Comparative modelling studies on 3,6-substituted 1,2,4-trioxan-5-ones

Jefford, Charles; Bernardinelli, Gérald Hugues; Josso, Martin; Morgantini, Pierre-Yves; Weber, Jacques

How to cite

JEFFORD, Charles et al. Comparative modelling studies on 3,6-substituted 1,2,4-trioxan-5-ones. In: Journal of molecular structure. Theochem, 1995, vol. 337, n° 1, p. 31–37. doi: 10.1016/0166-1280(94)04110-E

This publication URL: https://archive-ouverte.unige.ch/unige:2861
Publication DOI: 10.1016/0166-1280(94)04110-E

ELSEVIER

Journal of Molecular Structure (Theochem) 337 (1995) 31–37

THEO
CHEM

Comparative modelling studies on 3,6-substituted 1,2,4-trioxan-5-ones

Charles W. Jefford*, Gérald Bernardinelli, Martin C. Josso, Pierre-Yves Morgantini, Jacques Weber*

Departments of Organic and Physical Chemistry, University of Geneva, CH-1211 Geneva 4, Switzerland

Received 11 October 1994; accepted 12 December 1994

Abstract

The main geometric elements of three 3,6-substituted 1,2,4-trioxan-5-ones have been calculated by using molecular mechanics (MM2), and semiempirical (AM1, PM3) methods. The results are compared with those obtained by X-ray analysis.

1. Introduction

1,2,4-Trioxan-5-ones are essentially unknown as a chemical class. There has been a feeling, amongst chemists, that such entities, if capable of existence, would undergo spontaneous fragmentation to their carbonyl and carbon dioxide constituents [1,2]. However, it turns out that 3,6-substituted 1,2,4-trioxan-5-ones can be conveniently synthesized [3] and that they possess unexpected thermal stability [4,5]. Many are crystalline solids and several of their structures have been determined by X-ray crystallography [6]. In view of the central importance of the cyclohexane ring in organic chemistry [7] and the novelty of its 1,2,4-trioxane analogue [8], we decided to undertake a geometry optimization of some 1,2,4-trioxan-5-ones (**1**–**3**) by using molecular mechanics (MM2) and semiempirical AM1 and PM3 computational methods which would allow us to assess their reliability by comparing the results with X-ray data. The study should also provide useful information on the performance of these theoretical models, since the use of more sophisticated methods, such as ab initio or density functional theory, with such relatively large molecules, could be problematic.

2. Methods

2.1. Molecular mechanics calculations

The structures of the three 1,2,4-trioxan-5-ones were built from standard geometrical parameters by using MACROMODEL/BATCHMIN V3.1X [9], a modelling package based on molecular mechanics. Next, the geometries were optimized by recourse to the MM2 force field [10] as implemented in MACROMODEL with inclusion of the peroxide bond parameters [11]. The resulting optimized structures were then used as initial geometries to localize the global minima following a procedure based on Monte

---

* Corresponding author.

SSDI 0166-1280(94)04110-5

Table 1
Main geometric elements[a] of trioxanone **1**

Element	X-ray	MM2	AM1	PM3
O(1)–O(2)	1.478	1.467	1.290	1.558
O(2)–C(3)	1.422	1.412	1.434	1.386
C(3)–O(4)	1.439	1.413	1.426	1.422
O(4)–C(5)	1.352	1.366	1.378	1.368
C(5)–C(6)	1.521	1.530	1.508	1.533
C(5)–O(7)	1.206	1.216	1.229	1.211
O(1)–O(2)–C(3)	101.6	103.3	112.7	107.7
O(2)–C(3)–O(4)	107.9	104.6	106.1	107.4
C(3)–O(4)–C(5)	120.2	121.1	119.6	119.9
O(4)–C(5)–C(6)	118.8	116.5	119.8	122.3
O(4)–C(5)–O(7)	118.3	122.6	112.0	108.2
O(1)–O(2)–C(3)–O(4)	70.6	284.5	294.7	293.2
O(2)–C(3)–O(4)–C(5)	323.1	39.2	34.9	33.6
C(3)–O(4)–C(5)–C(6)	5.0	355.6	344.5	354.3
C(3)–O(4)–C(5)–O(7)	185.0	177.9	169.9	178.9
ΔH_f (kcal mol^{-1})	–	–	−93.297	−93.193
Gradient	–	0.040	0.242	0.409

[a] Bond lengths in Å, angles in deg.

Table 2
Main geometric elements[a] of trioxanone **2**

Element	X-ray	MM2	AM1	PM3
O(1)–O(2)	1.468	1.467	1.290	1.547
O(2)–C(3)	1.394	1.411	1.440	1.398
C(3)–O(4)	1.457	1.413	1.429	1.429
O(4)–C(5)	1.350	1.366	1.375	1.364
C(5)–C(6)	1.516	1.530	1.509	1.534
C(5)–O(7)	1.192	1.216	1.229	1.211
O(1)–O(2)–C(3)	104.4	103.2	110.6	105.8
O(2)–C(3)–O(4)	109.1	105.4	105.2	105.1
C(3)–O(4)–C(5)	120.0	121.5	118.9	118.9
O(4)–C(5)–C(6)	118.7	116.4	120.3	122.5
O(4)–C(5)–O(7)	119.0	122.7	112.2	108.6
O(1)–O(2)–C(3)–O(4)	295.8	286.3	290.1	287.3
O(2)–C(3)–O(4)–C(5)	18.0	32.5	36.5	38.2
C(3)–O(4)–C(5)–C(6)	14.2	3.9	349.3	356.8
C(3)–O(4)–C(5)–O(7)	194.7	184.2	173.2	180.2
ΔH_f (kcal mol^{-1})	–	–	−154.050	−143.445
Gradient	–	0.056	0.494	0.370

[a] Bond lengths in Å, angles in deg.

Table 3
Main geometric elements[a] of trioxanone **3**

Element	X-ray	MM2	AM1	PM3
O(1)–O(2)	1.436	1.465	1.287	1.543
O(2)–C(3)	1.430	1.413	1.446	1.407
C(3)–O(4)	1.486	1.415	1.434	1.436
O(4)–C(5)	1.337	1.363	1.371	1.360
C(5)–C(6)	1.497	1.528	1.517	1.539
C(5)–O(7)	1.201	1.217	1.229	1.212
O(1)–O(2)–C(3)	107.0	105.5	112.0	108.5
O(2)–C(3)–O(4)	107.5	109.0	105.0	106.7
C(3)–O(4)–C(5)	121.8	122.2	119.4	119.8
O(4)–C(5)–C(6)	119.7	116.5	120.8	123.0
O(4)–C(5)–O(7)	117.2	123.4	112.8	109.2
O(1)–O(2)–C(3)–O(4)	300.3	295.5	292.1	293.4
O(2)–C(3)–O(4)–C(5)	18.6	22.7	35.7	35.5
C(3)–O(4)–C(5)–C(6)	5.3	7.0	347.5	352.1
C(3)–O(4)–C(5)–O(7)	182.8	186.0	170.4	174.2
ΔH_f (kcal mol^{-1})	–	–	−133.805	−133.285
Gradient	–	0.022	0.250	0.511

[a] Bond length in Å, angles in deg.

Carlo/energy minimization techniques (MC/EM). This procedure entails a systematic *pseudo* Monte Carlo search [12] which employs a usage-directed algorithm [13]. In practice the initial structure at each step is selected from previously saved low energy geometries with preference being given to those least used previously. Energy minimization was performed by using the Polak–Ribière conjugate gradient [14] so that only conformers having energies less than 10 kJ mol^{-1} above the global minimum were saved.

2.2. Semiempirical calculations

Global minima obtained by the MC/EM procedure were used as input data for the semiempirical calculations. The geometries derived from the latter were optimized by employing the AM1 and PM3 hamiltonians as implemented in the SCAMP 4.2 program [15]. All optimizations were performed with the PRECISE option and without any geometrical constraints. The final geometries were obtained by applying Bartels non-linear least-squares gradient minimization routine [16].

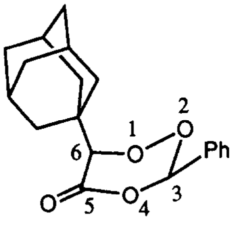
Molecular mechanics and semiempirical calculations were carried out on Silicon Graphics IRIS 4D/25 and 4D/35 workstations. All the calculated and X-ray values for the more important bond lengths, angles and dihedral angles are gathered in Tables 1–3.

3. Results and discussion

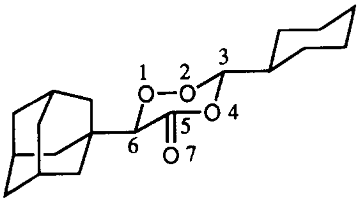
The 1,2,4-trioxan-5-ones were initially prepared [17] and selected for study on account of their suitability for X-ray analysis [6]. The first two, **1** and **2**, are representative of *cis*- and *trans*-3,5-disubstituted derivatives, while **3** is doubly spirocyclic at the 3- and 6-positions.

3.1. Conformations

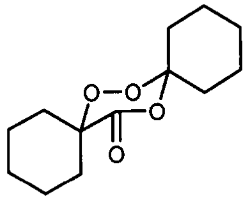
From the X-ray data, it was found that the trioxanone ring in the cis derivative **1** exists in an envelope conformation placing the adamantyl and phenyl groups in axial and equatorial positions respectively, whereas in the trans, **2**, and the tetrasubstituted, **3**, derivatives it adopts a half-chair conformation.



1



2



3

The MM2 global minimum for all three molecules corresponds to a half-chair conformation. Evidently, for the lowest energy conformations of **2** and **3**, MM2 modelling and X-ray data are in agreement. In the case of **1**, a conformation corresponding to that of the crystal structure could be found among the local minima of higher energy generated by the MC/EM procedure, which is only 2 kcal mol^{-1} higher in energy than the calculated global minimum. Packing effects in the crystal could be responsible for this discrepancy but were discounted after a careful study of their magnitude. It was concluded that the difference was more likely to be due to the MM2 parametrization. Subsequent optimization of the global minima by using the semiempirical methods AM1 and PM3 did not produce any major conformational changes but caused instead further variations in the geometry of the molecule within a given conformation, which usually deviated further from that of the crystal.

3.2. Bond lengths

MM2 yielded interatomic distances close to those observed in the crystal. Differences of 1–4% in bond length were observed (Fig. 1). In general, the error on a particular bond was not consistent but varied from molecule to molecule. For instance, the O2–C3 calculated length is too short by 0.030 Å for **1** and too long by 0.047 Å for **2**. The peroxide bond is well described for **1** and **2**, but is slightly too long for **3**. MM2 overestimates the lengths of the three bonds attached to the C5 atom for all three trioxanones by up to 2%. Overall, the calculated structure of **3** differed the most from that of the crystal structure.

One of the known shortcomings of the AM1 parametrization is its underestimation of the length of the peroxide linkage by 0.17 Å [18]. This same defect is characteristic of all three trioxanones, with large errors of 0.188, 0.178 (≈ 12%) and 0.149 Å (9%) being observed for **1**, **2** and **3** respectively (Fig. 1). The PM3 parametrization leads to a marked improvement, but overestimates the bond lengths, making them longer by 0.080, 0.079 and 0.107 Å (5–9% respectively).

Although semiempirical calculations generally fare better for **1** and **2** than for **3**, no general trend emerges favouring one of the parametrizations over the other. When the results of all three methods are compared it appears that, even if their relative success at predicting bond lengths changes dramatically with the bond or molecule in question, the difference between the different methods remains about the same for each bond studied regardless of the trioxanone. For instance, MM2 gives a better estimate than AM1 by about 0.013 Å for the carbonyl bond length for all three trioxanones. For the same bond, PM3 is the best, with the closer concordance for all three methods being seen for **1**.

3.3. Bond angles

The conformation of **1** predicted by MM2 is different from that observed by X-ray crystallography. Nevertheless, bond angles obtained by the three calculation methods for **1**–**3** can be compared (Fig. 2). As was the case with bond lengths, the results furnished by MM2 are slightly better overall than those derived from the semiempirical

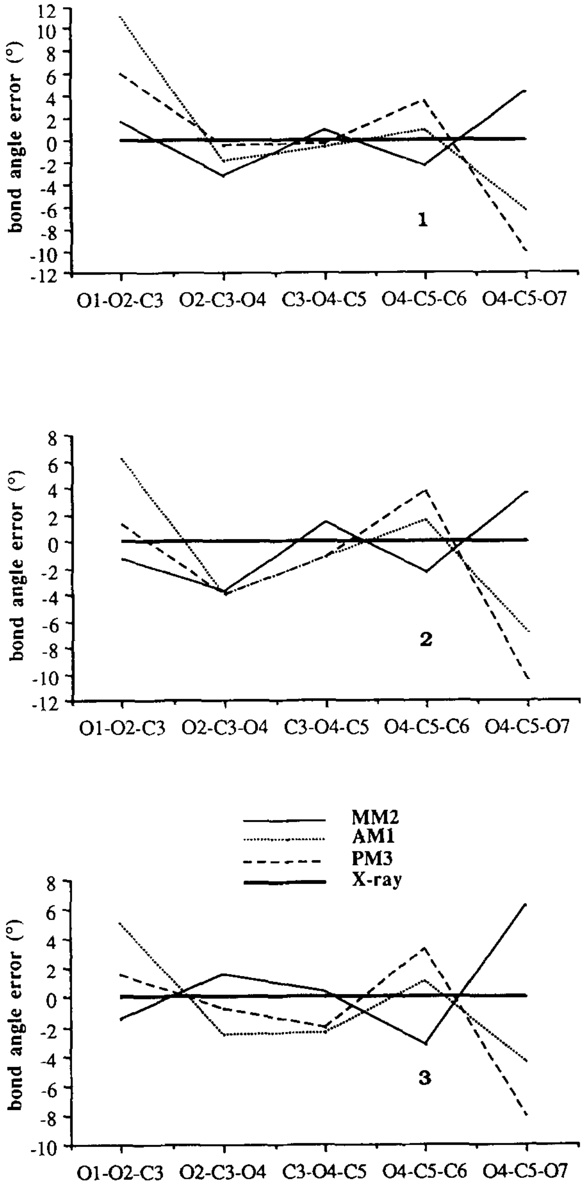


Fig. 1. Comparison of calculated and measured bond lengths in the trioxanone ring of **1**–**3**.

calculations. The angles O1–O2–C3 and O4–C5–C6 turn out to be far too wide (6–12°) when calculated by AM1, and still too wide by about 4° when PM3 is used. The largest error is found for the O4–C5–O7 angle, which is open too wide according to MM2 but too closed as calculated by the AM1 and PM3 methods.

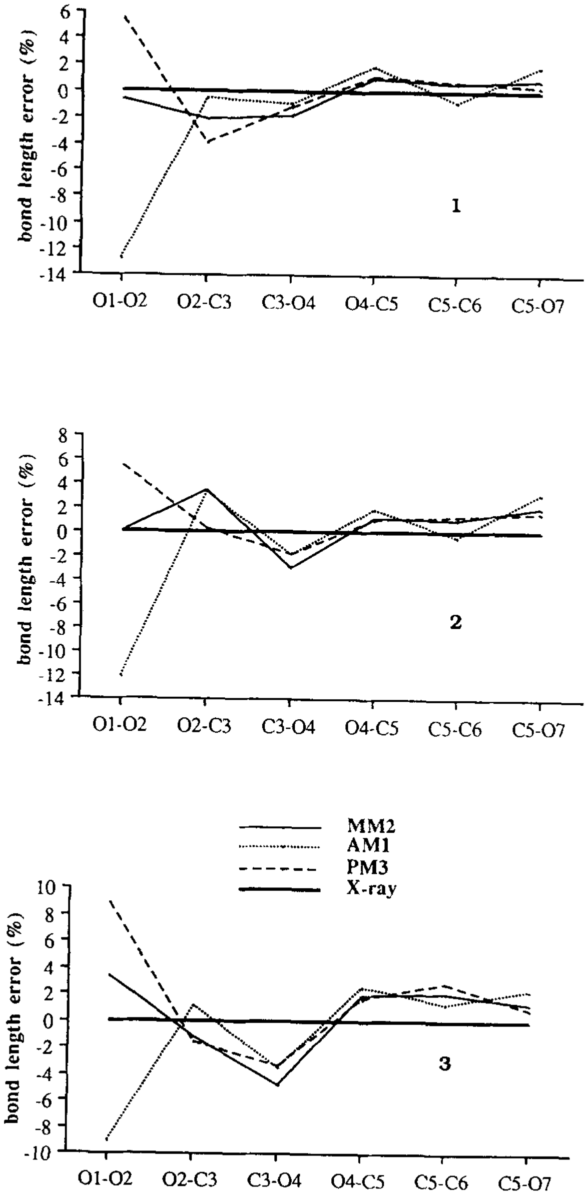


Fig. 2. Comparison of calculated and measured bond angles in the trioxanone ring of **1**–**3**.

3.4. Dihedral angles

As the crystal and calculated conformations of **1** are quite different, no comparison can be made. However, the calculated and experimental values for **2** and **3** are in good agreement (Fig. 3). Once

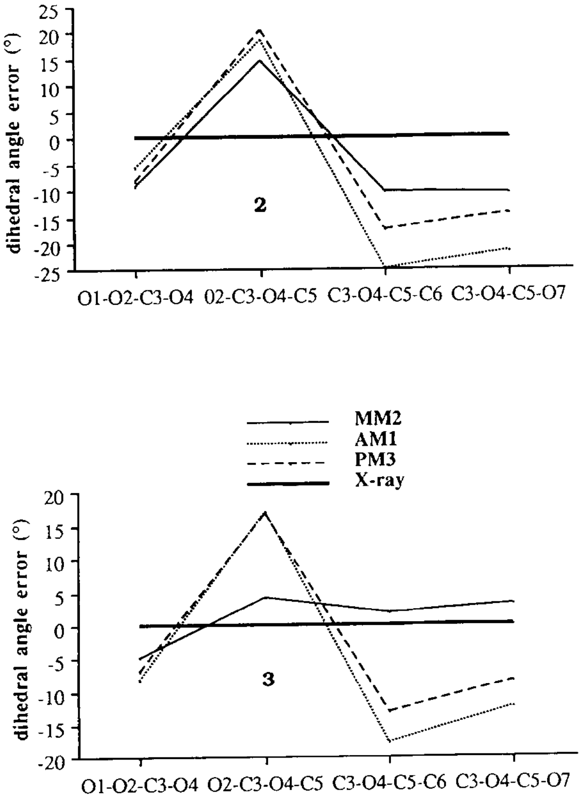


Fig. 3. Comparison of calculated and measured dihedral angles in the trioxanone ring of **2** and **3**.

again, MM2 yields the better results, especially for **3**, with dihedral angles never differing from those in the crystal by more than 5°. The two sets of semiempirical results lie close to each other and display sizable errors (14–18°), particularly for the O2–C3–O4–C5 and C3–O4–C5–C6 dihedral angles.

The lactone function resembles the peptide linkage in that delocalization of the electron pair on the O(4) atom with the carbonyl group imparts double bond character to the O(4)–C(5) bond. Consequently, the dihedral angle, C(3)–O(4)–C(5)–C(6) should ideally be 0°. In the case of the spirocyclic structure **3**, the MM2 value (7.0°) compares well with that measured (5.0°). For the trans-substituted derivative **2**, the deviation from planarity is greater (14.2°). All methods estimate this angle with considerable error. Nonetheless, MM2 comes the closest (3.9°).

4. Conclusion

When the relative errors on bond distances and angles are compared, MM2 is seen as the best calculational method overall, PM3 being slightly more accurate than AM1. However, when the mean relative errors on bond distances are compared, if the peroxide linkage is O1–O2 is excepted, the difference between molecular mechanics and semiempirical methods becomes negligibly small. It is when conformations are considered that MM2 becomes significantly more accurate, with the important restriction that the calculated gas-phase conformation of **1** is not the same as that in the crystal. The present study confirms the often poor performance of semiempirical methods at determining reliable conformational geometries of ring systems [19].

5. Envoi

The present studies complement others which have been undertaken in recent years [20]. A study of cyclic hydrocarbons, including cyclohexane itself, found that molecular mechanics (MM) was better than semiempirical methods at calculating the relative energies of conformations [21]. MM methods have also been applied with success to cyclic peroxides [22] and δ-valerolactone [23,24], molecules which have structural points in common with 1,2,4-trioxan-5-ones.

Acknowledgements

We thank the Swiss National Science Foundation for supporting this research [JW: 20-36131.92, CWJ: 20-32166.91].

References

[1] H.H. Wasserman and B. Lipshutz, Tetrahedron Lett., (1975) 4611.
[2] W. Adam and I. Erden, J. Am. Chem. Soc., 101 (1979) 5692.

[3] C.W. Jefford, J. Currie, G.D. Richardson and J.C. Rossier, Helv. Chim. Acta, 74 (1991) 1239.

[4] C.W. Jefford and M.G.H. Vicente, Heterocycles 35 (1993) 725.

[5] C.W. Jefford, M.C. Josso, M.G.H. Vicente, H.R. Hagemann, D. Lovy and H. Bill, Helv. Chim. Acta, 77 (1994) 1851.

[6] G. Bernardinelli, C.W. Jefford, G.D. Richardson and J.C. Rossier, Acta Crystallogr, Sect. C, 47 (1991) 388.

[7] D.H.R. Barton, Experientia 6 (1950) 316; J. Chem. Soc., (1953) 1027.
D.H.R. Barton and R.C. Cookson, Q. Rev., Chem. Soc., 10 (1956) 44.

[8] C.W. Jefford, Stud. Surf. Sci. Catal., 66 (1991) 555.

[9] F. Mohamadi, N.G.J. Richards, W.C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson and W.C. Still, J. Comput. Chem., 11 (1990) 440.

[10] N.L. Allinger, J. Am. Chem. Soc., 99 (1977) 8127.

[11] L. Carballeira, R.A. Mosquera and M.A. Rios, J. Comput. Chem., 9 (1988) 851.

[12] J.M. Goodman and W.C. Still, J. Comput. Chem., 12 (1991) 1110.

[13] G. Chang, W.C. Guida and W.C. Still, J. Am. Chem. Soc., 111 (1989) 4379.

[14] E. Polak and G. Ribière, Rev. Fr. Inf. Rech. Oper., 16 (1969) 35.

[15] T. Clark, SCAMP, version 4.2, Institute of Organic Chemistry, University of Erlangen-Nürnberg, D-91054 Erlangen, Germany, 1990.

[16] R.H. Bartels, Report CNA-44, University of Texas, Center for Numerical Analysis, Austin, TX, 1972.

[17] C.W. Jefford, J.C. Rossier and G.D. Richardson, J. Chem. Soc., Chem. Commun., (1983) 1064.

[18[J.J.P. Stewart, J. Comput.-Aided Mol. Des., 4 (1990) 1.

[19] J.A. Dobado, J. Molina Molina and M. Rodriguez Espinosa, J. Mol. Struct. (Theochem), 303 (1994) 205.

[20] E. Anders, J.G. Tropsch, E. Irmer and G. Sheldrick, Chem. Ber., 123 (1990) 321.
K. Gundertofte, J. Palm, I. Petterson and A. Stamwik, J. Comput. Chem., 12 (1991) 200.
W. Tochtermann, C. Vogt, E.-M. Peters, K. Peters, H.G. von Schwering and E.-U. Würthwein, Chem. Ber., 124 (1991) 2577.
R. Karaman, G.-X. He, F. Chu, A. Blaskó and T.C. Bruice, J. Org. Chem., 58 (1993) 438.
J. Molina Molina and M. Rodriguez Espinosa, J. Mol. Struct. (Theochem), 305 (1994) 35.

[21] D.M. Ferguson, I.R. Gould, W.A. Glauser, S. Schroeder and P.A. Kollman, J. Comput. Chem., 13 (1992) 525.

[22] L. Carballeira, R.A. Mosquera and M.A. Rios, J. Comput. Chem., 10 (1989) 911.

[23] F. Ronchetti and L. Toma, Tetrahedron 42 (1986) 6535.

[24] T. Philip, R.L. Cook, T.B. Malloy, Jr., N.L. Allinger, S. Chang and Y. Yuh, J. Am. Chem. Soc., 103 (1981) 2151.