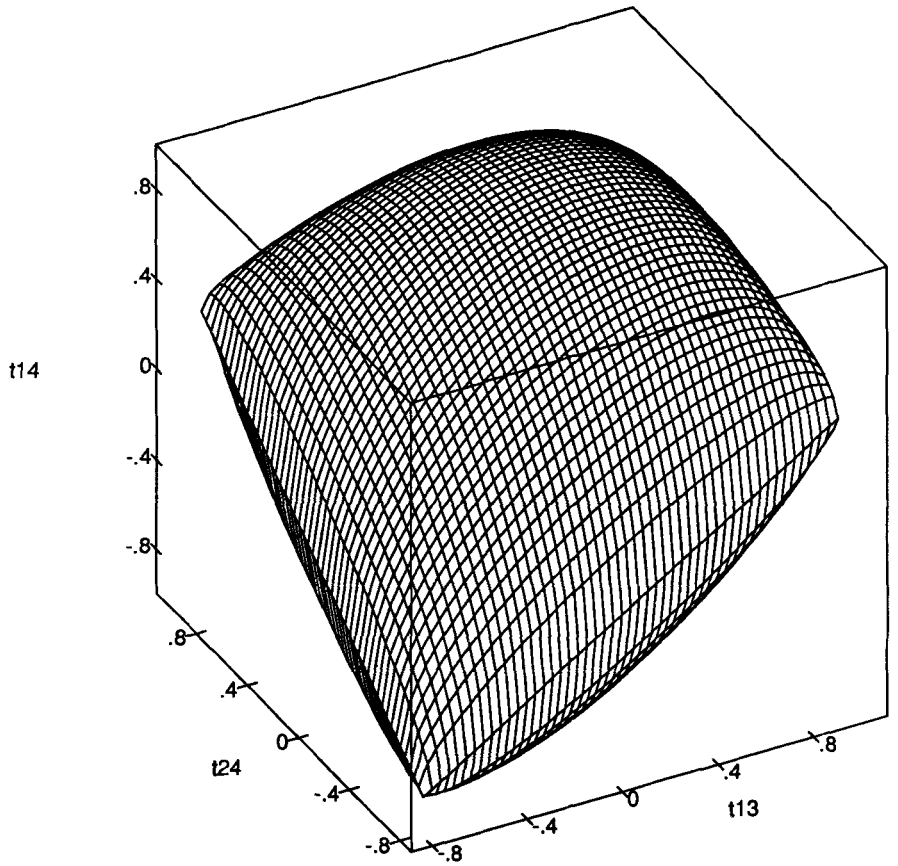

Figure 2. Conformation space allowed to a five-carbon chain, expressed in terms of the three variable elements of the metric matrix.

sionality constraint by requiring there be only three nonzero eigenvalues:

$$\mathbf{T} = \sum_{i=1}^{3} \lambda_i \mathbf{v}_i \mathbf{v}_i^T. \tag{12}$$

As long as the three eigenvalues are nonnegative, the atomic coordinates in R^3 for atom i can be immediately calculated from the components of the eigenvectors and eq. (1):

$$\mathbf{u}_i = (\lambda_1^{1/2} v_{1i}, \lambda_2^{1/2} v_{2i}, \lambda_3^{1/2} v_{3i})^T. \tag{13}$$

This follows the same derivation as the EMBED algorithm[5] of distance geometry.

In some of the applications described in the next sections, the elements of the metric matrix were varied to enforce the dimensionality constraint. An alternative approach is to construct a trial metric matrix, **M**, out of three nonnegative eigenvalues and three orthonormal eigenvectors chosen to be orthogonal to **e**. Then the eigenvalues can be adjusted subject to the constraint $\lambda_i \geq 0$, and the eigenvectors can be rotated in the subspace of R^n orthogonal to **e**, until the elements of **M** match the specified elements of **T**. Let the vectors $\mathbf{w}_1, \ldots, \mathbf{w}_n$ be an orthonormal basis set for R^n where $\mathbf{w}_n = \mathbf{e}$. Then, the $n \times n$ elementary rotation matrix for rotating through angle θ in the plane spanned by $\mathbf{w}_i$ and $\mathbf{w}_j$ is

$$\mathbf{R}_{ij}(\theta) = \cos\theta \mathbf{w}_i \mathbf{w}_i^T + \sin\theta \mathbf{w}_j \mathbf{w}_i^T - \sin\theta \mathbf{w}_i \mathbf{w}_j^T + \cos\theta \mathbf{w}_j \mathbf{w}_j^T + \sum_{k \neq i,j} \mathbf{w}_k \mathbf{w}_k^T. \tag{14}$$

In R^n, there are $(n-1)(n-2)/2$ such elementary rotations orthogonal to **e**, and any rotation can be produced as a composition of them.

Generally, conformations will be described in terms of Cartesian coordinates, where each axis of the coordinate system corresponds to some adjustable element of the metric matrix. In the case of cycloheptane, however, it is convenient to use the generalization of spherical coordinates to spaces of high dimension. Suppose we had a point $\mathbf{p} \in R^n$ that we need to convert to "hyperspherical" coordinates. As in spherical coordinates, there will be a radius r, an angular coordinate θ_1 with range 0 to 2π, and $n-2$ angular coordinates in the range 0 to π.

$$\begin{aligned} p_n &= r \cos\theta_{n-1} \\ p_k &= r \left(\prod_{j=k}^{n-1} \sin\theta_j \right) \cos\theta_{k-1} \\ &\quad \forall\, k = 2, \ldots, n-1. \\ p_1 &= r \left(\prod_{j=1}^{n-1} \sin\theta_j \right) \end{aligned} \tag{15}$$

It is easy to show that $\|\mathbf{p}\| = r$, so to convert further from Cartesian to hyperspherical coordinates, normalize **p** and proceed in the order indicated: $\theta_{n-1} = \arccos p_n$, $\sin\theta_{n-1} = +(1 - \cos^2\theta_{n-1})^{1/2}$, $\theta_{n-2} = \arccos(p_{n-1}/\sin\theta_{n-1})$, and so on, always taking the arccos in the range 0 to π. Finally, the sign of p_1 determines the sign of $\sin\theta_1$ and hence whether θ_1 is in the range π to 2π.

CYCLOPROPANE

For cyclopropane, the target metric matrix would be

$$\mathbf{T} = \begin{pmatrix} 1 & 1/3 & 1/3 \\ 1/3 & 1 & 1/3 \\ 1/3 & 1/3 & 1 \end{pmatrix} \tag{16}$$

but this fails to satisfy the closure constraint, eq. (11). If the bond angles are required to be all the same, and that value, β, is adjustable to ensure closure, the result is

$$\begin{pmatrix} 1 & \beta & \beta \\ \beta & 1 & \beta \\ \beta & \beta & 1 \end{pmatrix} \begin{pmatrix} 1 \\ 1 \\ 1 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}, \tag{17}$$

which has the unique solution $\beta = -1/2$. This corresponds to a bond angle of $\pi - \arccos\beta = \pi/3 = 60°$. The metric matrix with $\beta = -1/2$ has rank 2, corresponding to the fact that cyclopropane is planar.

CYCLOBUTANE

As in the cyclopropane case, the target metric matrix for cyclobutane with tetrahedral bond angles violates the closure constraint, so we once again relax to the variable but uniform bond angle problem, having trial metric matrix

$$\mathbf{M} = \begin{pmatrix} 1 & \beta & m_{1,3} & \beta \\ \beta & 1 & \beta & m_{2,4} \\ m_{1,3} & \beta & 1 & \beta \\ \beta & m_{2,4} & \beta & 1 \end{pmatrix}. \tag{18}$$

The closure constraint, eq. 11, has the unique solution

$$m_{1,3} = m_{2,4} = -1 - 2/\beta \tag{19}$$

and of course then **M** has rank ≤ 3 because it has order 4 and **e** is in its kernel. We can now explore the conformation space of cyclobutane in terms of one adjustable parameter, which we choose to be β. The constraint $-1 \leq m_{1,3} \leq 1$ together with eq. (19) implies the range $0 \geq \beta \geq -1$. The minimal value of β gives a rank 1 **M** matrix, corresponding to the physically unreasonable structure where the first and third carbon atoms are superimposed and lie one unit along the x-axis from the superimposed second and fourth carbon atoms (see Fig. 3). As β increases, the conformation immediately becomes three-dimensional, reaching a maximal thickness when $\beta = -1/3$, where the four carbons occupy the corners of the unit tetrahedron. Eventually, the max-

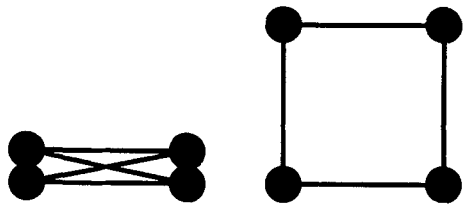

Figure 3. Extreme conformations of cyclobutane restricted to equal bond angles: the physically unrealistic one-dimensional 0° conformer and the experimentally observed two-dimensional 90° conformer.

imum bond angle of 90° is achieved when $\beta = 0$. At that point, **M** has rank 2, corresponding to the physically realistic square planar conformation of cyclobutane.

CYCLOPENTANE

Proceeding as before, we have a trial metric matrix

$$\mathbf{M} = \begin{pmatrix} 1 & \beta & m_{1,3} & m_{1,4} & \beta \\ \beta & 1 & \beta & m_{2,4} & m_{2,5} \\ m_{1,3} & \beta & 1 & \beta & m_{3,5} \\ m_{1,4} & m_{2,4} & \beta & 1 & \beta \\ \beta & m_{2,5} & m_{3,5} & \beta & 1 \end{pmatrix} \quad (20)$$

which satisfies the ring closure condition only when

$$m_{1,3} = m_{1,4} = m_{2,4} = m_{2,5} = m_{3,5} = -\tfrac{1}{2} - \beta, \quad (21)$$

leading as before to a single parameter exploration of conformation space. The constraints $-1 \leq m_{1,3} \leq 1$ and $-1 \leq \beta \leq 1$ together with eq. (21) implies the range $\tfrac{1}{2} \geq \beta \geq -1$. When **M** is expressed entirely in terms of β by substituting in eq. (21), one can analytically find the eigenvalues of **M** to be 0, $[5 - 5^{1/2}(4\beta + 1)]/4$ twice, and $[5 + 5^{1/2}(4\beta + 1)]/4$ twice. To ensure nonnegative eigenvalues, we must have $(-5^{1/2} - 1)/4 \leq \beta \leq (5^{1/2} - 1)/4$, where the lower limit corresponds to a nonphysical planar pentagram configuration with bond angles of 36°, and the upper limit corresponds to the realistic planar pentagon configuration with bond angles of 108° (see Fig. 4).

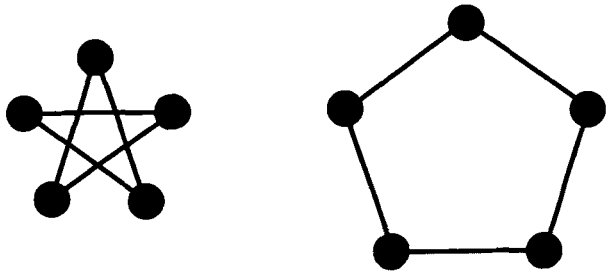

Figure 4. Extreme conformations of cyclopentane restricted to equal bond angles: the nonphysical planar pentagram configuration with bond angles of 36° and the realistic planar pentagon configuration with bond angles of 108°.

Between these two extremes, the molecule passes through a continuum of four-dimensional conformations. Of course, relaxing the constraint that all bond angles must be equal would allow also some three-dimensional puckered conformations.

CYCLOHEXANE

Cyclohexane is the smallest cycloalkane where tetrahedral bond angles are allowed in three dimensions, so the target metric matrix is

$$\mathbf{T} = \begin{pmatrix} 1 & \tfrac{1}{3} & t_{1,3} & t_{1,4} & t_{1,5} & \tfrac{1}{3} \\ \tfrac{1}{3} & 1 & \tfrac{1}{3} & t_{2,4} & t_{2,5} & t_{2,6} \\ t_{1,3} & \tfrac{1}{3} & 1 & \tfrac{1}{3} & t_{3,5} & t_{3,6} \\ t_{1,4} & t_{2,4} & \tfrac{1}{3} & 1 & \tfrac{1}{3} & t_{4,6} \\ t_{1,5} & t_{2,5} & t_{3,5} & \tfrac{1}{3} & 1 & \tfrac{1}{3} \\ \tfrac{1}{3} & t_{2,6} & t_{3,6} & t_{4,6} & \tfrac{1}{3} & 1 \end{pmatrix} \quad (22)$$

The ring closure condition yields six linear equations in the indeterminate $t_{i,j}$s, but an analytical solution of the characteristic equation is infeasible as a way of determining the eigenvalues. If one assumes in addition that $t_{1,4} = t_{2,5} = t_{3,6} = -1$, then the eigenvalues can be easily determined: 0, 0, 0, $\tfrac{2}{3}$, $\tfrac{8}{3}$, $\tfrac{8}{3}$. This corresponds to the chair form.

The various boat puckers and skew-boat conformations of cyclohexane are known to lie on a one-dimensional closed loop in conformation space, where the single parameter is often referred to as a pseudorotation. The idea is to start at one exact boat conformation and rotate its eigenvectors in $\mathbb{R}^6$ while adjusting the eigenvalues so as to always maintain the 12 target values in eq. (22), and thus explore the pseudorotation. Different values were chosen along the path for $t_{1,3}$, essentially a dihedral angle, to drive the exploration forward to new conformations. Thus, $t_{1,3}$ is chosen to be our single pseudorotation parameter. The starting boat conformation has metric matrix

$$\mathbf{B} = \begin{pmatrix} 1 & \tfrac{1}{3} & -\tfrac{7}{9} & -\tfrac{5}{9} & -\tfrac{1}{3} & \tfrac{1}{3} \\ \tfrac{1}{3} & 1 & \tfrac{1}{3} & -\tfrac{1}{3} & -1 & -\tfrac{1}{3} \\ -\tfrac{7}{9} & \tfrac{1}{3} & 1 & \tfrac{1}{3} & -\tfrac{1}{3} & -\tfrac{5}{9} \\ -\tfrac{5}{9} & -\tfrac{1}{3} & \tfrac{1}{3} & 1 & \tfrac{1}{3} & -\tfrac{7}{9} \\ -\tfrac{1}{3} & -1 & -\tfrac{1}{3} & \tfrac{1}{3} & 1 & \tfrac{1}{3} \\ \tfrac{1}{3} & -\tfrac{1}{3} & -\tfrac{5}{9} & -\tfrac{7}{9} & \tfrac{1}{3} & 1 \end{pmatrix}, \quad (23)$$

which has eigenvalues 0, 0, 0, $\tfrac{8}{3}$, $\tfrac{8}{9}$, $\tfrac{22}{9}$ and corresponding orthogonal but unnormalized eigenvectors

$$\mathbf{V} = \begin{pmatrix} 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \end{pmatrix} \begin{pmatrix} -1 \\ -3 \\ -1 \\ 1 \\ 3 \\ 1 \end{pmatrix} \begin{pmatrix} -1 \\ 0 \\ 1 \\ -1 \\ 0 \\ 1 \end{pmatrix} \begin{pmatrix} 1 \\ 0 \\ -1 \\ -1 \\ 0 \\ 1 \end{pmatrix} \begin{pmatrix} 1 \\ -8 \\ 1 \\ 10 \\ -14 \\ 10 \end{pmatrix} \begin{pmatrix} 2 \\ -2 \\ 2 \\ -1 \\ 0 \\ -1 \end{pmatrix} \quad (24)$$

To set up the 10 elementary rotations orthogonal to **e** in $\mathbb{R}^6$, one needs any orthornormal basis including

e, and that need not be the starting eigenvectors **V**. Denote such a basis as a *rotation basis*. I have experimented with a few possibilities and found the results do not depend significantly on the rotation basis used. Any new conformation of the boat family is determined by the target value of $t_{1,3}$, and it corresponds to certain values of the three nonzero eigenvalues and certain angles of the 10 rotations performed on the original eigenvectors **V** by elementary rotation matrices defined by the rotation basis. Thus there is a vector **r** of 13 variables

$$\begin{aligned} r_1 &= \lambda_1 \\ r_2 &= \lambda_2 \\ r_3 &= \lambda_3 \\ r_4 &= \theta_{1,2} \\ r_5 &= \theta_{1,3} \\ &\cdot \\ &\cdot \\ &\cdot \\ r_{13} &= \theta_{4,5} \end{aligned} \tag{25}$$

and a vector **s** of 13 equations

$$\begin{aligned} s_1(\mathbf{r}) &= m_{1,1} - 1 = 0 \\ &\cdot \\ &\cdot \\ &\cdot \\ s_6(\mathbf{r}) &= m_{6,6} - 1 = 0 \\ s_7(\mathbf{r}) &= m_{1,2} - \tfrac{1}{3} = 0 \\ &\cdot \\ &\cdot \\ &\cdot \\ s_{12}(\mathbf{r}) &= m_{1,6} - \tfrac{1}{3} = 0 \\ s_{13}(\mathbf{r}) &= m_{1,3} - t_{1,3} = 0 \end{aligned} \tag{26}$$

requiring certain metric matrix elements to have set target values. In eq. (25), θ_{ij} refers to the angle of rotation for the elementary rotation $\mathbf{R}_{ij}(\theta_{ij})$ defined by eq. (14) where the rotation basis is numbered such that $\mathbf{e} = \mathbf{w}_6$. As usual, the Jacobian matrix **J** for this system of equations has its ijth element defined to be $\partial s_i/\partial r_j$. The implicit closure constraint and symmetry often cause **J** to have rank 12 or less.

The exploration procedure is conceptually simple but computationally messy. Start at the boat conformation of eq. (23), which implies that $\mathbf{r} = (\frac{8}{3}, \frac{22}{9}, \frac{8}{9}, 0, \ldots, 0)$, the eigenvectors are **V** in eq. (24), and $t_{1,3} = -\frac{7}{9}$. Choose any orthonormal basis set **W** in R^6 such that $\mathbf{e} = \mathbf{w}_6$, for example, the boat eigenvectors **V** themselves, suitably rearranged. Initially, all 13 equations are satisfied: $\mathbf{s}(\mathbf{r}) = \mathbf{0}$. Whenever the equations are satisfied, we can always calculate the corresponding conformation from **r** by performing the 10 elementary rotations of **V** according to the rotation basis **W** and then building the metric matrix out of the first three rotated eigenvectors and the first three eigenvalues stored in the beginning of **r**. Now, if we increment $t_{1,3}$ slightly, the equations are no longer satisfied, but new values of the variables **r**′ can be found by Newton's method,

$$\mathbf{r}' = \mathbf{r} - \mathbf{J}^{-1}\mathbf{s}(\mathbf{r}), \tag{27}$$

where the Jocabian is approximated by differences and the change in variables is calculated by Gauss–Jordan elimination with partial pivoting. If the Jacobian is singular, the zero rows in the pivoted transformed Jacobian are deleted and the corresponding variables do not change ($r_i' = r_i$). The pseudorotation can be traced out in this fashion by incrementing $t_{1,3}$ from $-\frac{7}{9}$ to $-\frac{1}{3}$ in steps of $-\frac{1}{10}$, readjusting eigenvalues and rotations at each step. The pathway is simple in terms of metric matrix elements, but the small changes in eigenvalues are not monotonic. With a carefully chosen rotation basis, derived from the differences in eigenvectors between two successive boat conformations, there are only four rotation angles that change significantly.

Suppose that the global structure of the cyclohexane conformation space was not known in advance. How could one thoroughly locate all possibilities? Although the target matrix in eq. (22) has nine undetermined entries, there are six independent, linear, ring closure equations that can be solved for the six dihedral elements (t_{13}, t_{24}, etc.) in terms of the three transannular elements, t_{14}, t_{25}, and t_{36} (see Fig. 1).

$$\begin{aligned} t_{13} &= t_{46} = -t_{14}/2 + t_{25}/2 - t_{36}/2 - 5/6 \\ t_{24} &= t_{15} = -t_{14}/2 - t_{25}/2 + t_{36}/2 - 5/6 \\ t_{35} &= t_{26} = +t_{14}/2 - t_{25}/2 - t_{36}/2 - 5/6. \end{aligned} \tag{28}$$

Thus, the conformation space that must be searched is a cube, each side running through the range $[-1, +1]$ for each of the transannular elements, as shown in Figure 5. The restriction of each of the six dependent dihedral elements to the range $[-1, +1]$ introduces linear inequality constraints, further restricting the cyclohexane conformation space to the trigonal bipyramid drawn in the cube. The bipyramid's corners are at $(t_{14}, t_{25}, t_{36}) = (-1, -1, -1), (-1, -1, \frac{1}{3}), (-1, \frac{1}{3}, -1), (\frac{1}{3}, -1, -1)$, and $(\frac{1}{3}, \frac{1}{3}, \frac{1}{3})$. In general, any set of linear inequality constraints would leave a convex, fully three-dimensional feasible region, if any. However, the rank constraint on the metric matrix in this case reduces the allowed conformation space to a single point, the chair form, and a circle disjoint from it, the boat pseudorotation path. To locate these, I simply searched out the interior of the bipyramid on a three-dimensional grid with a 0.05 step size. At each grid point, the entire metric matrix is fully specified by the ring closure relations, eq. (28), so one may test the deviation of the rank from the desired value of three by transforming it to diagonal form using Gauss–Jordan elimination with partial pivoting and summing the absolute values of the entries in the last three rows. If this sum is less than, say, a cutoff

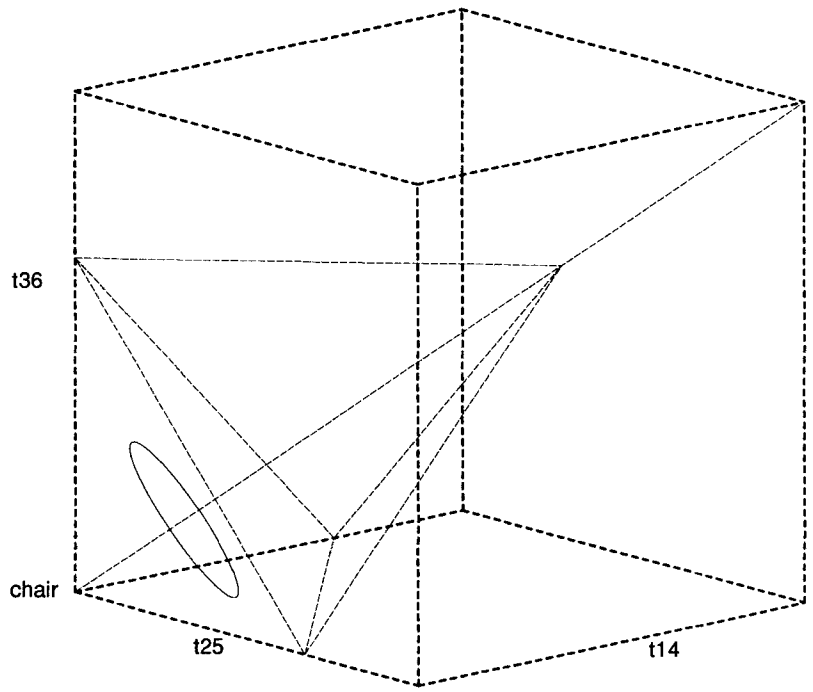

Figure 5. Conformation space of cyclohexane in terms of the three transannular bond vector inner products, t_{14}, t_{25}, and t_{36}. The cube in heavy broken lines is the entire space, with each inner product running from -1 to $+1$. The $(-1, -1, -1)$ corner is labeled "chair." The trigonal bipyramid formed by the chair corner and the thin broken lines is the region allowed by the linear ring closure constraints. The boat/skew boat pseudorotation family of conformations corresponds to the solid line circle, which is normal to and centered around the major diagonal of the cube.

value of 0.1, then the metric matrix had approximately rank three. In this way, I was able to map out the chair point at $(-1, -1, -1)$, and the boat pseudorotation one-dimensional continuum, and be sure there were no other possibilities. The boat and twist-boat conformations are located on the circle

$$(t_{14}, t_{25}, t_{36}) = \left(\frac{-19 + 4\cos\psi + 4\sqrt{3}\sin\psi}{27}, \frac{-19 + 4\cos\psi - 4\sqrt{3}\sin\psi}{27}, \frac{-19 - 9\cos\psi}{27}\right) \quad (29)$$

and perfect boat conformations occur at $\psi = 0, 2\pi/3$, and $4\pi/3$, which is where the circle in Figure 5 touches the faces of the cube. Using eqs. (29), (28), and (8), one can easily calculate the dihedral angles for any boat or twist-boat conformation. Curiously enough, there is a narrow double line, not shown in the figure, running from each boat to the chair. Each line corresponds to a conversion between chair and boat while maintaining perfectly rigid bond lengths and angles by making a minor excursion ($\lambda_4 \approx 0.27$) into the fourth dimension. By way of comparison, the first three eigenvalues of such a transition conformation are typically 2.66, 2.5, and 0.55. Of course, a real cyclohexane molecule converts between boat and chair mostly via a slight bond angle deformation.

CYCLOHEPTANE

There have been relatively few studies published on the conformation space of cycloheptane, and most have focused on a few local energy minima, such as the chair, twist-chair, boat, and twist-boat.[8] It is generally conceded that the exact bond length and tetrahedral bond angle constraints imply two separate one-dimensional pseudorotation paths, the chair/twist-chair and the boat/twist-boat, but this appears to rest upon examination of physical models, rather than an exhaustive mathematical analysis. Bocian et al.[9] give a parameterization of cycloheptane pseudorotations based on the displacements of the carbon atoms from planarity, but it is not clear that all allowed conformations have been accounted for. Bottomley[10] has numerically determined the full paths of the two pseudorotations in terms of a particular Cartesian coordinate system and dihedral angles. His specialized analysis is actually rather equivalent to that given below.

Proceeding as in the cyclohexane case, we now

have a larger target metric matrix with more undetermined elements.

$$\mathbf{T} = \begin{pmatrix} 1 & 1/3 & t_{1,3} & t_{1,4} & t_{1,5} & t_{1,6} & 1/3 \\ 1/3 & 1 & 1/3 & t_{2,4} & t_{2,5} & t_{2,6} & t_{2,7} \\ t_{1,3} & 1/3 & 1 & 1/3 & t_{3,5} & t_{3,6} & t_{3,7} \\ t_{1,4} & t_{2,4} & 1/3 & 1 & 1/3 & t_{4,6} & t_{4,7} \\ t_{1,5} & t_{2,5} & t_{3,5} & 1/3 & 1 & 1/3 & t_{5,7} \\ t_{1,6} & t_{2,6} & t_{3,6} & t_{4,6} & 1/3 & 1 & 1/3 \\ 1/3 & t_{2,7} & t_{3,7} & t_{4,7} & t_{5,7} & 1/3 & 1 \end{pmatrix}. \quad (30)$$

Ring closure provides 7 linear equations among the 14 indeterminate elements, leaving 7 variables, which we will now take to be the dihedral elements $t_{1,3}$, $t_{2,4}$, etc.

$$\begin{array}{lccccccc} t_{1,4} = & -t_{1,3} & -t_{2,4} & & & +t_{5,7} & & -5/6 \\ t_{2,5} = & & -t_{2,4} & -t_{3,5} & & & +t_{1,6} & -5/6 \\ t_{3,6} = & & & -t_{3,5} & -t_{4,6} & & & +t_{2,7} \quad -5/6 \\ t_{4,7} = & +t_{1,3} & & & -t_{4,6} & -t_{5,7} & & -5/6 \\ t_{1,5} = & & +t_{2,4} & & & -t_{5,7} & -t_{1,6} & -5/6 \\ t_{2,6} = & & & +t_{3,5} & & & -t_{1,6} & -t_{2,7} \quad -5/6 \\ t_{3,7} = & -t_{1,3} & & & +t_{4,6} & & & -t_{2,7} \quad -5/6. \end{array} \quad (31)$$

At this point in cyclohexane, one could simply find all the approximate solutions by a grid search in the three indeterminate elements. Now, however, the corresponding grid search over the seven dihedral elements would not only be computationally very lengthy for a reasonably fine grid, but even for a fine grid, the 7-dimensional grid points are in general so distant from the 1-dimensional solution sets that it is very hard to recognize grid points that are approximate solutions in that the corresponding metric matrices are nearly of rank 3 and all the elements have absolute value ≤ 1.

Likewise, exploring the conformation space in terms of rotating eigenvectors is not very thorough because it is much harder in the case of cycloheptane to determine a few correct metric matrices for different conformations by inspection. One can find the exact boat, for example, by demanding the metric matrix **M** for this conformation be the target matrix **T** of eq. (30) plus the symmetry constraints, $\{m_{1,6} = m_{4,6}, m_{2,7} = m_{3,5}, m_{1,3} = m_{2,4}\}$, and that the blunt end of the boat be exactly cis: $m_{5,7} = -7/9$. Then, requiring the determinant of the submatrix of the first 4 rows and columns of **M** to be zero yields a quartic equation in $m_{2,4}$, two roots of which are real. Choosing one of those roots and then setting to zero the determinant of the submatrix of the last four rows and columns of **M** gives one root for $m_{4,6}$. After substituting back in, the determinant of the submatrix of rows and columns 2, . . . , 5 yields one root for $m_{3,5}$. Finally, the rest of the elements are determined by the closure equations. The result is

$$\mathbf{M} = \begin{pmatrix} 1 & 1/3 & m_{1,3} & m_{1,4} & m_{1,5} & m_{1,6} & 1/3 \\ & 1 & 1/3 & m_{1,3} & m_{2,5} & m_{2,6} & m_{2,7} \\ & & 1 & 1/3 & m_{2,7} & m_{2,6} & m_{2,5} \\ & & & 1 & 1/3 & m_{1,6} & m_{1,5} \\ & & & & 1 & 1/3 & -7/9 \\ & & & & & 1 & 1/3 \\ & & & & & & 1 \end{pmatrix}, \quad (32)$$

where

$$\begin{aligned} m_{1,3} &= -5/3 + 5\sqrt{6}/9 \\ m_{1,4} &= 31/18 - 10\sqrt{6}/9 \\ m_{1,5} &= -8/9 + 2\sqrt{6}/9 \end{aligned}$$

$$\begin{aligned} m_{1,6} &= -5/6 + \sqrt{6}/3 \\ m_{2,6} &= -\sqrt{6}/3 \\ m_{2,5} &= \frac{104\sqrt{6} - 378 \pm 3(46833 - 18268\sqrt{6})^{1/2}}{-117 + 180\sqrt{6}} \\ m_{2,7} &= \frac{46 - 26\sqrt{6} \mp (46833 - 18268\sqrt{6})^{1/2}}{-39 + 60\sqrt{6}} \\ m_{2,5} &= 2\sqrt{6}/9 - m_{2,7}. \end{aligned} \quad (33)$$

The boat conformation corresponds to the + alternative for $m_{2,5}$ and the − alternative for $m_{2,7}$; the chair corresponds to the opposite alternatives. In either conformation, bond vectors 1 and 4 appear to be antiparallel, but more precisely $m_{1,4} = -.999433$ . . . , corresponding to the slight taper observed earlier.[10]

This general approach of solving for a conformation as a sequence of equations in terms of determinants of submatrices can be used to explore the entire conformation of cycloheptane. Since we require a conformation in R^3, the determinant of any order 4 principal minor of the metric matrix must be zero. Given the ring closure eq. (31), one can choose a sequence of row/column subsets whose determinants = 0 amount to quadratic equations in a single unknown dihedral matrix element. Thus, the procedure is simply: choose values for $m_{1,3}$ and $m_{2,4}$; det ([1, 2, 3, 4]) = 0 produces 2 roots for $m_{5,7}$; the value of $m_{1,3}$ and the two values of $m_{5,7}$ with det ([4, 5, 6, 7]) = 0 produces 4 roots for $m_{4,6}$; the value of

$m_{1,3}$ and the 4 values of $m_{4,6}$ with det ([1, 2, 3, 7]) = 0 produces 8 roots for $m_{2,7}$; the value of $m_{2,4}$ and the 2 values of $m_{5,7}$ with det ([1, 5, 6, 7]) = 0 produces 4 roots for $m_{1,6}$; the value of $m_{2,4}$ and the 4 values of $m_{1,6}$ with det ([2, 3, 4, 5]) = 0 produces 8 roots for $m_{3,5}$. The conformations of cycloheptane are located by searching the full ranges for $m_{1,3}$ and $m_{2,4}$ in a two-dimensional grid with step size 0.01, using this solution sequence to produce between 0 and 8 approximate solutions at each grid point. Since in general a grid point need not intersect some part of the exact one-dimensional solution space, all approximate solutions are refined using Newton's method. Refinement is carried out in terms of 18 coordinates of unit vectors (u_{1x}, u_{2x}, u_{2y}, and all three coordinates of each of the other unit vectors), so approximate unit vector coordinates are first calculated from the approximate metric matrix according to eq. (13). Then, the matching 18 equations are the 7 bond length constraints, the 7 bond angle constraints, the fixed value of $m_{1,3}$ at the grid point, and the ring closure constraint expressed as each coordinate of the sum of the unit vectors being zero. Very few approximate solutions failed to converge, and most succeeded within a few iterations.

The result of this exhaustive search is a large number of points within the seven-dimensional cube of the dihedral elements of the metric matrix. These points do indeed lie along one-dimensional, closed paths, one for the chair pseudorotation and one for the boat. The two loops do not intersect each other or themselves, although it is difficult to see this using a three-dimensional projection of the full space, and one must instead examine the interpoint distance matrix. Figures 6 and 7 show two different views of three-dimensional projections of these paths, as traced out by the numerical exhaustive search. The simple, slightly wavy loop corresponds to the boat pseudorotation, and the double loop is the chair pseudorotation. Indeed, the seven cyclic permutations of eq. (33) for the boat lie precisely on the numerical boat loop, and the seven exact chair conformations lie on the chair loop. Since the seven exact boat(/chair) conformations are only cyclic permutations of each other, their center of mass **c** must lie on the major diagonal of the cube, where every component $c_b(/c_c)$ is the mean of the seven values in eq. (33). Of course, the seven conformations are equidistant from this center at a radius $r_b(/r_c)$ that can be readily calculated from eq. (33). What is not so obvious is that all the numerical points on the boat pseudorotation path lie quite accurately on a four-dimensional sphere embedded in the seven-dimensional cube having center c_b and radius r_b, while all the numerical points on the chair pseudorotation path lie on a six-dimensional sphere at center c_c and radius r_c.

The further characterize the two pseudorotation paths, I turned to numerical fitting techniques, given the exact sphere centers and radii, and 300 numerical twist boat conformations plus 500 numerical twist chair conformations. First, translate the origin of the points making up one loop to the appropriate exact sphere center. Then, determine the local principal coordinate axes by diagonalizing the inertial tensor of the points. The eigenvalues corresponding to the

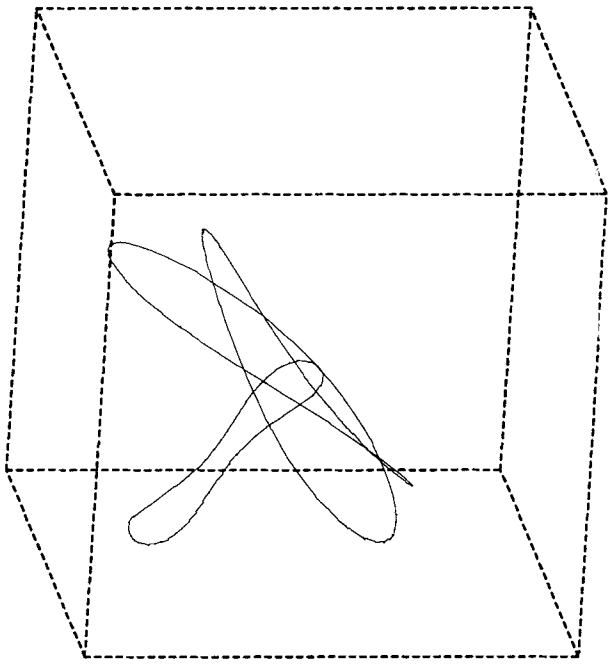

Figure 6. One possible projection of the conformation space of cycloheptane in terms of the seven dihedral angle metric matrix elements. The cube in heavy broken lines is the entire space, with each inner product running from −1 to +1. The boat pseudorotation family of conformations corresponds to the wavy solid line loop centered around the major diagonal of the cube.

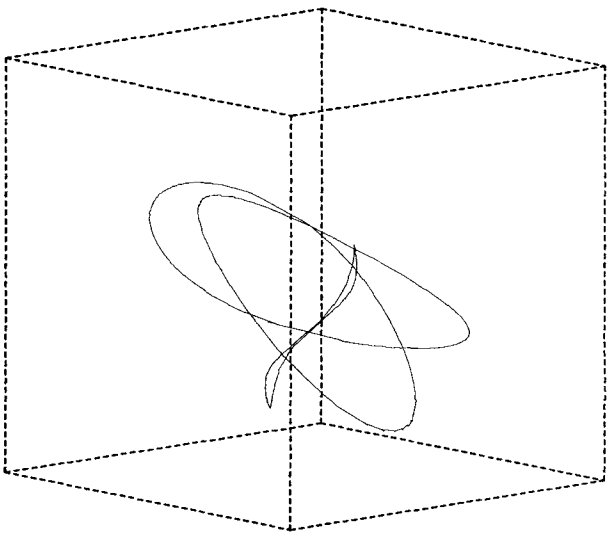

Figure 7. Another possible projection of the conformation space of cycloheptane in terms of the seven dihedral angle metric matrix elements. The cube in heavy broken lines is the entire space, with each inner product running from −1 to +1. The chair pseudorotation family of conformations corresponds to the two-fold solid line loop centered around the major diagonal of the cube.

Table I. Description of the cycloheptane boat pseudorotation in terms of the sphere center and radius in the seven-dimensional space of metric matrix dihedral elements, the principal axes of the path, and the dependence of the hyperspherical coordinate angles of the path in principal axes space on the pseudorotation parameter.

	$m_{1,3}$	$m_{2,4}$	$m_{3,5}$	$m_{4,6}$	$m_{5,7}$	$m_{6,1}$	$m_{7,2}$
$\mathbf{v}_1$ =	0.2072	0.0152	−0.2335	0.4208	−0.5319	0.5273	−0.4052
$\mathbf{v}_2$ =	−0.4795	0.5288	−0.4809	0.3289	−0.1043	−0.1411	0.3467
$\mathbf{v}_3$ =	0.0181	−0.5364	0.2148	0.4317	−0.3954	−0.2463	0.5124
$\mathbf{v}_4$ =	−0.5342	0.1093	0.4819	−0.3357	−0.3529	0.4554	0.1606

c_b = −0.3709613; r_b = 0.7196961. $\theta_2 = \pi/2 + 0.0078 \cos\theta_1 - 0.0079 \sin\theta_1 + 0.0667 \cos(3\theta_1) + 0.0180 \sin(3\theta_1)$; $\theta_3 = \pi/2 - 0.0124 \cos\theta_1 + 0.0206 \sin\theta_1 - 0.0185 \cos(3\theta_1) + 0.0675 \sin(3\theta_1)$.

last three axes of the boat and the last axis of the chair are smaller than the others by one or two orders of magnitude, and the components of the points along these axes look like noise. After converting the points to the principal axes system, I changed to hyperspherical coordinates, according to eq. (15), where p_1 is the most significant component, so that θ_1 corresponds to the most significant angle, having the full range 0 to 2π. Then the other angles were easy to fit to trigonometric series in θ_1 for all the numerical points and the seven exact ones. In this representation, if we were in only three dimensions the pseudorotation paths would look like wavy lines wrapped around the equator, θ_1 would be the longitude, and θ_2 would be the latitude measured from the north pole. The results are summarized in Tables I and II. Note that the full boat pseudorotation is described as θ_1 runs from 0 to 2π, but for the chair it runs from 0 to 4π, corresponding to the double loop seen in Figure 7. Bocian et al.[9] describe these pseudorotation paths as lines wound on a torus, but they are not necessarily in conflict with these results because they parameterized cycloheptane conformation in terms of displacements of the seven carbons from the mean plane, rather than using the seven dihedral metric matrix elements.

To calculate any conformation along the path, choose a value of θ_1, the principal pseudorotation parameter, use the equations in the tables to find the other hyperspherical angles, convert to Cartesian coordinates in the principal axes frame using eq. (15) and the radius in the table, convert to the seven-dimensional space of metric matrix elements according to the principal axis components given in the table, translate the origin from the sphere center to the cube center, and finally convert to the seven dihedral angles according to eq. (8). As it so happens, $\theta_1 = 0$ does not correspond to an exact boat or chair, but one could easily phase shift the trigonomertic fits in the table to do so. Incrementing θ_1 by $2\pi/7$ permutes the dihedral angles two steps in the boat pseudorotation, but incrementing by $4\pi/7$ permutes the chair dihedral angles by one step.

CONCLUSIONS

I have presented a barrage of results for several different cyclic hydrocarbons that the mathematically diligent reader can at least verify, and even reproduce, with the help of a symbolic mathematics program. The underlying point, however, should not be lost: How can we be sure we have found *all* the conformations of a given molecule? For n atoms, a very general algorithm like distance geometry reaches R^{3n} by means of a random sampling that may suffer from various biases. Yet, we have seen that even such a small molecule as cycloheptane has available to it only small, one-dimensional subspaces due to the rigid valence geometry and ring closure constraints, For extremely small molecules, the linearized embedding parameterization of the conformation space in terms of a few unit vectors permits the constraints to be expressed very conveniently,

Table II. Description of the cycloheptane chair pseudorotation in terms of the sphere center and radius in the seven-dimensional space of metric matrix dihedral elements, the principal axes of the path, and the dependence of the hyperspherical coordinate angles of the path in principal axes space on the pseudorotation parameter.

	$m_{1,3}$	$m_{2,4}$	$m_{3,5}$	$m_{4,6}$	$m_{5,7}$	$m_{6,1}$	$m_{7,2}$
$\mathbf{v}_1$ =	−0.0213	0.5033	−0.2097	−0.4362	0.4160	0.2675	−0.5171
$\mathbf{v}_2$ =	−0.5444	0.0904	0.4948	−0.3101	−0.3402	0.4682	0.1398
$\mathbf{v}_3$ =	−0.3746	−0.5947	−0.2296	0.2270	0.5860	0.3130	−0.1122
$\mathbf{v}_4$ =	−0.2792	0.2582	−0.3759	0.5538	−0.0713	−0.2872	−0.5640
$\mathbf{v}_5$ =	−0.3939	0.3345	−0.6476	0.4159	−0.1825	0.2366	0.2281
$\mathbf{v}_6$ =	−0.4346	0.2403	0.0826	−0.1918	0.4352	−0.5785	0.4309

c_c = −0.1292542; r_c = 0.8999872. $\theta_2 = \pi/2 + 0.1984 \cos(\theta_1/2) - 0.1001 \sin(\theta_1/2) + 0.0134 \cos\theta_1 + 0.0238 \sin\theta_1 - 0.0239 \cos(3\theta_1/2) - 0.0301 \sin(3\theta_1/2)$; $\theta_3 = \pi/2 + 0.1072 \cos(\theta_1/2) + 0.1915 \sin(\theta_1/2) + 0.0064 \cos\theta_1 - 0.0126 \sin\theta_1 + 0.0019 \cos(3\theta_1/2) + 0.0440 \sin(3\theta_1/2)$; $\theta_4 = \pi/2 + 0.0203 \cos(\theta_1/2) - 0.0612 \sin(\theta_1/2) - 0.0015 \cos\theta_1 - 0.0097 \sin\theta_1 + 0.1080 \cos(3\theta_1/2) + 0.1352 \sin(3\theta_1/2)$; $\theta_5 = \pi/2 + 0.0141 \cos(\theta_1/2) + 0.0273 \sin(\theta_1/2) + 0.0088 \cos\theta_1 - 0.0084 \sin\theta_1 + 0.1425 \cos(3\theta_1/2) - 0.1067 \sin(3\theta_1/2)$.

such that all conformations can be located analytically. For cyclohexane and cycloheptane, the corresponding equations are such high-order polynomials that exact solutions are in general impossible. In such cases, it is still possible to either explore conformational degrees of freedom numerically from a known starting structure (as in the exploration of cyclohexane's boat pseudorotation by rotation of the eigenvectors of its metric matrix) or by setting up a solving sequence derived from the requirement that each piece of the larger molecule must lie in R^3 (as in the cycloheptane analysis). This latter approach reduces the number of undetermined variables to be explored in a grid search while giving exact, multiple solutions to all other variables.

When is this approach useful? As stated in the introduction, if the constraints are few and weak, as in an acyclic molecule with flexible valence geometry, the allowed conformation space is large, of high dimension, and typically well enough connected so that random distance geometry sampling or coarse grid searches are likely to be cost effective and not miss significant regions of conformation space. On the other hand, the small cyclic hydrocarbons with fixed bond lengths and angles are so heavily constrained per atom that they have low dimensional and sometimes disconnected allowed regions of conformation space. For example, cyclohexane has only its six dihedral angles as conformational variables but six ring closure constraints interrelating them. By such a dimensional analysis, one would expect in general one or zero allowed conformations, but not the isolated chair point and the boat pseudorotation loop that arise from the great symmetry of the molecule. The analytical approach given here has the advantage of systemically finding all solution sets, which can be a great help for tight constraints and highly symmetric molecules.

There is actually nothing in this approach restricting one to tetrahedral bond angles and uniform bond lengths. The equations have the same form, but they are more complicated numerically. Each ring closure in an arbitrary (possibly bridged and fused) ring system has a corresponding vector like **e** that must be in the kernel of the metric matrix, except that its components are not necessarily all unity. Acyclic molecules can also be treated this way, but unless there are sufficient tight interatomic distance constraints on it (thus in effect making it a polycyclic molecule) the solution space will have such high dimension that this approach is hardly worth it.

Applying these same techniques to larger cyclic hydrocarbons is certainly possible, but it is not clear that any general insights would result. Cyclooctane would be expected to have one or more two-dimensional subspaces of allowed conformations embedded in R^8. Judging from cycloheptane, these surfaces would be complicated to describe analytically and computationally more difficult to map out. However, for molecules consisting of n atoms and nearly $3n - 6$ equality constraints, these techniques may be well worth the trouble, even for $n = 50$ or more.

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