Molecular Mechanics Calculations on Lactones; an Interpretation of the Preferential C(8) Relactonization of Germacranolides containing C(6) and C(8) Lactonizable α-Oxygen Functions

By **Michael H. P. Guy, George A. Sim,** and **David N. J. White,**[*] Chemistry Department, The University, Glasgow G12 8QQ

Molecular mechanics calculations reproduce the free energy differences between pairs of substituted γ-butyrolactones and allow an interpretation of the observation that germacranolides containing lactonizable α-oriented oxygen functions at C(6) and C(8) preferentially relactonize at C(8).

MOLECULAR mechanics calculations have been applied successfully to molecules representing a wide variety of structural types.[1] Our calculations for several isomers of the sesquiterpenoid lactone santonin gave reasonable values for the geometric and enthalpy differences amongst these compounds, although the lactone portion of the force field was derived on an *ad hoc* basis.[2] The lactone function is an important constituent of natural products and recent structural and synthetic investigations have been stimulated by the discovery of biological activity associated with α-methylene γ-lactone sesquiterpenoids.[3] It is therefore clearly desirable that a force field be available to facilitate quantitative molecular mechanics calculations on such compounds.

The alkane, alkene, and carbonyl contributions to our force field were taken from Allinger's parameterisation [4,5] which has been tested against the observed properties (such as gas-phase heats of formation and molecular geometries, derived by electron diffraction) of a large number of compounds, including some steroids.[6,7] On the other hand testing of the lactone portion of the force field has been confined to the santonins but should ideally be extended to cover a similar diversity of structural types as the remainder of the force field. Unfortunately experimental data for lactones are not available on the required scale [*e.g.* Cox and Pilcher [8] give ΔH_f^0(g) for only one lactone and there is no reference to electron diffraction studies of lactones in Specialist Periodical Reports [9]] and consequently it is not possible, as yet, to construct a general, quantitative lactone force field.

However, there is some evidence to suggest that whilst approximate (*i.e.* semi-quantitative) force fields may give rise to errors in the *absolute* level of calculated enthalpies for unrelated compounds, they may satisfactorily reproduce the *relative* energies of closely related systems.[10] Fortunately, the free energy differences between a series of isomeric γ-butyrolactones have recently been measured [11] and we have used these results to demonstrate that our lactone force field is indeed capable of reproducing the energy differences between pairs of structurally similar isomers. This capability, although limited in scope, is ideally suited to our present objective of investigating the energy differences between C(6)–C(7) and C(7)–C(8) *trans*-fused lactones.

---

[*] For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1975, Index issue. Items less than 10 pp. are supplied as full-size copies.

[1] For a review see E. M. Engler, J. D. Andose, and P. von R. Schleyer, *J. Amer. Chem. Soc.*, 1973, **95**, 8005.

[2] D. N. J. White and G. A. Sim, *Tetrahedron*, 1973, **29**, 3933.

[3] S. M. Kupchan, D. C. Fessler, M. A. Eakin, and T. Giacobbe, *Science*, 1970, **168**, 376; S. M. Kupchan, *Pure Appl. Chem.*, 1970, **21**, 227.

[4] N. L. Allinger and J. T. Sprague, *J. Amer. Chem. Soc.*, 1972, **94**, 5734.

[5] N. L. Allinger, M. T. Tribble, and M. A. Miller, *Tetrahedron*, 1972, **28**, 1173.

[6] N. L. Allinger and F. Wu, *Tetrahedron*, 1971, **27**, 5093.

[7] N. L. Allinger and M. T. Tribble, *Tetrahedron*, 1972, **28**, 1191.

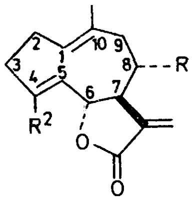
[8] J. D. Cox and G. Pilcher, ' Thermochemistry of Organic and Organometallic Compounds,' Academic Press, London, 1970.

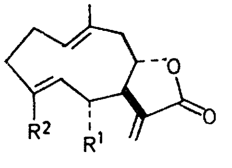
[9] ' Specialist Periodical Reports, Molecular Structure by Diffraction Methods,' The Chemical Society, London, vols. 1—3, 1973—1975.

[10] C. Altona and D. H. Faber, *Topics Current Chem.*, 1974, **45**, 1.

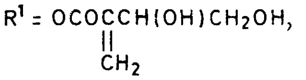
[11] S. A. M. Tayyeb Hussain, W. D. Ollis, C. Smith, and J. F. Stoddart, *J.C.S. Chem. Comm.*, 1974, 873.

Following earlier observations of lactone rearrangements[12] Yoshioka *et al.* noted that germacranolides which contain C(6) and C(8) lactonizable α-oriented oxygen functions relactonize at C(8) when treated with strong alkali and subsequently acidified;[13] salonitenolide (1) and cnicin (2), for example, yield artemisiifolin (3). We have employed molecular mechanics calculations on isomeric lactones, with the force field described above and a previously defined full-matrix energy minimisation procedure,[14,15] to investigate this effect and confirm the generality of the rule.





(1) $R^1 = OH$, $R^2 = CH_2OH$

(2) 
$R^1 = \mathrm{OCO}\underset{\underset{\mathrm{CH_2}}{\|}}{\mathrm{C}}\mathrm{CH(OH)CH_2OH}$,

$R^2 = CH_2OH$

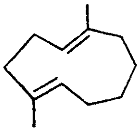
(4) $R^1 = OH$, $R^2 = CH_3$

(6) $R^1 = H$, $R^2 = CH_3$

(3) $R^1 = OH$, $R^2 = CH_2OH$

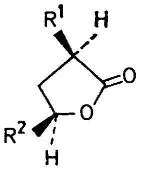
(5) $R^1 = OH$, $R^2 = CH_3$

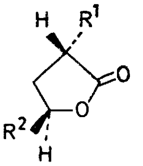
(7) $R^1 = H$, $R^2 = CH_3$



(8)

Force Field.—The force field employed in the calculations to be described is given in full in Supplementary Publication No. SUP 21850 (8 pp.)* and our results for the substituted γ-butyrolactones (9)—(16) are compared with the experimental free energy differences[11] in Table 1. It is unlikely that entropy contributes significantly to the observed Δ*G* values, as the symmetry number for each lactone is one, the lactone ring is fairly rigid, the alkyl side chains are identical in each pair of compounds, and so it seems justifiable to relate the calculated enthalpy difference with the observed free energy difference. The agreement between the two sets of results is very good (*cf.* Allinger's comparisons of isomeric steroids[6,7]) and taken together with the calculations on the santonins, enables some degree of confidence to be placed in the calculated enthalpy differences between the germacranolides. This conclusion is reinforced by the agreement between the observed and calculated geometries for the germacranolides.





(9) $R^1 = Me$, $R^2 = Me$

(10) $R^1 = Me$, $R^2 = Me$

(11) $R^1 = Bu^t$, $R^2 = Bu^t$

(12) $R^1 = Bu^t$, $R^2 = Bu^t$

(13) $R^1 = Et$, $R^2 = Me$

(14) $R^1 = Et$, $R^2 = Me$

(15) $R^1 = Bu^n$, $R^2 = Me$

(16) $R^1 = Bu^n$, $R^2 = Me$

TABLE 1

The calculated steric energy and observed free energy differences (kcal mol^{-1}) between the *cis*- and *trans*-2,4-disubstituted γ-butyrolactones

Isomers	$E_s(cis)$	$E_s(trans)$ †	$\Delta E_s(c - t)$	ΔG
(9), (10)	2.39	2.70	−0.31	−0.14
(11), (12)	−1.21	−0.18	−1.03	−1.20
(13), (14)	2.50	2.74	−0.24	0.00
(15), (16)	1.86	2.13	−0.27	−0.19

† Boltzmann weighted mean of E_s for both possible configurations.[11]

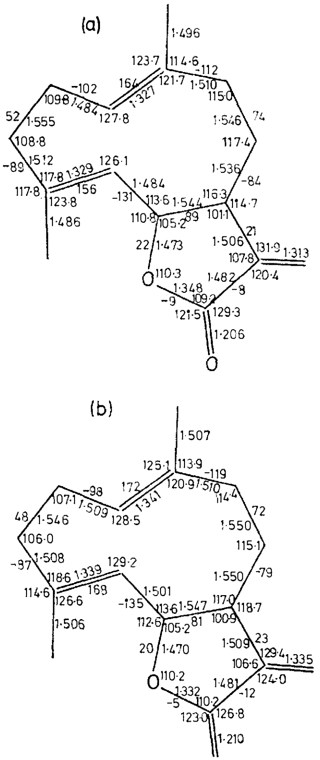


FIGURE 1 Observed (a) and calculated (b) structures of costunolide. Bond lengths (Å) are inner, torsion angles (°) outer, and valency angles (°) apical values

The geometry of costunolide as determined by *X*-ray crystal structure analysis[16] is shown in Figure 1(a) and

---

[12] *E.g.* D. H. R. Barton, O. C. Bockman, and P. de Mayo, *J. Chem. Soc.*, 1960, 2263; W. Herz, Y. Kishida, and M. V. Lackshmikantham, *Tetrahedron*, 1964, **20**, 979.

[13] H. Yoshioka, W. Renold, and T. J. Mabry, *Chem. Comm.*, 1970, 148.

[14] D. N. J. White and M. H. P. Guy, *J.C.S. Perkin II*, 1975, 43.

[15] D. N. J. White and O. Ermer, *Chem. Phys. Letters*, 1975, **31**, 111.

[16] M. J. Bovill, P. J. Cox, P. D. Cradwick, M. H. P. Guy, G. A. Sim, and D. N. J. White, *Acta Cryst.*, in the press.

the calculated structure in Figure 1(b). The root-mean-square (r.m.s.) differences in bond lengths, bond angles, and torsion angles are 0.013 Å, 2.0°, and 5.0° which may be compared with the r.m.s. experimental estimated standard deviations of 0.003 Å, 0.2°, and 0.3°.

X-Ray and spectroscopic studies have disclosed two frequently occurring conformations for the cyclodeca-1,5-diene ring in germacranolides; one conformation is typified by that in costunolide, where the methyl groups at C(4) and C(10) are *syn* and on the β-face of the molecule [conformation A, Figure 2(a)],[17] and the other by that in dihydromikanolide, where the methyl groups are *syn* and on the α-face of the molecule [conformation B, Figure 2(b)].[18] Steric energies have been calculated for compounds (4)—(8) on the basis of conformations A and B with optimised geometries, and the results, shown in Table 2, establish that a C(8) lactone with an oxygen function at C(6) is thermodynamically more stable than the corresponding C(6) lactone with an oxygen function at C(8).

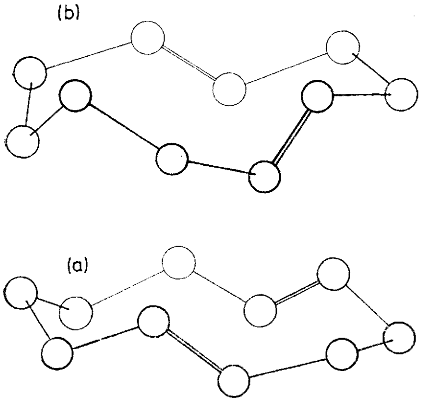


FIGURE 2 The A (a) and B (b) type conformations of cyclodeca-1,5-diene

TABLE 2

Steric energies (kcal mol⁻¹)

Compound	Conformation A E_s	Conformation B E_s
(4)	18.7	21.8
(5)	16.9	16.2
(6)	15.9	20.4
(7)	14.5	14.5
(8)	9.1	10.9

We have rationalised this behaviour in the following manner: when the geometric constraints imposed by the γ-lactone ring are removed from (4) or (5) by cleavage of the O–CO bond the cyclodeca-1,5-diene ring will retain its A or B type topography whilst relaxing to a minimum-energy conformation characterised by the torsion angles given in Table 3. More drastic conformational changes (*e.g.* B ⟶ A) are precluded by the steric requirements of the substituents (*cf.* shiromodiol).[19] Subsequent relactonization will take place at the least hindered position, so that the steric environments of C(6) and C(8) must be examined to determine the most favourable site.

Newman projections down C(6)–C(7) and C(7)–C(8) for the calculated geometries of the A and B type conformations of dimethylcyclodeca-1,5-diene (8) are shown in Figures 3(a)—(d). In order to accommodate a ***trans***-fused α-methylene γ-lactone the torsion angles indicated should ideally lie in the vicinity of 20°, corresponding to the complementary torsion angle in the minimum-energy conformation of an isolated α-methylene lactone (Figure 4), so that a minimal increase in strain results from relactonization.

TABLE 3

Calculated torsion angles (°) appropriate to conformations A and B of dimethylcyclodeca-1,5-diene (germacranolide numbering system)

	Conformation A	Conformation B
ω_{1-2}	−97	106
ω_{2-3}	48	−40
ω_{3-4}	−87	92
ω_{4-5}	172	−172
ω_{5-6}	−135	83
ω_{6-7}	77	50
ω_{7-8}	−82	−118
ω_{8-9}	76	57
ω_{9-10}	−120	61
ω_{10-1}	171	−172

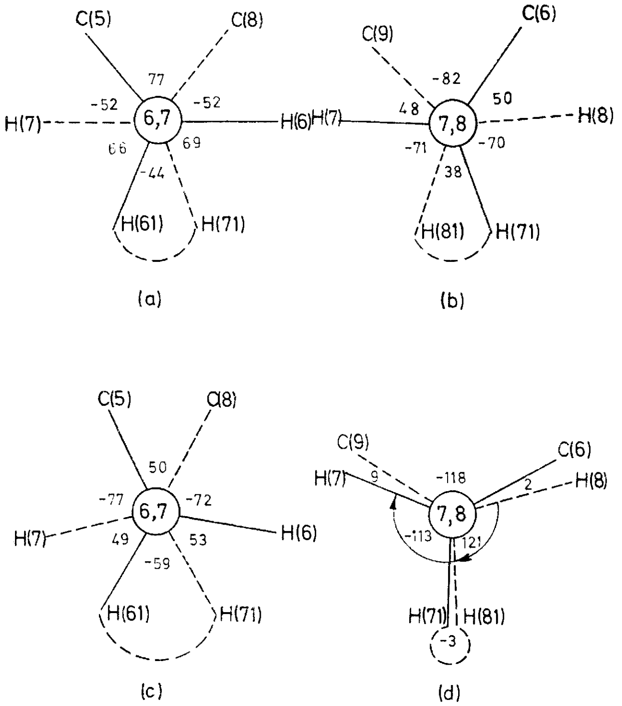


FIGURE 3 Newman projections down C(6)–C(7) (a) and C(7)–C(8) (b) for the calculated geometry of the A-type conformation of dimethylcyclodeca-1,5-diene. Similar projections, (c) and (d) respectively, are shown for the B-type conformation

If we examine conformation B first, the relevant torsion angles are 59° for C(6)–C(7) fusion and 3° for

---

[17] F. Šorm, M. Suchý, M. Holub, A. Línek, I. Hadine, and C. Novák, *Tetrahedron Letters*, 1970, 1893; K. Tori, I. Horibe, Y. Tamura, and H. Tada, *J.C.S. Chem. Comm.*, 1973, 620.

[18] W. Herz, P. S. Subramaniam, P. S. Santhanam, K. Aota, and A. L. Hall, *J. Org. Chem.*, 1970, **35**, 1453; P. J. Cox and G. A. Sim, *J.C.S. Perkin II*, 1974, 1355.

C(7)–C(8) fusion. Obviously the latter figure is much closer to 20° and therefore C(7)–C(8) fusion is preferred. It might then be expected that a certain amount of distortion would be necessary in order to effect C(7)–C(8) fusion of the lactone ring so that the exocyclic torsion angle of the macrocycle moved up towards 20°. In fact the calculated change is very small and the B-type conformation of (5) has a nearly planar lactone ring (Figure 5). If the lactone of Figure 4 is flattened then the Baeyer strain is reduced because the mean endocyclic valency angle moves up closer to 108° [20] (and therefore the individual values move closer to their equilibrium or unstrained values of 109—120°), Pitzer strain is reduced around all bonds except C_{sp^3}–C_{sp^3}, where it is maximised, and this latter effect is sufficient to maintain a non-planar conformation. However, if the lactone is to be fused with a system where the appropriate torsion angle is already close to 0° then Baeyer and Pitzer strain may be reduced without any opposing effect. This type of behaviour has been observed experimentally in an *X*-ray crystal structure analysis of a florilenalin derivative where the α-methylene γ-lactone is fused to a cycloheptane ring.[21]

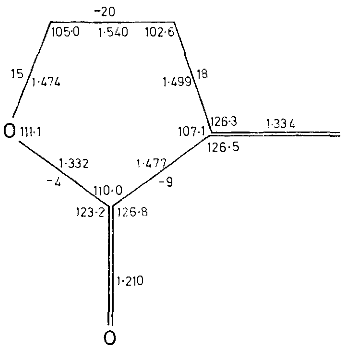


FIGURE 4 The calculated minimum energy geometry for α-methylene-γ-butyrolactone. Geometric values are given in the same order and units as those in Figure 1

For subsequent relactonization with an A-type conformation the torsional situation around C(7)–C(8) is again more conducive to the accommodation of a *trans*-fused γ-lactone ring, although to a much lesser extent, and the torsion angles (Figure 3) are sufficiently removed from zero that the lactone is accommodated in its isolated minimum-energy conformation. This small difference between the two alternative positions seemed unlikely to account completely for the 1.8 kcal mol^{-1} energy difference between the C(6)–C(7) and C(7)–C(8) fused isomers and additional possibilities were investigated, the most obvious of which appeared to be the environment of the hydroxy-group. Replacing the bulky hydroxy-groups by hydrogen atoms reduced the energy difference from 1.8 to 1.4 kcal mol^{-1} and indicated some difference between the steric environments of the hydroxy-groups. The possibility remains that even the hydrogen atoms are not small enough to remove all the differences in steric compression and indeed with no α-atom or group at the hydroxy-positions the energy difference is further reduced to only 0.4 kcal mol^{-1}. This latter figure is small enough to be accounted for by the difference in the torsional situation around C(6)–C(7) and C(7)–C(8). The hydroxy-group at C(8) is therefore in a more crowded environment and this factor additionally destabilises the C(6)–C(7) fused lactone. There is a much smaller distinction between the alternative environments of the lactone ester oxygen atom because closure of the lactone ring obviates the crowding at C(8).

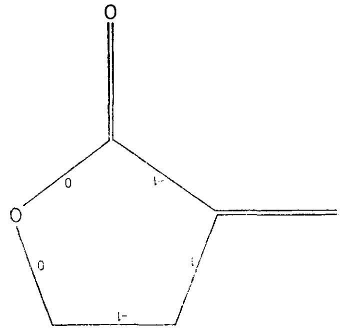


FIGURE 5 Calculated torsion angles (°) for the lactone in the the B-type conformation of (5)

[6/611 *Received*, 30*th March*, 1976]

---

[19] R. J. McClure, G. A. Sim, P. Coggan, and A. T. McPhail, *Chem. Comm.*, 1970, 128.

[20] J. D. Dunitz and J. Waser, *Elemente der Mathematik*, 1972, **27**, 25.

[21] A. T. McPhail and K. D. Onan, *J.C.S. Perkin II*, 1975, 492.