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A MODEL FOR DESCRIBING THE CONFORMATIONS OF FLEXIBLE 6-MEMBERED RINGS—I

THE NON-CHAIR CONFORMATIONS

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Abstract—An empirical model for calculating the torsional angles for flexible 6-membered rings is presented in terms of three independent parameters, two geometrical and one pseudorotation angle. The rings are classified according to four estimators, the fit of the model depending upon their values. Equations are given for defining any conformation by a point in a 2-dimensional pathway. Some examples have been examined in the light of this model.

The starting point of this study was a series of regularities found among the torsional angles of several 6-membered rings studied by X-ray diffraction techniques.[1] Then, following the idea of Altona *et al.*[2] in describing the conformations of 5-membered rings, we carried out a model for the description of some types of 6-membered rings. Here we have used three independent parameters, but the philosophy is the same as in the Altona *et al.*[2] model, and many rings described as distorted, now agree with the model as do the normal conformations.

The criteria

Initially we will define concisely the points which determine the choice.

(a) The criterion for the sign of angles is that given by Klyne and Prelog.[3]

(b) We situate any ring with two sides vertical, calling ϕ_0 the torsional angle on the left hand side, and then the ϕ_j, up to $j = 5$ with the numbering sequence clockwise.

(c) We include in the description three levels: chairs, chairs-like and non-chairs, named as opposite to chairs. By chairs we mean the perfect chairs, which can be twisted in some way as chair-like towards the third level, and main goal of this work, the non-chair conformations. The latter are present in rings which show a defined flattened part which is reflected in the different values of the torsional angles, and include the typical mono-planar and diplanar conformations (see Bucourt *et al.*[4] and Fig. 1).

(d) Several parameters are used in the model. The geometrical ones are: τ_m which measure the average torsion in the ring; q is the amplitude of a pseudorotation perturbation established in the ring; Φ_M is the maximum torsional angle held by the ring, compatible with τ_m and q. Φ_M and q are taken as always positive. The pseudorotation phases are two α_1 and α_2. They locate the exact position of the non-chair conformation on a periodic 2-dimensional pathway and they are opposite in direction to the flattened part of the ring. We use them through their sum Σ and their difference δ. There are only three independent parameters, so that given τ_m, q and Σ the torsional angles in the ring, ϕ_j are defined.

(e) Two estimators have to be fulfilled before the model can be applied properly $E_2 \equiv (\phi_0 - \phi_3) = (\phi_4 - \phi_1) = (\phi_2 - \phi_5)$ and $E_1 \equiv \sum_j \phi_j = 0$. They provide a check for the fitting of the model to any ring and define the perfect non-chair conformations and so we agree in the existence of a fourth level, not following the estimators, which are being studied at present.

The model

For a given ring, $\phi_j = [\tau_m + q\cos(\Sigma/2 + 60j)](-1)^j + T$, such that if E_1 and E_2 are fulfilled, $T = 0$. This formula has not been mathematically proved, but was obtained empirically.

Now from the equations we have:

$$6\tau_m = (\phi_0 - \phi_3) + (\phi_4 - \phi_1) + (\phi_2 - \phi_5) \gtrless 0 \qquad (1)$$

$$q^2 = \frac{1}{4}(\phi_0 + \phi_3)^2 + \frac{1}{12}[(\phi_1 - \phi_5) + (\phi_4 - \phi_2)]^2 \qquad (2)$$

$$\mathrm{tg}\frac{\Sigma}{2} = \frac{1}{\sqrt{3}}\frac{(\phi_1 - \phi_5) + (\phi_4 - \phi_2)}{(\phi_0 + \phi_3)}. \qquad (3)$$

So (2) and (3) can be described with a rectangular triangle, one angle being $\Sigma/2$ and q the hypotenuse.

Now,

$$q^2 = \frac{1}{12}[(\phi_1 - \phi_5) + (\phi_4 - \phi_2)]^2 + \phi_0\phi_3 + \tau_m^2$$

so if

$$E_3 \equiv \frac{1}{4}[(\phi_1 - \phi_5) + (\phi_4 - \phi_2)]^2 + 3\phi_0\phi_3 \geq 0$$

then $\tau_m < q$, and we can define a new phase angle δ such that

$$\tau_m = q\cos\delta/2 \qquad (4)$$

that is:

$$\cos^2\frac{\delta}{2} = \frac{(\phi_0 - \phi_3)^2 + (\phi_4 - \phi_1)^2 + (\phi_2 - \phi_5)^2}{3(\phi_3 + \phi_0)^2 + 2(\phi_1 - \phi_5)^2 + 2(\phi_4 - \phi_2)^2} \equiv E_4 \qquad (5)$$

so α_1 and α_2 are defined in terms of their sum and their difference (Σ, δ).

Finally, if $\tau_m > 0$ then $\Phi_M = \tau_m + q$ and if $\tau_m < 0$,

$$\Phi_M = -\tau_m + q \qquad (6)$$

and so the maximum angle of puckering can be calculated.

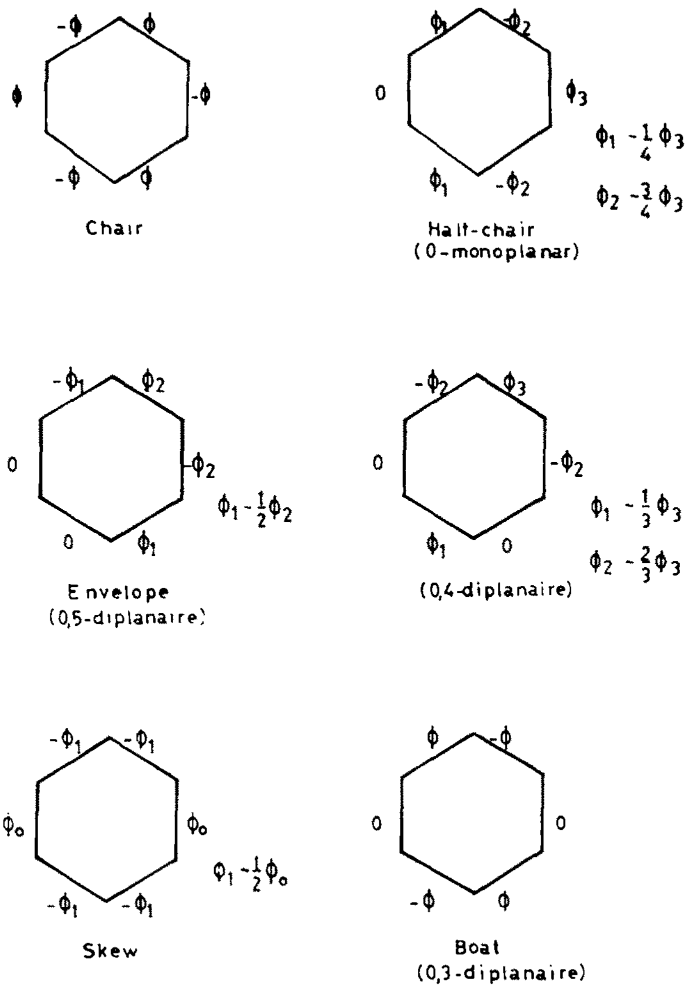

Fig. 1. The usual types of conformations.

In Table 1 we have defined the three described levels in terms of the four estimators (E_1, E_2, E_3, E_4).

The ambiguities

A few doubts may arise in the course of the parameter calculations for a given ring.

(a) If $T \neq 0$ the model is not fitting the ring; these distortions are being investigated.

(b) For a given value of $\mathrm{tg}\,\Sigma/2$, as $\Sigma/2$ and $\Sigma/2 + 180°$ could be uncertain, this is solved by checking the signs of numerator and denominator.

(c) The possibility of an indeterminate 0/0 value for $\mathrm{tg}\,\Sigma/2$ exists, which means $q = 0$, and gives a conformation which is part of the study in progress.

(d) α_1 and α_2 are indistinguishable as they have the same meaning. This makes the choice between δ and δ', such that $\delta + \delta' = 4\pi K$ (K integer) irrelevant.

The conformations pathway

For the non-chair level the 2-dimensional pseudorotation pathway is shown in Fig. 2. Many ways can be

Table 1. Rings classification and the corresponding empirical values of the estimators and geometrical parameters.

CONFORMATIONS		E_1	E_2	E_3	E_4	τ_m	q	δ
Chairs		0	$\pm 2\Phi_M$	$-3\Phi_M^2$	∞	$\pm\Phi_M$	0	-
Chairs-like		0	$(\pm 2\Phi_M, \pm\Phi_M)$	<0	>1	$(\pm\Phi_M, \pm\frac{\Phi_M}{2})$	$(0, \frac{\Phi_M}{2})$	-
	Half-chairs	0	$\pm\Phi_M$	0	1	$\pm\frac{\Phi_M}{2}$	$\frac{\Phi_M}{2}$	0°, 360°, 720°
Non-chairs	Intermedium	0	$(\pm\Phi_M, 0)$	>0	<1	$(\pm\frac{\Phi_M}{2}, 0)$	$(\frac{\Phi_M}{2}, \Phi_M)$	(0°,180°), (180°,360°), (360°,540°), (540°,720°)
	Skew and boats	0	0	$3\Phi_M^2$	0	0	Φ_M	180°, 540°

chosen to transform any conformation into another, even changing Φ_M if the torsional barriers so demand.

At $\delta = 0$ we have the half-chair forms, while at $\delta = 180°$ we have the boat-skew cycle described by Schawarz.[5] From any given (Σ, δ) we find de enantiomorph at $(\Sigma + 360°, \delta + 360°)$, and at $(\Sigma + 720°, \delta + 720°)$ we get again the original ring.

Moving at any $\delta = $ cte we find the repetition of any conformation at $\Sigma + 240°$, passing at $\Sigma + 120°$ through its enantiomorph. This includes a rotation of 60° in the ring anticlockwise. In this way the following formulae can be established:

$$\phi_j(\delta, \Sigma) = (-1)^n \phi_{j-n}(\delta, \Sigma + n120°)$$
$$\phi_j(\delta, \Sigma) = (-1)^n \phi_{j+n}(\delta, \Sigma - n120°)$$
$$\phi_j(\delta, \Sigma + n120°) = (-1)^n \phi_{j+n}(\delta, \Sigma)$$
$$\phi_j(\delta, \Sigma - n120°) = (-1)^n \phi_{j-n}(\delta, \Sigma)$$
(n integer)

In Fig. 3, we have included the calculated torsional angles at $\Phi_M = 75°$ (as a typical value), of a part of the pathway, including the intermedium diplanar conformations at $\delta = 60°$ and $\delta = 120°$.

The $\phi_j - \phi_0$ ellipses

From the equation giving ϕ_j we can eliminate Σ to obtain the ϕ_j vs ϕ_0 plot, yielding curves which are ellipses.

ϕ_0 and ϕ_3 give vs ϕ_0 two degenerated ellipses, two straight lines of slope +1 and passing through $(\tau_m, \pm\tau_m)$ respectively. Namely $\phi_0 = \phi_0$ and $\phi_3 = \phi_0 - 2\tau_m$. Although they are lines, the variation is limited to the diagonal of two squares, 2q in side, and centered at $(\tau_m, \pm\tau_m)$ (Fig. 4). When q and τ_m change through the different levels defined in Table 1, the two squares move along the bisecting lines of the reference.

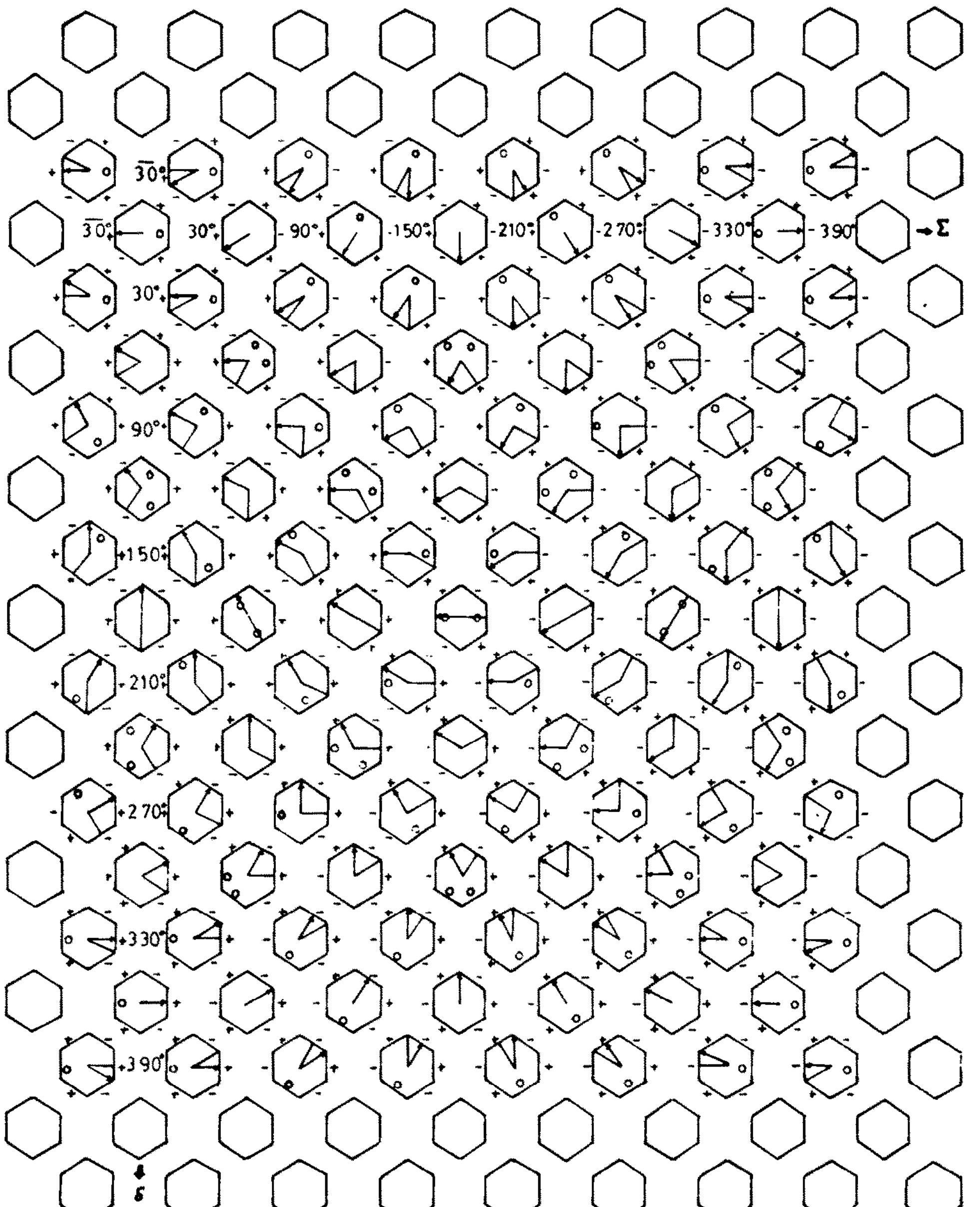

Fig. 2. The two-dimensional pseudorotation pathway.

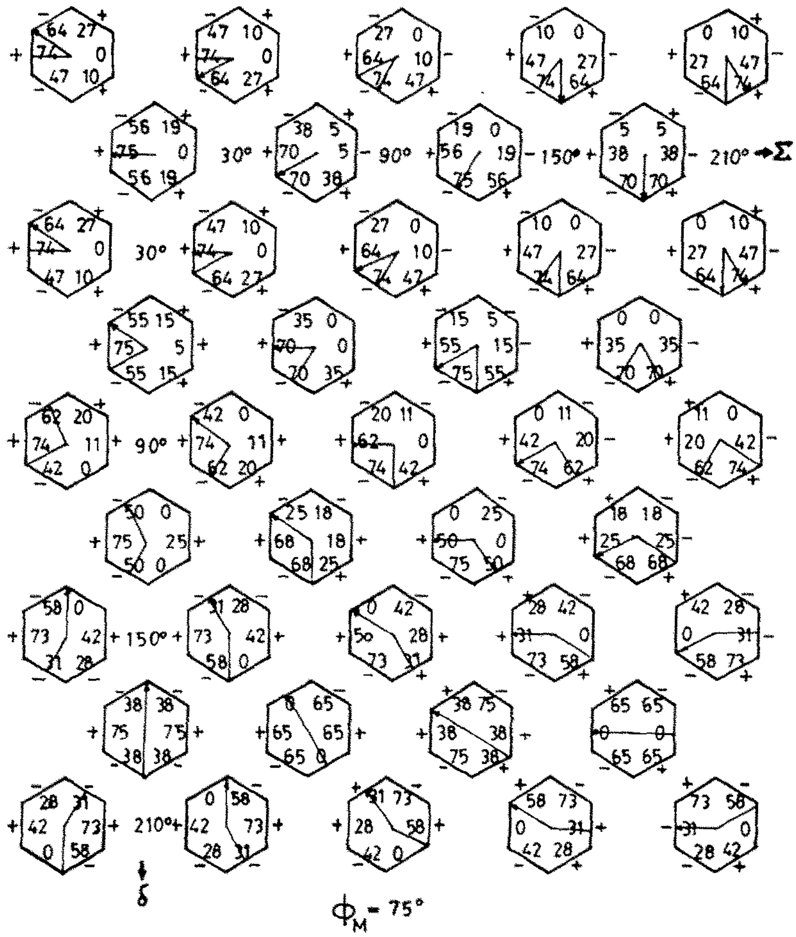

Fig. 3. Calculated torsional angles at $\Phi_M = 75°$ including the typical non-chair conformations.

The two ellipses:

$$\phi_j^2 + \phi_0^2 + \phi_j\phi_0 - 3\tau_m\phi_j - 3\tau_m\phi_0 + \left(3\tau_m^2 - \frac{3}{4}q^2\right) = 0 \quad (j = 2, 4)$$

and

$$\phi_j^2 + \phi_0^2 + \phi_j\phi_0 + \tau_m\phi_j - \tau_m\phi_0 + \left(\tau_m^2 - \frac{3}{4}q^2\right) = 0 \quad (j = 5, 1)$$

one centered at $(\tau_m, \pm\tau_m)$ respectively, and inscribed inside the mentioned squares. Both ellipses are equal but displace $2\tau_m$ from each other, as $E_2 = 2\tau_m$.

They have one axis of $q\sqrt{3/2}$ in length along a line of -1 for slope. The other is $q\sqrt{1/2}$ in length, so the ratio is constant and equal to $\sqrt{3}$.

At $q = 0$, all lines and curves degenerate to just two points.

The examples

The model has been applied to 18 examples drawn from the X-ray literature, namely the following compounds:

1 and 2 Diterpene tinophyllone;[6]

3 D-glucono-(1,5)-lactone;[7]

4 3,4,6 - Tri - 0 - acetyl - 1,2,0 - [1 - (exo-ethoxy)ethylidene] - α - D - glucopyranose;[8]

5 8 - Carboxy - 1 - hydroxy - 2 - oxobicyclo - [3,2,2]non - 6 - ene - 9,4 carbolactone;[9]

6 Jativatriol;[10]

7 1,6: 8,13 - Propane - 1,3 - diylidene[14] - annulene;[11]

8 Methyl 2,6 - dichloro - 2,6 - dideoxy - 3,4,0 - isopropylidene - α - D - altropyranoside;[12]

9 3β - Hydroxy - 17 - oxo - 5 - androstem - 19 - al;[13]

10 3,4,6 - Tri - 0 - acetyl - 1,2,0 - (1 - cyano-ethylidene) - α - D - glucopyranose;[7]

11 9 - Benzoyl - 3α - bromo - 9 - azabicyclo[3.3.1] - nonan - 2 - one;[14]

12 9 - Benzoyl - 3α - bromo - 2β - hydroxy - 9 - azabicyclo[3,3,1] - nonane;[15]

13 and 14 1,6: 2,3 - Dianhydro - β - D - gulopyranose;[16]

15 4-Bromoestradiol;[17]

16 and 17 (23R) - 3α - Methoxy - 5α,9β - lanosta - 7,24 diene - 26,23 - lactone;[18]

18 4-Bromoestrone.[19]

We have tried to include the rare sign combinations, as in 2 and 7 in Table 2. In this table, together with the values for the torsional angles, we give the estimators and parameters describing the conformations. The values are given in degrees.

In general we can speak of a fit measured with a conventional crystallographic R-index of about 0.02. We can see that the individual fit (measured by $\Sigma|\phi_0 - \phi_c|$ or some related value) is almost linear vs the discrepancies in the E_1 and E_2 estimators. The better the adjustment in the estimators the better the fit of the model. This is the cause for $E_3/3\Phi_M^2$ being greater than 1 in some cases, for Φ_M being lower than some ϕ_i values.

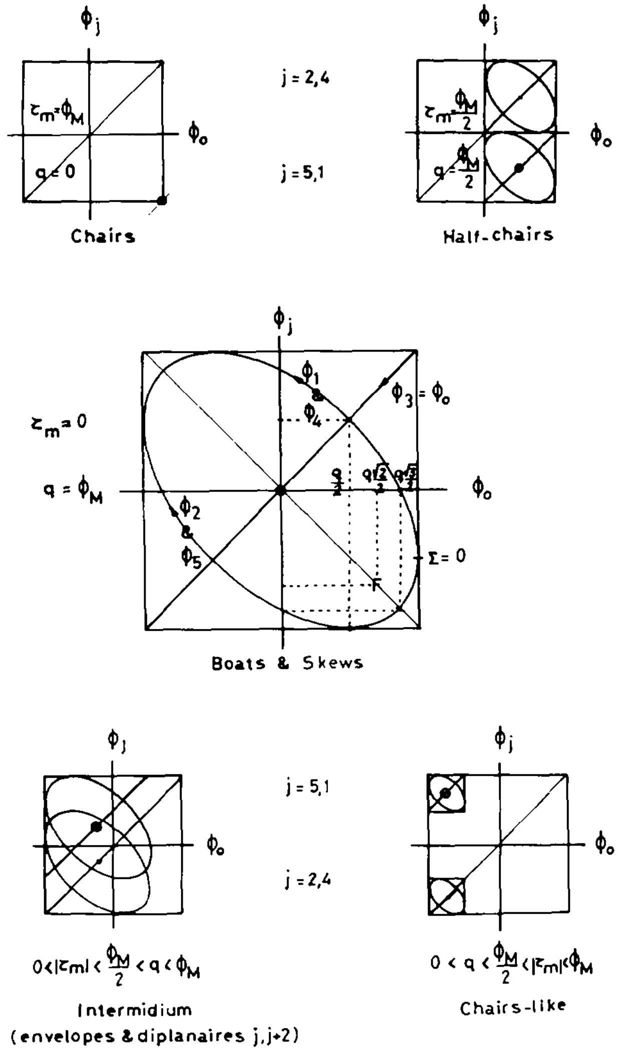

Fig. 4. $\phi_i - \phi_0$ ellipses at some values of the $\tau_m - \delta$ pathway.

Table 2(a). Studied examples with the calculated values from the model.

	1		2		3		4		5		6		7		8		9	
	obs.	calc.	obs.	calc.	obs.	calc.	obs.	calc.	obs.	calc.	obs.	calc.	obs.	calc.	obs.	calc.	obs.	calc.
ϕ_0	-51.9	-50.3	46.3	45.9	-47.3	-47.5	-40.0	-41.9	-30.7	-31.7	58.8	58.3	-57.3	-57.5	-33.8	-32.9	24.2	25.0
ϕ_1	-6.7	-6.5	-51.1	-52.4	24.8	24.6	72.0	70.1	-16.9	-17.8	-64.0	-63.9	24.0	23.3	76.2	73.9	14.0	13.6
ϕ_2	56.3	54.8	32.3	31.3	-15.2	-15.1	-42.0	-41.9	56.5	56.6	5.3	5.2	11.2	10.6	-47.3	-50.5	-57.4	-58.5
ϕ_3	-44.7	-46.3	-4.1	-3.7	28.2	28.5	-16.0	-14.3	-46.7	-45.7	59.7	59.1	-10.5	-10.3	-13.2	-13.9	65.5	64.8
ϕ_4	-10.4	-10.5	-3.8	-2.8	-50.9	-51.4	42.0	42.5	-2.9	-3.8	-65.3	-64.7	-24.5	-23.9	54.9	54.9	-26.0	-26.2
ϕ_5	57.3	58.8	-18.7	-18.3	61.7	60.9	-13.0	-14.4	44.7	42.6	5.6	6.0	57.5	57.8	-32.1	-31.5	-19.5	-18.7
E_1	-0.1		0.9		1.3		3.0		4.0		0.1		0.4		4.7		0.8	
	-7.2		50.4		-75.5		-24.0		16.0		-0.9		-46.8		-20.6		-41.3	
E_2	-3.7		47.3		-75.7		-30.0		14.0		-1.3		-48.5		-21.3		-40.0	
	-1.0		50.8		-76.9		-29.0		11.8		-0.3		-46.3		-15.2		-37.9	
τ_m	-2.0		24.8		-38.0		-13.8		7.0		-0.4		-23.6		-9.5		-19.9	
q	61.3		28.9		23.0		56.3		52.1		71.2		39.3		65.2		48.6	
Φ_M	63.3		53.7		61.0		70.1		59.1		71.6		62.9		74.7		68.5	
$E_3 \cdot 3\Phi_M^2$	0.9		0.1		-0.2		0.1		0.9		1.0		0.3		0.7		0.4	
Σ	436		-86		491		240		444		-69		421		222		45	
E_4	0.		0.7		2.8		0.2		0.		0.		0.7		0.		0.2	
δ	184		62		-		208		165		181		253		198		228	
α_1	126		-74		-		16		140		-125		84		12		-92	
α_2	310		-12		-		224		305		56		337		209		137	

Table 2(b). Studied examples (continuation).

	10 obs. calc.	11 obs. calc.	12 obs. calc.	13 obs. calc.	14 obs. calc.	15 obs. calc.	16 obs. calc.	17 obs. calc.	18 obs. calc.
ϕ_0	42.4 43.7	0. -2.1	5.7 6.1	-71.1 -71.9	-71.0 -71.4	20.5 20.4	-62.9 -62.9	21.5 21.3	10.3 10.5
ϕ_1	-14.9 -15.6	62.1 63.9	51.7 52.6	31.8 31.9	31.9 31.3	-0.3 -0.2	24.7 25.8	6.5 6.2	-12.8 -12.8
ϕ_2	-38.7 -40.4	-65.8 -62.0	-55.8 -55.5	-1.7 -1.3	-0.4 -0.3	14.0 14.2	34.7 36.2	1.4 1.1	39.8 39.7
ϕ_3	69.7 68.5	-4.0 -1.7	0.6 0.3	11.0 10.7	8.8 9.4	-48.4 -48.4	-61.1 -61.1	-35.9 -35.9	-64.1 -64.3
ϕ_4	-39.8 -40.4	62.0 63.5	58.7 59.0	-50.2 -50.7	-48.7 -49.5	69.7 68.6	23.7 24.0	63.3 63.4	62.4 62.0
ϕ_5	-16.5 -15.6	-61.0 -61.6	-62.7 -61.9	82.0 81.3	81.6 80.5	-53.7 -54.6	37.5 38.0	-56.1 -56.1	-34.8 -35.1
E_1	2.2	-6.7	-1.8	1.8	2.2	1.8	-3.4	0.7	0.8
	-27.3	4.0	5.1	-82.1	-79.8	68.9	-1.8	57.4	74.4
E_2	-24.9	-0.1	6.0	-82.0	-80.6	70.0	-1.0	56.8	75.2
	-22.2	-4.8	6.9	-83.7	-82.0	67.7	-2.8	57.5	74.6
τ_m	-12.4	-0.2	3.2	-41.3	-40.4	34.4	-0.9	28.6	37.4
q	56.1	72.5	66.2	41.8	42.0	34.4	62.4	36.7	29.8
Φ_M	68 5	72 7	69.4	83.1	82.4	68.8	62.3	65.3	67.2
$E_3:3\Phi_M^2$	1.1	1.0	0.9	0.	0.	0.	1.0	0.1	-0.1
Σ	0	183	175	446	445	226	373	203	309
E_4	0.1	0.	0.	1.	0.9	1.	0.	0.6	1.5
δ	206	180	174	342	328	0	182	77	-
α_1	-103	-2	1	52	59	114	96	63	-
α_2	103	181	175	394	387	114	277	140	-

CONCLUSIONS

First we have the perfect chair with Σ undeterminate and all torsional angles equal to Φ_M, Φ_M having values down to 0 (benzene rings). Next we have deformed chairs (chairs-like) where a value for Σ exists but not for δ. Finally it appears δ ($E_3 \geq 0$) and we enter the zone of defined planarities.

Keeping the E_1, E_2 estimators in mind, we can calculate the values for the torsional angles ϕ_i. With Eqns (1)–(6) we obtain the parameters describing the conformation.

We think that the model would be useful when there are distortions due to steric effects, fused rings, etc. Energy calculations would be very interesting, in relation with this model.

Further analysis on the T-term when E_1 and E_2 are not fulfilled is in progress but the so far observed distortions are not very great.

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