

Conformational Analysis of 12-Crown-4

JAROSŁAW KOSTROWICKI and JAN F. BIERNAT

Institute of Inorganic Chemistry and Technology and Corrosion, Technical University of Gdańsk, 80-952 Gdańsk, Poland

(Received: 17 July 1990; in final form: 11 June 1991)

Abstract. An extensive conformational analysis of 12-crown-4 was performed. A new method for the generation of the approximate geometry was proposed and applied. More than 100 new low energy conformations of the compound were calculated.

Key words. Crown ethers, conformational energy calculation, starting geometry generation.

1. Introduction

Macrocyclic polyethers (crown ethers) play an important role in chemistry due to their ability to form stable complexes with alkali metal cations. When the macrocyclic ring is not condensed to rigid groups the crown ether molecule is highly flexible. Rotation around endocyclic bonds in such molecules is not hindered and the number of conformations of comparable energy becomes great, even for medium sized rings.

Molecular mechanics (MM) is a commonly used technique for the calculation of molecular geometry. It locally minimizes the steric energy expressed as an algebraic function. When there are many energy minima the geometry obtained as the result of MM calculations depends on the initial starting point. A reasonable choice of **starting** geometry to be refined by molecular mechanics becomes the crucial point of the study. When one is interested in the most stable conformer one should find minima of the lowest energy. A *very many random starts* technique is extremely computer time consuming. Alternatively one can apply certain geometrical, combinatorial and logical considerations to construct initial geometries in a systematic way. We have chosen the second way to explore the conformational space of 12-crown-4 (12C4). The compound (Figure 1) is an example of a medium ring with a fairly large number of minima.

2. Generation of Starting Geometries

When studying chains or rings formed by atoms in sp^3 hybridization we can consider geometries superimposable on the diamond lattice [1]. A review of all these geometries helps to classify them and choose the best one. However, this analysis is restricted to even numbered rings. Moreover, among medium sized rings the 14-membered ring is the first one for which an ideal conformation without overlaps exists, i.e. without close contacts of substituent atoms (e.g. hydrogens in hydrocarbons).

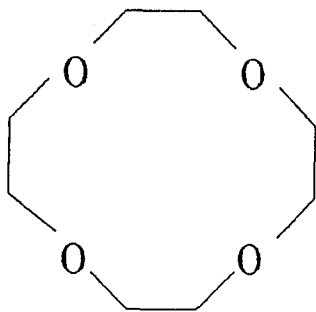


Fig. 1. 12-crown-4.

Table I. Signs of torsional angles for conformations of 12-crown-4 superimposable on the diamond lattice and energies obtained by local minimization from their geometries as starting estimates.

Number ^a	Sequence ^b of angles	$E^{c,d}$
25	+ + 0 + - 0 - - + 0 0 -	135.2
61	+ + - - 0 0 + + - - 0 0	147.8
62	- + + 0 + - 0 - - + 0 0	147.8
65	+ 0 0 - + 0 0 - + 0 0 -	149.5
72	0 + + 0 + + - 0 0 - + +	151.4
76	0 + + - - 0 0 + + - - 0	154.1
92	+ 0 + + 0 + + - 0 0 - +	170.6

^aEvery conformation is labelled by the ordinal number in the series of all conformations obtained in this work in the order of increasing energy.

^bFirst torsional angle is defined by the sequence of atoms OCCO.

^cMM2 force field.

^dValues in kJ mol^{-1} .

There are 7 different conformations of 12-crown-4 superimposable on the diamond lattice [2]. The signs of the torsional angles for these conformations are shown in Table I. Each of them has a very large steric energy due to overlaps (Fig. 1). We performed MM2 [3] calculations using all these conformations as starting approximations. The calculated conformations differed substantially from the starting ones. The van der Waals terms responsible for contacts occurring in the ideal conformations decreased significantly. Torsional and 1,4 van der Waals terms became dominant in the energy expression. The energies and endocyclic torsional angles for those minima are collected in Tables I and II, respectively. The energy difference between the highest and lowest energy conformer is very large (over 33.5 kJ mol^{-1}).

The geometries calculated above are completely different from those found in crystal structures. Crystallographic structures were thus used as the second set of initial geometries. There are three different geometries of 12-crown-4 found in the crystalline state [4]: of approximate C_4 symmetry observed in $[\text{Na}^+(\text{12C4})_2][\text{Cl}^- \cdot 5\text{H}_2\text{O}]$, $[\text{Na}^+(\text{12C4})_2][\text{ClO}_4^-]$, $[\text{Ca}^{2+}(\text{12C4})_2][2\text{Cl}^- \cdot 8\text{H}_2\text{O}]$,

Table II. Torsional angles for conformations obtained by minimization from ideal geometries (Table I).

Number ^a	Torsional angles ^b					
25	52.9	-100.4	153.3	-156.8	113.6	-61.5
	-57.5	173.6	-94.8	68.5	-172.8	83.4
61	43.7	84.6	-80.6	-46.3	166.6	-169.2
	43.9	84.6	-80.5	-46.2	166.8	-169.4
62	84.0	-179.5	178.7	-84.3	52.3	65.0
	-166.8	95.2	-97.9	168.9	-63.7	-51.4
64	70.4	-127.7	165.5	-119.7	92.7	-62.1
	-172.9	172.6	53.4	-79.4	162.2	-144.2
72	69.6	157.2	162.0	71.4	-56.0	-58.7
	170.6	-69.1	-69.7	169.3	-58.6	-57.1
76	85.1	89.3	-164.4	116.8	-65.0	-62.4
	86.2	86.8	-163.4	119.2	-65.4	-61.2
92	45.5	67.2	-88.8	-179.9	-139.9	-56.2
	62.2	68.9	-163.0	59.7	80.2	-171.7

^{a, b}see Table I.

and $[\text{Co}^{2+}(\text{12C4})][(\text{NO}_3^-)_2]$; of C_i symmetry in free 12C4 crystals and in $[\text{Mg}^{2+}(\text{H}_2\text{O})_6][2\text{Cl}^- \cdot (\text{12C4})]$ and of C_s symmetry found in $[\text{Cu}^{2+}(\text{12C4})][\text{Cl}^-]_2$. The results of MM2 calculations applied to the crystalline state geometries are summarized in Table III and IV. Only slight modifications of the starting angles were necessary to attain the local minimum. It seems that crystal packing forces play a minor role when the qualitative description of the molecular shape is considered. The energy of the conformation calculated from the initial crystalline state geometry was always lower than that obtained using the diamond lattice matrix.

As overlaps appeared to be an essential obstacle to reach low-energy conformations we introduced another generation technique for starting points. The first step was based on the generation of all **chain** conformations without overlaps [2, 5] superimposable on the diamond lattice. In the second step closure of those chains was carried out by making slight changes in torsional angles so as to obtain rings of similar local shape. Mathematical details of the procedure are given in the Appendix. Local energy minimization from closed geometries as the starting estimates was the final step. The results are very interesting. Among the low energy

Table III. Energies for conformations obtained by minimization from crystallographic geometries as starting estimates.

Number ^a	Crystalline compound	Approximate symmetry	$E^{\text{c, d}}$
3	$\text{Cu}(\text{12C4})\text{Cl}_2$	C_s	122.8
5	12C4	C_i	124.1
7	$\text{Na}(\text{12C4})_2\text{Cl} \cdot 5 \text{H}_2\text{O}$	C_4	125.6

^{a, c, d}see Table I.

Table IV. Torsional angles for conformations obtained by minimization from crystallographic geometries as starting estimates (Table III).

Number ^a	Torsional angles ^b					
3	55.4	-167.2	169.4	-55.9	-71.6	130.2
	-67.5	169.5	-167.9	67.3	-131.5	71.2
5	71.7	-165.0	102.2	-76.7	154.3	-91.3
	-73.1	164.2	-101.9	77.8	-154.7	91.8
7	58.1	80.7	-164.8	58.9	81.1	-163.6
	58.1	80.7	-164.8	58.9	81.1	-163.6

^a, ^bsee Table I.

conformers obtained approximately 100 are new and not reported elsewhere. Forty-nine different conformations have been found in the range of 21 kJ mol⁻¹ starting from the one with the lowest energy. The energies and torsional angles for the conformations are shown in Table V. Most OCCO dihedral angles are *gauche* while most CCOC angles are *anti*.

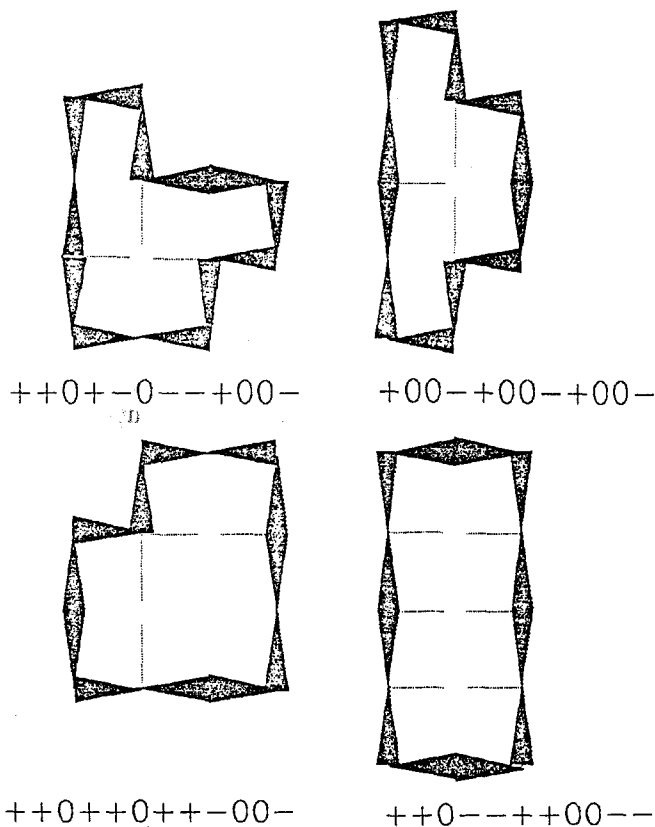


Fig. 2. Ideal conformations of a 12-membered ring projected onto the plane perpendicular to the bisector of the valence angle. The signs of endocyclic torsional angles are given. The number of ideal 12-crown-4 conformations is equal to 7 because there are two types of atoms in the ring.

Table V. Energies and torsional angles for conformations obtained by minimization from closed, ideal chains without overlaps as starting estimates. Only conformations of energy below 142 kJ mol^{-1} are shown. All conformations obtained by the other methods (Table I–IV) also resulted from this method but are not repeated here.

Number ^a	$E^{c, d}$	Torsional angles ^b					
1	121.4	57.7	-175.7	160.3	-71.6	136.8	-78.4
		-61.6	174.4	-82.6	-68.4	155.8	-99.1
2	121.9	72.7	-159.3	99.0	-72.8	158.7	-98.6
		72.7	-159.3	99.0	-72.8	158.7	-98.7
4	123.2	64.7	-159.7	90.3	-84.3	167.5	-108.6
		67.7	-159.1	85.6	66.1	-155.9	85.6
6	125.5	39.7	-179.0	163.1	-76.4	126.0	-83.2
		-63.8	176.1	-98.8	83.0	-155.8	74.8
8	127.7	44.4	-173.0	174.7	-75.4	76.4	-111.0
		164.1	-157.0	69.8	44.9	-161.5	72.1
9	127.9	51.4	-175.7	158.9	-64.0	103.0	-158.9
		96.9	-80.8	159.8	-58.1	-106.4	66.8
10	128.7	62.0	-158.1	171.9	-70.1	83.3	-127.5
		167.3	-147.8	92.4	-68.2	156.4	-156.2
11	129.8	54.5	-156.2	97.3	-58.8	-179.3	-167.4
		86.7	-49.4	-64.6	164.3	-152.4	75.1
12	129.9	54.8	-100.9	141.4	-82.3	162.0	-176.4
		55.0	-100.9	141.4	-82.1	162.3	176.6
13	130.0	48.4	176.9	157.5	-71.7	97.4	-148.3
		76.1	98.4	-154.2	88.3	-136.8	77.1
14	130.8	62.1	-111.7	164.4	-104.5	71.0	-128.8
		177.2	-122.5	83.4	-69.5	174.4	-169.2
15	131.2	63.3	-176.8	127.0	-67.4	109.6	-167.8
		71.2	92.5	-144.6	86.6	-140.8	86.3
16	131.7	67.6	-80.0	120.2	-175.2	76.2	81.0
		-81.5	-78.2	140.7	-69.8	162.7	-177.3
17	132.3	61.4	-100.0	160.6	-65.5	-99.7	93.7
		69.2	-160.7	103.7	-61.8	167.2	-169.8
18	132.5	54.5	-179.1	161.0	-72.1	98.6	-135.0
		65.5	147.9	-165.3	61.5	-132.7	69.6
19	133.8	44.4	-168.6	173.0	-48.5	-70.7	98.6
		53.0	-176.8	71.5	56.2	-154.6	73.2
20	133.9	42.5	-169.4	160.1	-65.2	94.9	-156.8
		142.4	-117.5	67.3	61.4	179.1	62.5
21	134.9	37.5	-167.1	161.6	-65.7	101.2	-172.8
		67.2	75.5	-119.5	120.7	-166.2	67.1
22	135.0	57.4	178.8	81.1	81.3	-78.5	-66.3
		90.8	94.6	-159.4	84.7	-126.5	77.7
23	135.1	35.2	70.9	-160.2	76.3	-89.6	153.7
		-153.2	111.1	-70.7	80.6	173.5	68.5
24	135.2	29.6	64.4	-172.8	44.5	74.7	-164.4
		66.7	85.9	-127.0	86.8	-166.1	75.2
26	135.5	67.1	-104.7	162.7	-100.2	72.4	-136.3
		177.4	-64.7	-59.3	83.9	86.7	-169.5
27	135.5	57.1	-125.1	68.8	60.6	-179.2	77.6
		91.5	-62.6	-67.6	77.3	159.3	-176.5
28	137.7	32.8	-160.3	164.5	-49.9	-76.9	174.5
		-89.7	73.1	-120.0	161.7	-154.7	61.9
29	138.0	43.9	-168.4	85.6	73.2	-170.2	111.3

Table V. (continued).

Number ^a	$E^{c, d}$	Torsional angles ^b					
30	138.2	-61.9	101.4	-163.5	153.0	-128.9	61.3
		65.1	-77.2	110.6	-134.4	167.1	-78.6
		-84.3	70.2	61.2	-97.3	170.4	168.2
31	138.4	44.2	-158.1	81.3	52.7	-178.0	81.4
		77.7	-59.8	-63.3	166.7	-157.4	67.0
32	138.5	79.6	-72.0	103.2	-131.0	174.2	-165.3
		79.7	-72.0	103.2	-130.9	174.2	-165.4
33	139.0	54.1	-95.9	132.7	-107.2	154.9	-86.9
		-90.0	66.6	67.5	-91.6	169.9	179.2
34	139.0	32.2	179.7	158.0	-89.7	52.9	64.9
		173.1	125.1	-72.8	103.0	-163.9	77.6
35	139.8	53.5	-160.4	149.9	-143.0	61.9	46.0
		-84.4	-178.6	-178.9	74.6	-125.9	71.7
36	140.1	40.1	-162.1	167.5	-41.0	-68.4	169.9
		-62.1	-90.2	98.7	57.1	-170.8	63.2
37	140.3	36.4	69.7	-140.3	63.5	-165.8	162.7
		-73.3	129.1	-97.0	75.2	-180.0	61.3
38	140.3	72.6	-76.1	118.3	-162.1	72.2	67.9
		-175.2	63.4	50.9	-86.8	175.4	171.2
39	140.5	76.1	-157.6	89.8	81.9	-63.3	-69.6
		174.1	-76.7	-74.2	84.0	81.4	-140.2
40	140.6	46.3	-110.5	155.3	-169.9	107.3	-70.4
		83.2	-176.0	105.8	55.3	-167.7	78.8
41	140.7	65.7	-87.6	138.6	-150.9	65.6	59.9
		179.6	64.7	55.0	-85.2	174.15	-178.9
42	140.7	75.6	-152.8	87.6	83.1	-65.8	-71.8
		173.4	-75.4	-71.0	84.3	83.3	-144.3
43	140.8	34.5	-169.8	149.7	-65.6	149.6	-165.4
		34.6	63.9	-151.5	150.8	-143.6	64.2
44	141.2	32.3	-169.9	156.0	-65.0	135.6	-167.3
		43.8	68.5	-144.0	144.2	-150.7	64.1
45	141.5	64.5	-131.7	94.2	-68.5	161.1	-162.9
		127.4	-60.4	-52.9	77.4	167.5	168.4
46	141.7	40.4	-176.9	167.0	-80.8	70.2	-107.5
		-172.4	-65.0	-62.9	119.5	-152.1	78.5
47	141.8	62.7	85.8	-153.8	67.9	-158.1	166.7
		-83.3	53.6	61.8	177.3	121.5	-106.1
48	141.8	53.6	121.5	-84.2	-95.3	70.3	77.7
		-88.8	-87.1	170.6	-73.6	88.3	-145.7
49	141.9	21.2	67.2	-162.7	63.3	-106.5	176.8
		-86.4	72.7	-113.3	137.9	-169.9	67.0

a, b, c, d see Table I.

3. Discussion

Previously [6], to calculate conformations of 12-crown-4 of low energy the modified White-Bovill alkane-alkene force field (WBFF) extended for calculations of the geometrical and thermodynamic properties of saturated compounds containing isolated 1,4-dioxa groupings was applied. Comparison of our results with WBFF

calculations suggests that the energy sequence may depend significantly on the applied field, but geometries are comparable and it is possible to distinguish geometries of certain features for different fields. The differences of torsional angles for conformation number 5 computed by WBFF and MM2 are smaller than those observed in crystalline 12C4 and $[\text{Mg}^{2+}(\text{H}_2\text{O})](12\text{C}4)$ (in the latter case the crown does not complex the magnesium ion). It is only a confirmation of the rule that for systems with many degrees of freedom the applied force field is not decisive but a properly chosen starting geometry is decisive [17]. Excellent agreement between crystal data and the results of computations for both force fields can be observed for conformation number 7. The energy differences for conformations 5 and 7 in the WB force field is 12 kJ mol^{-1} which is probably much too high. The other four conformations considered by Bovill *et al.* [6] correspond to those of numbers 6, 12, 18 and 36 in this paper. The 10 lowest energy conformations of 12-crown-4 are presented in Figure 3.

In order to unify projections and help the reader study differences between the structures obtained we have chosen the C and O atoms mean plane [8] for all drawings (Figure 3).

Substantial differences in shapes for very close energy conformations have been found. The best conformation appeared to be a nonsymmetric one with relatively

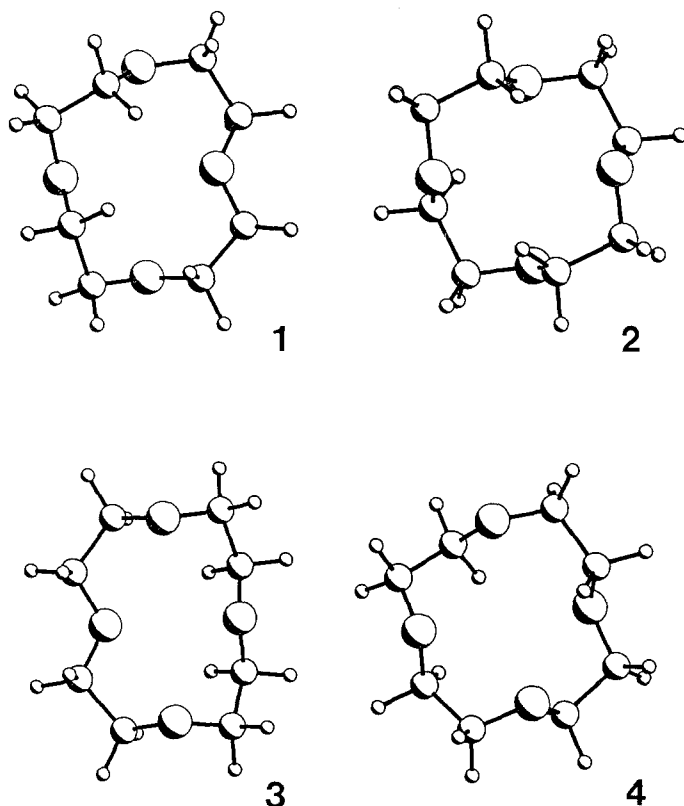


Fig. 3.

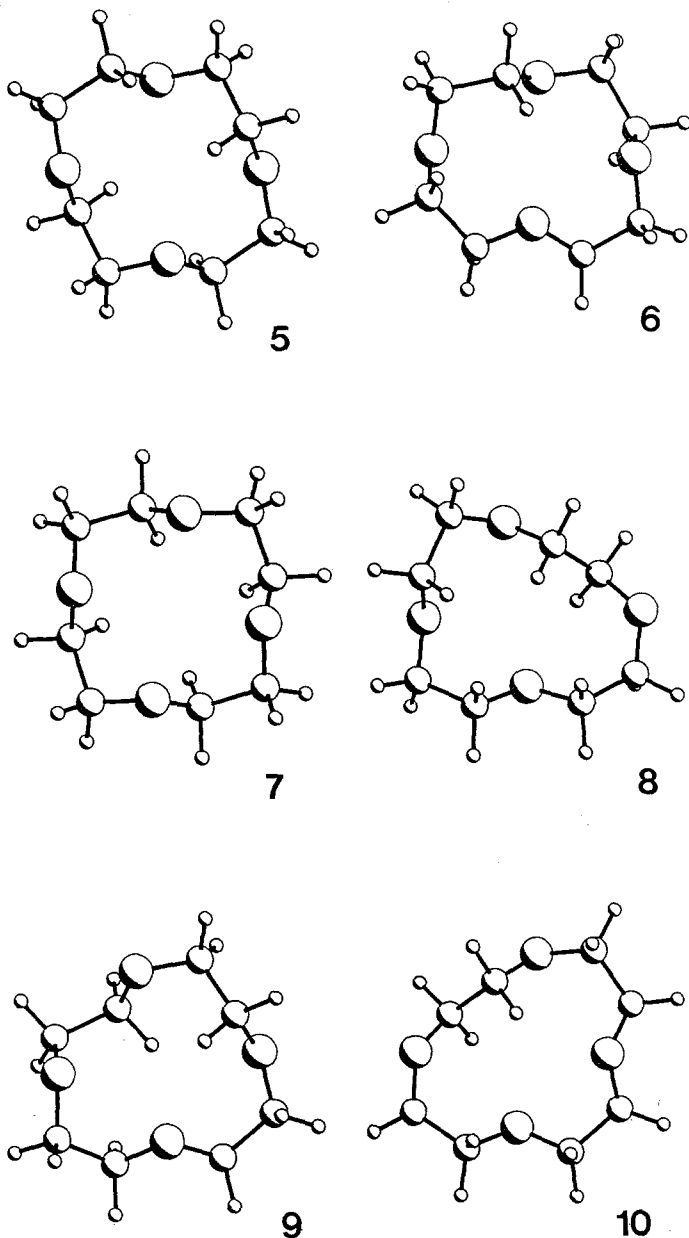


Fig. 3. The 10 lowest energy conformations of 12-crown-4. Projections onto the mean plane.

small torsional and bending energies and medium dipole-dipole intramolecular interactions. The next one has a S_4 symmetry with very advantageous dipole orientations. The next conformation with C_s symmetry is observed in the complex with CuCl_2 . Conformation number 4 is nonsymmetric like the first one but has a more favourable dipole-dipole interaction energy and higher torsional strain energy. The next centrosymmetric conformation is known from the structure of free

12-crown-4 in the crystalline state. Geometry number 6 was also described [6] as the second best. There is no reason to describe all the calculated conformations in detail. The reader can compare the drawings in Figure 3 and consult Table V to further analyse the geometry-energy relationships.

4. Conclusions

The problem of finding the conformation of lowest energy even for small molecules is difficult but it is important for understanding their physical and chemical properties. Evaluations of conformational space shearing by using both systematic and random methods may lead to a global energy minimum. Calculations of energy minima for cycloheptadecane [9] may serve as an example of such searching and the associated difficulties. Our new approach to the generation of starting approximate conformations gives a convenient way for finding all conformations of 12-crown-4 evaluated previously, in addition to many others, including probably the global energy minimum. Although the conformations were calculated with the use of the classical MM2 [3] method taking into account the dipole-dipole interactions, any other method, using for example the electrostatic charge distribution [10, 11], is also applicable for the conformational minimum determination by this new approach.

Acknowledgements

The authors wish to express their thanks to Dr A. Cygan for help and fruitful discussions. This work was supported by the Polish Academy of Sciences within the project CPBP 01.15.

Appendix

All valence angles and bond lengths and the majority of torsional angles defining the geometry of the chain (open conformation) were fixed. The only adjustable parameters were dihedral angles for atoms which were to form the ring. There were nine of them: $w_{1,2,3,4}$, $w_{2,3,4,5}$, ... $w_{9,10,11,12}$ (subscripts label subsequent endocyclic C or O atoms). Redundant valence angles and bond lengths which were to become endocyclic after closing the ring, had initially improper values. Those valence angles and bond lengths, not necessary to define the geometry but of obligatory values, were $a_{11,12,1}$, $a_{12,1,2}$ and $r_{12,1}$. Because the number of the parameters to be changed (nine) (see Equation (4)) exceeded the number of conditions to hold (three) (see Equation (3)) we could apply additional degrees of freedom to make the changes of parameters being adjusted as few as possible. Thus we restricted the change of parameters to be linear combinations of gradients to be held. It gave in practice very slight changes of geometry during the closing procedure. The Newton-Raphson iterative formula for this method was as follows:

$$x^{(p+1)} = x^{(p)} + f(x)^{(p)} T_t^{(p)} \quad (1)$$

where $t^{(p)}$ is the solution of equation:

$$f_x(x^{(p)}) f_x(x^{(p)})^T t^{(p)} = -f(x^{(p)}) \quad (2)$$

where

$$f(x) \equiv \begin{bmatrix} a_{11,12,1}(x) - a_{11,12,1}^* \\ a_{12,1,2}(x) - a_{12,1,2}^* \\ \dots \\ r_{12,1}(x) - r_{12,1}^* \end{bmatrix} \quad (3)$$

$$x \equiv \begin{bmatrix} \omega_{1,2,3,4} \\ \omega_{9,10,11,12} \end{bmatrix} \quad (4)$$

$r_{i,j}(x)$ is the distance between the i th and j th atom computed for parameters x ; $r_{i,j}^*$ is the required value of the distance between the i th and j th atom; $a_{i,j,k}(x)$ is the valence angle for atoms i, j, k computed for parameters x ; $a_{i,j,k}^*$ is the required value of the valence angle for atoms i, j, k ; $\omega_{i,j,k,l}$ is the torsional angle for atoms i, j, k, l ; f_x is the Jacobi matrix; p is the iteration number; and superscript T denotes matrix transposition.

References

1. J. Dale: *J. Chem. Soc.* 93 (1963).
2. J. W. H. M. Uiterwijk, S. Harkema and B. W. van der Waal: *J. Chem. Soc. Perkin Trans. 2*, 1843 (1983).
3. N. L. Allinger: *J. Am. Chem. Soc.* **99**, 8127 (1977).
4. P. Groth: *Acta Chem. Scand* **A32**, 279 (1978); M. A. Neuman, E. C. Steiner, F. P. van Remoortere and F. P. Boer; *Inorg. Chem.* **14**, 734 (1975); F. P. van Remoortere and F. P. Boer; *ibid* **13**, 2071 (1974); F. P. Boer, M. A. Neuman, F. P. van Remoortere and E. C. Steiner: *ibid.* **13**, 2826 (1974); P. P. North, E. C. Steiner, F. P. van Remoortere and F. P. Boer: *Acta Crystallogr.* **B32**, 370 (1976); F. P. van Remoortere, F. P. Boer and E. C. Steiner: *ibid* **B31**, 1420 (1975); E. M. Hoit, N. W. Alcock, R. R. Hendrixon, G. D. Malpass Jr., R. G. Ghirardelli and R. A. Palmer: *ibid* **B37**, 1080 (1981); E. Mason and H. A. Eick: *ibid* **B38**, 1821 (1982).
5. M. Saunders: *Tetrahedron* **23**, 2105 (1967).
6. M. J. Bovill, D. J. Chadwick, I. O. Sutherland and D. Watkin: *J. Chem. Soc. Perkin Trans 2*, 1529 (1980).
7. O. Burkert and N. L. Allinger: *Molecular Mechanics*, ACS Monograph 177, American Chemical Society, Washington DC (1982).
8. D. Cremer and J. A. Pople: *J. Am. Chem. Soc.* **97**, 1354 (1975).
9. M. Saunders, K. N. Houk, Y.-D. Wu, W. C. Still, M. Lipton, G. Chang and W. C. Guida: *J. Am. Chem. Soc.* **112**, 1419 (1990).
10. N. L. Allinger and M. T. Wuesthoff: *Tetrahedron* **33**, 3 (1976); U. Chandra Singh and P. A. Kollman, *J. Comput Chem.* **5**, 129 (1984).