Puckering Coordinates of Monocyclic Rings by Triangular Decomposition

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We describe a new method of describing the pucker of an *N*-member monocyclic ring using $N - 3$ parameters. To accomplish this, three ring atoms define a reference plane, and the remainder of the ring is decomposed into triangular flaps. The angle of incidence for each flap upon the reference plane is then measured. The combination of these angles is characteristic of the ring's pucker. This puckering coordinate system is compared to existing reduced parameter systems to describe rings using a cyclohexane molecule. We show that this method has the same descriptive power of previous systems while offering advantages in molecular simulations.

INTRODUCTION

It has been previously shown that $N - 3$ parameters can meaningfully describe *N*-member nonaromatic monocyclic rings.[1-4] These reduced parameter representations are attractive because their mathematics are not difficult, while their parameters retain much of the information about ring conformation. However, as nonaromatic rings are typically puckered, it is necessary to describe not only the bonding pattern of these rings but also their pucker.

Besides cyclic alkanes, several biologically active aliphatic monocycles exist with one or more ring positions substituted by either oxygen, nitrogen, or sulfur. Describing the pucker of cyclic aldoses is useful in studies of their reaction mechanisms and molecular interactions.[5,6] Nearly always, carbohydrate−protein associations, as well as the reactions involving the carbohydrate, require a change of ring conformation. Six-member carbohydrate rings may be described as moving through 38 canonical states (Figure 1), previously mapped in spherical coordinates. This spherical projection connects these states as continuous movements in each of the $N - 3$ dimensions. The intuitiveness of this concept has nearly cemented the Cremer−Pople (CP) formalism[1] as the de facto descriptor of puckered rings.

Recently, an alternative reduced parameter set proposed by Bercés et al. used endocyclic dihedral angles to describe ring pucker.[3] The parameters allow the direct use of NMR coupling constants to resolve the pucker. Additionally, the endocyclic torsions allow one to describe a particular pucker as the linear combination of three ideal puckers, $^1C_4$, $^{1,4}B$, and $^OS_2$, using IUPAC nomenclature.[7,8]

For all the advantages of the CP and Bercés et al. systems, each has drawbacks. With the former, it is relatively difficult to calculate the Cartesian coordinates of all the ring atoms based solely on the reduced parameters. Three coordinates, θ, ϕ, and Q, giving six relative elevations above and below an average plane, exist for a six-member ring. It is possible to use these six elevations and 12 additional system constraints to simultaneously solve 18 equations to yield the
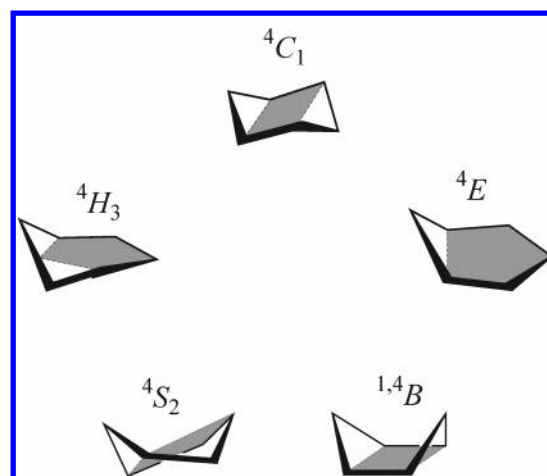
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Figure 1. The five canonical shapes of a puckered pyranosyl ring: chairs (*C*, two states), envelopes (*E*, 12 states), boats (*B*, six states), skew-boats (*S*, six states), and half-chairs (*H*, 12 states). Four atoms are coplanar in four of the conformations, and a fifth is coplanar in envelopes. Superscripts and subscripts denote the atoms not in the plane.

full 18 Cartesian coordinates that describe the positions of the six ring atoms. Instead, in general, the elevation constraints are used in a molecular mechanics simulation to find the Cartesian coordinates of each atom.[5,6]

With the Bercés et al. system, a straightforward algorithm can calculate all the Cartesian coordinates by using sequential dihedral angles to sequentially place each of the atoms around the ring. However, this system lacks some intuitiveness. Although any three dihedrals can be translated into a linear combination of three ideal puckered states, this is not easily done without a computer. In addition, any three of the six endocyclic dihedrals may be specified. Although useful for calculating a pucker from NMR coupling constants, it is difficult to connect three arbitrary dihedrals to one of the 38 canonical puckering states without resorting to a table or computer.

Finally, neither the CP formalism nor the Bercés et al. system helps one to deduce the change induced in a ring's pucker by external forces. For this reason, we propose a system based upon the decomposition of a monocylic ring
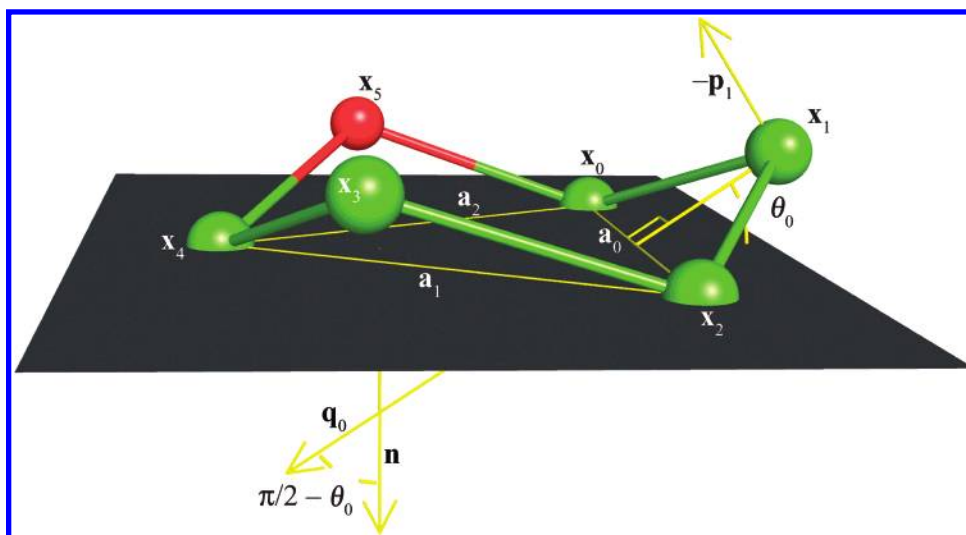
Figure 2. A $^4C_1$ aldopyranosyl ring. The yellow lines are vectors used to compute the angles θ_i. To simplify the illustration, the opposite of $\mathbf{p_1}$ is shown. Vectors $\mathbf{p_1}$, $\mathbf{q_o}$, and $\mathbf{n}$ are not to scale so that intersections can be demonstrated, although their directions are correct. The three vectors shown must be computed for each angle θ_i.

into $N - 2$ triangles, with one triangle forming a reference plane against which the angle of elevation is measured for the remaining triangles (Figure 2). Thus, a ring can be completely described as three atoms in a plane, with $N - 3$ flaps that have some angle of orientation to that plane. Formulating the puckered state in this way is not only intuitive, since it is easy to picture the positions of flaps above or below the plane, but it allows both easy computation of the Cartesian coordinates of the atoms and a quantitative way to measure the effect of external forces on the ring conformation.

CALCULATION OF THE ANGLES

The calculation of each of the $N - 3$ puckering angles requires that we first define the axes of puckering, $\mathbf{a}_i$. These are based on the Cartesian coordinates of each ring atom, $\mathbf{x}_i$ (numbering starts at zero to simplify subscripts, and $i = i$ mod 6 due to the cyclic nature of the numbering):

$$\mathbf{a}_i = \mathbf{x}_{2(i+1)} - \mathbf{x}_{2i} \qquad (1)$$

Using two of the axes, we calculate the vector normal to the reference plane, $\mathbf{n}$, using the cross product:

$$\mathbf{n} = \mathbf{a}_1 \otimes \mathbf{a}_0 \qquad (2)$$

We also calculate the vectors representing each of the bonds between atoms, denoting a bond vector as $\mathbf{r}_i$:

$$\mathbf{r}_i = \mathbf{x}_{i+1} - \mathbf{x}_i \qquad (3)$$

Using the bond vectors on either side of an atom, we compute an atom's orientation vector relative to the plane, $\mathbf{p}_i$. This vector will be orthogonal to both bond vectors, as well as to the axis about which this atom puckers:

$$\mathbf{p}_i = \mathbf{r}_{i-1} \otimes \mathbf{r}_i \qquad (4)$$

To calculate the angle of puckering with the appropriate sign, we create a vector $\mathbf{q}_i$ orthogonal to $\mathbf{p}_{2i+1}$ and $\mathbf{a}_i$:

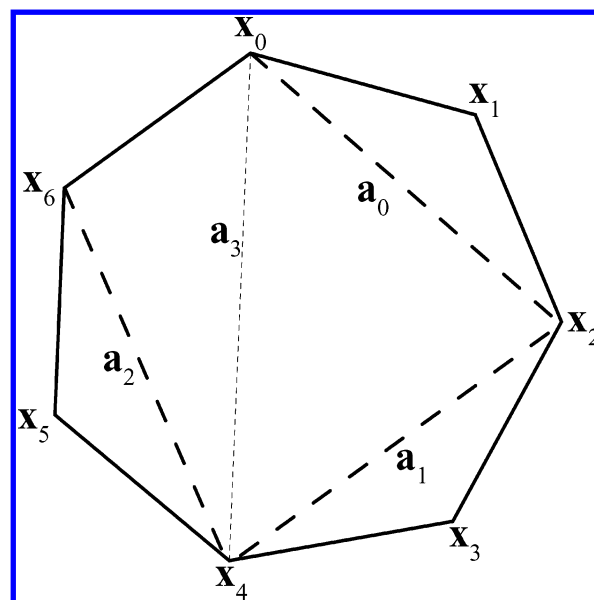$$\mathbf{q}_i = \mathbf{a}_i \otimes \mathbf{p}_{2i+1} \qquad (5)$$

Figure 3. A seven-membered ring with the four axes shown by dotted lines. The first three axes (computed using the unmodified eq 5) are shown in heavy dotted lines, and the fourth axis is shown with a light dotted line. As can be seen, the first three axes do not form a triangle, and the fourth axis is needed to bisect the surface created by the first three axes.

The angles of intersection between this vector, $\mathbf{q}_i$, and $\mathbf{n}$ are $\pi/2 - \theta_i$, yielding a positive θ_i when the flap is above the plane, and $\pi/2 + \theta_i$, yielding a negative θ_i when the flap is below the plane (eq 6):

$$\theta_i = \pi/2 - \cos^{-1}[(\mathbf{q}_i \bullet \mathbf{n}) \bullet (||\mathbf{q}_i|| \bullet ||\mathbf{n}||)^{-1}] \qquad (6)$$

These calculations are valid for $N \leq 6$ and produce $N - 3$ angles of puckering with respect to the reference plane. For $N > 6$, the first three axes do not form a triangle (Figure 3). For each odd/even pair of numbers when $N > 6$, that is, {7, 8}, there will be an additional axis cutting the rectangle formed by the first three axes to form two triangles. In these cases, eqs 1 and 5 must be modified. The remaining equations still produce valid puckering angles about the nearest hinge. This parametrization will be used primarily

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on monocyclic rings of five and six atoms, so the modified equations are not shown.

CONVERSION TO CARTESIAN COORDINATES

Any restoration to a full coordinate system from a reduced system requires significant additional information. A total of 18 Cartesian coordinates must be specified for six-member rings. From an $N - 3$ parameter system, we must specify 15 additional degrees of freedom to have a fully defined system. One method is to use MM3 or a similar program to solve for the remaining coordinates.[5,6] However, a reconstruction algorithm can be proposed that should be reasonably accurate and sufficiently fast that it could be included as part of a molecular simulation. Including the puckering coordinates, three positional coordinates, and three orientation coordinates leaves nine more coordinates to fully define the system. We could then use bond lengths and bond angles (ϕ_i), although neither can be known with perfect accuracy, since both change from ideal values when a ring is puckered. Thus, we must either use all 12 values in an overspecified system or choose nine for a system that is neither over- nor underdefined. For expediency, we choose six bond lengths and three bond angles, since a low-energy change in bond angle would yield a larger change in the atomic positions than a change in bond length of similar energy.[9] This yields the following algorithm:

1. Place one atom ($\mathbf{x}_1$) using three Cartesian coordinates.
2. Use ϕ_0, $||\mathbf{r}_0||$, $||\mathbf{r}_1||$, and an orientation vector to place $\mathbf{x}_0$ and $\mathbf{x}_2$.
3. Use $\mathbf{x}_0$, $\mathbf{x}_2$, and θ_0 to calculate the normal vector, $\mathbf{n}$.
4. Use ϕ_1, ϕ_2, and $||\mathbf{r}_2||$ through $||\mathbf{r}_5||$ to calculate $||\mathbf{a}_1||$ and $||\mathbf{a}_2||$.
5. Use $\mathbf{n}$, $\mathbf{x}_0$, $\mathbf{x}_2$, $||\mathbf{a}_1||$, and $||\mathbf{a}_2||$ to place $\mathbf{x}_4$.
6. Use θ_1, $\mathbf{n}$, $\mathbf{x}_2$, $\mathbf{x}_4$, ϕ_1, $||\mathbf{r}_2||$, and $||\mathbf{r}_3||$ to place $\mathbf{x}_3$.
7. If $N = 6$, repeat step 6 to place $\mathbf{x}_5$, using the appropriate variables.
8. Check the nonspecified ϕ's for consistency with those specified and adjust the specified ϕ's as necessary; then, iterate steps 2−7 until the ϕ's converge.

IMPLICATIONS OF PUCKERING COORDINATES

Expressing the pucker of an aldopyranose or aldofuranose ring as a plane with puckered flaps has a large advantage in molecular simulations over the other cited representations for rings. Since one of the planar axes can be seen as a puckering axis, one can compute the moment of puckering from the atoms pendant to that axis. For molecular dynamics, rather than moving each of the atoms in the ring at each time step, the moment of puckering can be calculated and the puckering flap rotated accordingly.

Forces can be computed for a docked conformation of atoms.[10,11] This has been used to elucidate the transition-state pathway of a pyranose conformation.[12] However, this method is very subjective. To understand which direction the ring moves in puckering coordinates requires comparing the force components on the ring and pendant atoms, inspecting a chart of puckering pathways, comparing the binding energy of the nearby docked conformations, and then subjectively deciding which puckered state is next in the transition-state pathway. Representing a ring with flexible flaps and puckering moments allows one to reduce the

subjectivity by calculating the latter about each axis and determining how the conformation will pucker.

A small Python script has been included in the Supporting Information to demonstrate the straightforward nature of converting between Cartesian coordinates and puckering angles. A further step would be to incorporate this code into a docking suite to allow nonaromatic rings to pucker realistically.

Internal coordinates have been used to describe the fast vibrational motion in molecular dynamics (MD) simulations while still allowing the rest of a MD simulation to be computed with longer time steps.[13−16] Such an optimization allows one to achieve greater computational efficiencies while still accounting for fast motions. The set of internal coordinates proposed here is different, in that, rather than allowing for temporal adjustments, these coordinates reduce the number of circular dependencies in monocyclic rings. Additionally, the coordinate set described in this paper allows a ring to be fully puckered using few parameters, a definite advantage in automated docking algorithms, where each degree of freedom adds a dimension to the search space.

For example, AutoDock 3.0−4.0 uses a genetic algorithm to search the conformational space for the lowest-energy configuration between a ligand and a macromolecule.[17] The position and configuration of the bulk of the macromolecule is held fixed, while internally the conformation of the ligand is represented by a gene of internal coordinates: six transformational plus one for every rotatable bond. In this scheme, rings are not allowed to pucker, because the rotations of every bond in the ring are not independent, and a ring would not be guaranteed to maintain closure as the torsions were adjusted independently. By using the coordinates proposed here, a ring could be represented by $N - 3$ puckering coordinates. One would simply add the puckering coordinates to the list of parameters in the gene that represents the conformation of the ligand. Throughout the optimization, the genotype is translated into a phenotype—in this case, from internal coordinates to Cartesian coordinates—and then the energy of interaction is evaluated. Incorporating the coordinates proposed in this paper would then affect that step where the puckering coordinates are translated into Cartesian coordinates, as already demonstrated here and in the Supporting Information. With this change, AutoDock would be able to run the same optimization algorithm but would be able to pucker rings. This example demonstrates the benefit of the proposed parametrization in molecular simulations.

COMPATIBILITY WITH OTHER REDUCED COORDINATE SETS

Table 1 demonstrates equivalent reduced coordinate sets for the 38 canonical puckers in CP parameters, Bérces et al. dihedrals, and puckering angles. All three systems completely and uniquely describe all 38 canonical puckers, and each system is compatible with the other two.

This system demonstrates a pleasing symmetry among similar conformations: the ${}^4C_1$ angles are exactly opposite the ${}^1C_4$ angles, the ${}^{1,4}B$ angles are opposite the $B_{1,4}$ angles, the ${}^6E$ angles are opposite the E_6 angles, and so forth. Also pleasing is the conservation of patterns among the same types of pucker; that is, the chairs all have angles in the same

Table 1. Puckering Coordinates of Each Reduced Coordinate System for the 38 Canonical Ring Puckers[a]

conformer	Bercés et al. dihedrals			Cremer−Pople coordinates			this work		
	τ_1 (deg)	τ_2 (deg)	τ_3 (deg)	ϕ (deg)	θ (deg)	Q (Å)	θ_0 (deg)	θ_1 (deg)	θ_2 (deg)
$^1C_4$	60	−60	60	0−360	180	0.57	−35.26	−35.26	−35.26
$^4C_1$	−60	60	−60	0−360	0	0.57	35.26	35.26	35.26
$^{1,4}B$	0	60	−60	240	90	0.76	−35.26	74.20	−35.26
$B_{1,4}$	0	−60	60	60	90	0.76	35.26	−74.20	35.26
$^{2,5}B$	−60	0	60	120	90	0.76	74.20	−35.26	−35.26
$B_{2,5}$	60	0	−60	300	90	0.76	−74.20	35.26	35.26
$^{3,6}B$	60	−60	0	0	90	0.76	−35.26	−35.26	74.20
$B_{3,6}$	−60	60	0	180	90	0.76	35.26	35.26	−74.20
$^1H_2$	45	−15	0	270	129	0.42	−42.16	9.07	−17.83
$^2H_1$	−45	15	0	90	51	0.42	42.16	−9.07	17.83
$^2H_3$	−60	45	−15	150	51	0.42	42.16	17.83	−9.06
$^3H_2$	60	−45	15	330	129	0.42	−42.16	−17.83	9.06
$^3H_4$	45	−60	45	30	129	0.42	−17.83	−42.16	9.07
$^4H_3$	−45	60	−45	210	51	0.42	17.83	42.16	−9.07
$^4H_5$	−15	45	−60	270	51	0.42	−9.07	42.16	17.83
$^5H_4$	15	−45	60	90	129	0.42	9.07	−42.16	−17.83
$^5H_6$	0	−15	45	150	129	0.42	9.07	−17.83	−42.16
$^6H_5$	0	15	−45	330	51	0.42	−9.07	17.83	42.16
$^6H_1$	−15	0	−15	30	51	0.42	17.83	−9.07	42.16
$^1H_6$	15	0	15	210	129	0.42	−17.83	9.07	−42.16
$^1S_3$	−30	60	−30	210	88	0.62	0	50.84	−50.84
$^3S_1$	30	−60	30	30	92	0.62	0	−50.84	50.84
$^5S_1$	−30	−30	60	90	92	0.62	50.84	−50.84	0
$^1S_5$	30	30	−60	270	88	0.62	−50.84	50.84	0
$^6S_2$	60	−30	−30	330	88	0.62	−50.84	0	50.84
$^2S_6$	−60	30	30	150	92	0.62	50.84	0	−50.84
^1E	30	0	0	240	125	0.45	−35.26	17.37	−35.26
E_1	−30	0	0	60	55	0.45	35.26	−17.37	35.26
^2E	−60	30	0	120	55	0.45	46.86	0	0
E_2	60	−30	0	300	125	0.45	−46.86	0	0
^3E	60	−60	30	360	125	0.45	−35.26	−35.26	17.37
E_3	−60	60	−30	180	55	0.45	35.26	35.26	−17.37
^4E	−30	60	−60	240	55	0.45	0	46.86	0
E_4	30	−60	60	60	125	0.45	0	−46.86	0
^5E	0	−30	60	120	125	0.45	17.37	−35.26	−35.26
E_5	0	30	−60	300	55	0.45	−17.37	35.26	35.26
^6E	0	0	−30	360	55	0.45	0	0	46.86
E_6	0	0	30	180	125	0.45	0	0	−46.86

[a] Structures were generated using the coordinates of Bercés et al.[3] (using the 6ring.py program included in the Supporting Information), and then coordinates were measured using both the CP system and the puckering angles described in this paper, assuming a cyclohexane ring. Position 6 is signified as O in aldopyranosyl rings.

direction and of the same magnitude; the boats all have two moderately sized angles of the same sign and one large angle of the opposite sign, and the envelopes all have either two zero angles and one large angle or two moderately sized angles and a smaller angle about half their magnitude and opposite in sign. In addition, one can easily visualize the flaps of the puckered ring elevated above and below the planar atoms.

The Bércés et al. dihedral angles associated with the 38 canonical puckers are all multiples of 15°, as are all the ϕ values and those θ values associated with chair and boat rings in the CP system. This is not so for the angles occurring in the proposed method. However, several values do appear frequently; for instance, 35.26° appears in all chair and boat and some envelope conformations. This angle is significant in tetrahedral geometry (Figure 4), so its occurrence is not surprising. Only chair and boat conformations have perfect tetrahedral bond geometries, so this angle does not appear elsewhere except in some envelopes, due to the geometry of their pitch with regard to the reference plane caused by their out-of-plane atoms. Thus, the angles observed in the proposed system are reasonable and are merely a reflection of the geometry of the carbon atom's tetrahedral bonding.

The principle of least motion can be applied to ring structures by stating that two ring conformations can be adjacent in a transition-state pathway if the movement required to transform one to the other is minimal. This principle is observed in the proposed coordinate system, as puckered rings related by least motion are also related by minimal change in puckering coordinates, measured by summing the changes in each of the coordinates. In some transitions, such as $B_{3,6} \rightarrow {}^1S_3 \rightarrow {}^{1,4}B$, all three coordinates change simultaneously, while in others, like $^1C_4 \rightarrow {}^3E \rightarrow {}_{3,6}B$, only one coordinate changes. Thus, this puckering coordinate system agrees with a pseudorotational map of ring conformations. It has been observed that not every conformational pathway follows the pseudorotational itinerary.[4] Regardless, a continuous change in Cartesian coordinates also results in a continuous change in internal coordinates, allowing a full description of puckering whether on or off the pseudorotational itinerary.

CONCLUSIONS

We have shown that an alternate set of reduced coordinates exists for monocyclic nonaromatic rings. We have also highlighted the application of these coordinates to describing
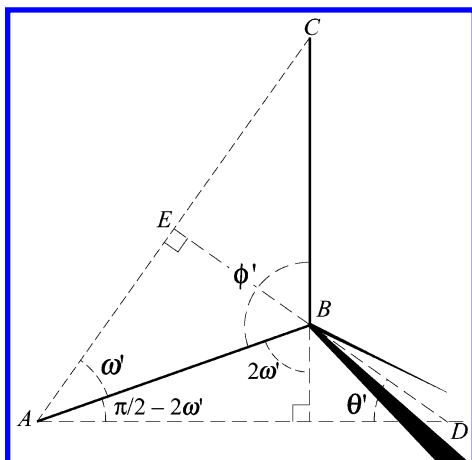
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Figure 4. A diagram of tetrahedral geometry. In considering a flap's pucker, ϕ' is the bond angle between the exocyclic groups, the three atoms at the bottom are in the reference plane, and θ' is the angle of puckering. When triangle ABC is used, ω' is easily computed as $0.5(180° - \phi')\psi' = 180° - \phi'$, giving $\psi' = 2\omega'$. When triangle ADE is used, $\theta' + \omega' + \pi/2 - 2\omega' = \pi/2$. Consequently, we observe that $\theta' = \omega'$ and is directly related to the bond angle between exocyclic groups. For a tetrahedron, $\phi' = 109.47°$, giving $\theta' = 35.26°$.

aldopyranosyl rings. We have further demonstrated that these coordinates are especially useful in molecular simulations. These coordinates can be used in either descriptive or prescriptive modes.

It would be very useful to integrate these parameters into molecular mechanics or molecular dynamics simulation packages. To do this, it would be necessary to modify not only the source code of the relevant software but also the force fields of these programs to accommodate the puckering terms. The energy changes caused by variations in puckering have been studied,[5,6] but no effort to fit these data to these puckering coordinates has been made. Such work is beyond the scope of this article, but not out of the realm of future research.

Meanwhile, the proposed puckering angle system provides a new and useful method to describe monocyclic ring conformation. In particular, breaking a ring down into groups of flaps that move as the ring puckers allows a quantitative assessment of the effect that intermolecular forces on pendant atoms[10-12] will have upon the conformation of the ring to which they are attached.

ACKNOWLEDGMENT

Supporting Information Available: Included in the Supporting Information is the Python source code to carry out the calculations described in the article. Additionally, the source code for a program to calculate the Cremer–Pople puckering parameters from a series of Cartesian coordinates is included. Finally, the source code to a bash script is included to create the appropriate data file needed for the included programs using a series of PDB files. This information is available free of charge via the Internet at http://pubs.acs.org.

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