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Note

Driving the pyranoid ring conformation in molecular mechanics calculations

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It is customary, in the conformational analysis of sugar derivatives by the methods of molecular mechanics, to assume that pyranosidic rings are rigid and in either the $^4C_1$ or $^1C_4$ chair conformation. However, $^3J_{H,H}$ values obtained in ^{1}H-n.m.r. spectroscopy suggest the existence of conformations other than chair forms and it is important to evaluate their structures and relative energies.

In a study of the conformation of methyl 4-*O*-methyl-2-*O*-sulfo-α-L-idopyranosiduronic acid, three conformers ($^4C_1$ and $^1C_4$ chairs, and the skew-boat form ^2S_O) were computed to possess similar energies[1]. The analysis of a series of iduronate-containing compounds showed that significant proportions (up to 64%) of the ^2S_O conformer may occur, accounting for a wide range of $^3J_{H,H}$ values[2]. More recently, unusual $^3J_{H,H}$ values for the glucuronate residue in chondrosine were rationalised in terms of an equilibrium of the $^4C_1$ chair and one or more boat-like forms with comparable energies[3].

To our knowledge, the method of computation involved has not been described. Several molecular mechanics packages afford a feature, the 'drive' (see, for example, Allinger and Yuh[4]), which allows the conformational energy to be minimised whilst constraining one or two dihedral angles to maintain, or reach, a given value. However, this method is not practical when dealing with pyranoid rings, because of the interdependence of the six angular values that define its geometry.

A sub-routine, built according to the mathematical methods described below, which makes use of suitable puckering co-ordinates, has been implemented in the molecular mechanics package REFINE[†], and was employed in the work cited above[1-3].

Derivation of the algorithm. — The conformations of pyranoid rings are best described by a generalised set of puckering co-ordinates given by Cremer and Pople[5] (CP).

These authors showed that the three puckering degrees of freedom for a six-membered ring can be described by a 'spherical polar set' (Q, θ, ϕ), easily derived from

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[†] Package REFI90 (I.C.M., Milano) is available from the authors.

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generalised co-ordinates (q_2, θ_2, q_3). This co-ordinate system permits all types of puckering (for a given amplitude Q) on the surface of a sphere to be mapped.

In REFINE, the function F to be minimised includes the usual force-field energy terms (*e.g.*, those due to stretching, bending, torsion, and van der Waals interactions), together with constraint terms (expressed as energies).

In order to drive a ring from one conformation to another, the function F is supplemented by a term E_D defined by only two ring puckering co-ordinates θ and ϕ,

$$E_D = \frac{1}{2}k_\theta(\theta - \theta_O)^2 + \frac{1}{2}k_\phi(\phi - \phi_O)^2, \tag{1}$$

where θ_O and ϕ_O are the co-ordinates of the target conformation, and k_θ and k_ϕ are the corresponding 'force constants'. This new function, F′ = F + E_D, is then minimised with respect to all Cartesian co-ordinates. The result is a structure that corresponds to the final values θ and ø of the puckering co-ordinates, which will be more or less close to the target values θ_O and $ø_O$, depending on the values assigned to the force constants. A value of 10^4 kcal.mol^{-1}.deg^{-2} was chosen arbitrarily for k_θ and k_ϕ, which yields discrepancies of a few tenths of degree from the target for the least favorable conformations.

Since the minimisation procedure is based on the gradient of this function, the derivatives of E_D need to be calculated with respect to Cartesian co-ordinates of the six ring atoms which define the puckering.

From equation *1* and definitions of the CP puckering co-ordinates, it is straightforward to obtain these derivatives as follows:

$$\frac{\partial E_D}{\partial X_{kl}} = \frac{\partial E_D}{\partial \theta}\frac{\partial \theta}{\partial X_{kl}} + \frac{\partial E_D}{\partial \phi}\frac{\partial \phi}{\partial X_{kl}}, \tag{2}$$

where X_{kl} (k = 1,2,3; l = 1,...6) is the k-th Cartesian co-ordinate of the l-th atom in a six-membered ring.

The CP treatment is based on a linear transformation of co-ordinates X_{kl} into a reference system so chosen that the origin is at the geometric centre of the ring and the z axis is normal to the mean plane passing through the six ring atoms. The puckering parameters θ and ϕ (and Q) are functions of the six new co-ordinates z_i, *i.e.*, the atomic displacements from the mean plane. Therefore,

$$\frac{\partial E_D}{\partial \theta} = k_\theta \theta \quad \text{and} \quad \frac{\partial E_D}{\partial \phi} = k_\phi \phi, \tag{3}$$

$$\frac{\partial \theta}{\partial X_{kl}} = \sum_{i=1}^{6} \frac{\partial \theta}{\partial z_i}\frac{\partial z_i}{\partial X_{kl}} \quad \text{and} \quad \frac{\partial \phi}{\partial X_{kl}} = \sum_{i=1}^{6} \frac{\partial \phi}{\partial z_i}\frac{\partial z_i}{\partial X_{kl}}. \tag{4}$$

With equation *22* of CP, which defines θ as a function of z_i,

$$\theta = \mathrm{acos}\left(\frac{q_3}{Q}\right),$$

by using equations *12–14* and *17* of CP, substituting

$$A = 3^{-1/2} \sum_{i=1}^{6} z_i \cos\frac{2\pi}{3}(i-1)$$

$$\text{and} \quad B = -3^{-1/2} \sum_{i=1}^{6} z_i \sin\frac{2\pi}{3}(i-1)$$

gives

$$\frac{\partial\theta}{\partial z_i} = -(1 - q_3{}^2Q^{-2})^{-1/2}\Bigg\{6^{-1/2}Q^{-1}(1 - q_3{}^2Q^{-2})\cos\pi(i-1)$$

$$-3^{-1/2}q_3Q^{-3}\left[A\cos\frac{2\pi}{3}(i-1) - B\sin\frac{2\pi}{3}(i-1)\right]\Bigg\}. \qquad (5)$$

Similarly, from equation *12* of CP,

$$\phi = \mathrm{acos}\left(\frac{A}{q_2}\right),$$

so that equation *6* can be derived.

$$\frac{\partial\phi}{\partial z_i} = -3^{-1/2}(1 - A^2q_2^{-2})^{-1/2}\Bigg[q_2^{-1}(1 - A^2q_2^{-2})\cos\frac{2\pi}{3}(i-1)$$

$$+ ABq_2^{-3}\sin\frac{2\pi}{3}(i-1)\Bigg] \qquad (6)$$

In order to calculate $\partial z_i/\partial X_{kl}$, equation *11* of CP was used,

$$z_i = \sum_{k=1}^{3} R_{ki}n_k,$$

where

$$R_{ki} = X_{ki} - \frac{1}{6}\sum_{l=1}^{6} X_{kl}$$

are the ring atom co-ordinates with respect to a new frame of reference, with the origin in the geometrical center, $\vec{n} = (n_1,n_2,n_3)$ being normal to the mean plane passing through the origin, as defined below. Now, since

$$\frac{\partial z_i}{\partial X_{kl}} = \sum_{h=1}^{3}\left(n_h\frac{\partial R_{hi}}{\partial X_{kl}} + R_{hi}\frac{\partial n_h}{\partial X_{kl}}\right), \tag{7}$$

where

$$\frac{\partial R_{hi}}{\partial X_{kl}} = \begin{cases} \frac{5}{6} \text{ if } h = k \text{ and } i = l \\ -\frac{1}{6} \text{ if } h = k \text{ and } i \neq l \\ 0 \text{ if } h \neq k \text{ and } i \neq l \end{cases} \tag{8}$$

and

$$\frac{\partial n_h}{\partial X_{kl}} = \sum_{j=1}^{6}\frac{\partial n_h}{\partial R_{ji}}\frac{\partial R_{ji}}{\partial X_{kl}}, \tag{9}$$

$\vec{n}$ is defined in equation *10* of CP as $\vec{u}/|\vec{u}|$, where $\vec{u} = \vec{a} \times \vec{b}$ and

$$\vec{a} = \left(\sum_{j=1}^{6} R_{1j}\sin\frac{\pi}{3}(i-1),\ \sum_{j=1}^{6} R_{2j}\sin\frac{\pi}{3}(i-1),\ \sum_{j=1}^{6} R_{3j}\sin\frac{\pi}{3}(i-1)\right)$$

and

$$\vec{b} = \left(\sum_{j=1}^{6} R_{1j}\cos\frac{\pi}{3}(i-1),\ \sum_{j=1}^{6} R_{2j}\cos\frac{\pi}{3}(i-1),\ \sum_{j=1}^{6} R_{3j}\cos\frac{\pi}{3}(i-1)\right).$$

Therefore, with $u = |\vec{u}|$,

$$\frac{\partial n_h}{\partial R_{ji}} = \frac{1}{u}\frac{\partial u_h}{\partial R_{ji}} - \frac{u_h}{u^3}\sum_{k=1}^{3} u_k\frac{\partial u_k}{\partial R_{ji}} \tag{10}$$

and

$$\frac{\partial u_h}{\partial R_{ji}} = a_s\frac{\partial b_v}{\partial R_{ji}} + b_v\frac{\partial a_s}{\partial R_{ji}} - a_v\frac{\partial b_s}{\partial R_{ji}} - b_s\frac{\partial a_v}{\partial R_{ji}}, \tag{11}$$

where $s = h + 1$ and $v = h + 2$ (if $s > 3$, $s = s - 3$; if $v > 3$, $v = v - 3$) and

$$\frac{\partial a_k}{\partial R_{ji}} = \sin\frac{\pi}{3}(i-1) \text{ if } k = j \quad \text{or} \quad = 0 \text{ if } k \neq j, \tag{12}$$

and

$$\frac{\partial b_k}{\partial R_{ji}} = \cos\frac{\pi}{3}(i-1) \text{ if } k=j \quad \text{or} \quad =0 \text{ if } k \neq j. \qquad (13)$$

The expressions obtained in equations *12* and *13* can now be substituted in equation *11*, the latter in equation *10* and so on, back to equation *2* which yields the required derivatives.

Applications. — The applications of this procedure fall into two main categories, namely, the evaluation of an energy profile as a function of the ring form and the generation of possible minimum-energy conformers.

An example of the first application[1] involved computation of the two-dimensional map, $E(\theta, \phi)$, and the minimum energy profiles, along the pseudorotational path, $E(\phi)$, and along a meridian-like path connecting the three minima, $E(\theta)$.

For chondrosine[3], experimental $^3J_{H,H}$ values for the glucuronate moiety do not correspond to a single ring conformer: the straightforward application of the Haasnoot–Altona equation[6] leads to dihedral angles which do not allow ring closure. Starting from the supposedly stable $^4C_1$ form, the ring was pushed towards the equatorial region (θ only was driven from 180° to 90°) and the pseudorotational path (now driving ϕ alone) was explored with variations of the puckering angles in steps of 5–10°. In a further stage, a 'conventional' drive was performed on the interglycosidic angles, ϕ and ψ, followed by a final free (unconstrained) minimisation.

The algorithm detailed above is based on the use of the Cartesian co-ordinates X referred to the external frame, rather than to the mean plane of the ring, as independent variables. The advantage of this choice was apparent when the procedure was used to obtain the theoretical structures of dermatan sulphate in the crystalline state[7]. Starting from the co-ordinates given by Mitra *et al.*[8], based on the $^4C_1$ form of the iduronate ring, alternative 3D structures for the polysaccharide with ^2S_O and $^1C_4$ forms were derived by means of the (ϕ, Ψ) driving.

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