PERKIN 2

Configurational assignments of diastereomeric γ-lactones using vicinal H–H NMR coupling constants and molecular modelling†

Carlos A. Stortz* and Marta S. Maier

Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales,
Universidad de Buenos Aires, 1428 Buenos Aires, Argentina

Received (in Cambridge, UK) 15th May 2000, Accepted 5th July 2000
Published on the Web 9th August 2000

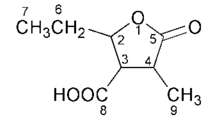
The conformational features of four diastereomers of the γ-lactone 2-ethyl-4-methyl-5-oxotetrahydrofuran-3-carboxylic acid were investigated by calculations which included molecular mechanics (MM3), semiempirical (AM1) and *ab initio* molecular orbital theory (HF/6-31G), the latter including solvent emulation. Results were compared with those obtained by ^{1}H NMR spectroscopy of natural and synthetic analogues in which a long aliphatic chain replaces the ethyl side chain. A notable agreement was found between the experimental vicinal ring coupling constants and those computed by the *ab initio* calculation; MM3 also gave rise to a fair agreement, while AM1 shows large failures to encounter the potential energy surface of these and other five-membered rings.

Introduction

Five-membered rings are widely distributed in Nature. Steroids, alkaloids, sugars, and amino acids carry hetero- or carbocyclic five-membered rings, whose conformational features can be influential to their properties and reactivity. The conformational flexibility of cyclopentane and its derivatives was described a long time ago.[1] Cyclopentane is puckered and undergoes a rapid and energetically facile interconversion of conformers (pseudorotation).[1,2] For heterocyclic and substituted rings, the degree of puckering and the pseudorotational barrier are altered, making several of the puckered conformations more stable than the others, or than planar conformations.[2–6] Computer-aided calculations showed only a few conformational minima in substituted five-membered rings, but still the presence of low-energy barriers to the pseudorotational pathway.[2c,5–8] Experimental evaluation of the conformation of five-membered rings, for example using three-bond NMR coupling constants, suffered the problem that many combinations of Boltzmann-averaged rapidly interconverting conformers or even the presence of a single one can match experimental values, thus making their conformational analysis difficult.[4b,8,9] Furthermore, without the knowledge of the conformational features, NMR coupling constants of vicinal protons are of little help in the assignment of relative configurations of five-membered rings.[9a]

When the substitution in the five membered ring leads to a γ-lactone (for example, γ-butyrolactone), the pseudorotational pathway is restricted due to the constraints introduced by the planar O–C(=O)–C group. Only two envelope (or near envelope) conformations are possible, thus simplifying the problem.[4,6,8,10–12] The pathway from one envelope to the other does not go through the pseudorotational pathway, but through the planar form, leading to higher barriers.[8] In substituted γ-lactones, the two envelope forms are not equivalent, and thus their equilibrium population will define their experimental features (as coupling constants).[4,6,8,10–12] The conformational features of γ-lactones and other five-membered rings have been studied by several molecular modelling procedures, including molecular mechanics,[6,7,11,13a] semiempirical,[6,7] and *ab initio* molecular orbital calculations.[5,7,8,12,13] A tandem molecular mechanics–coupling constant determination method has been proposed.[11]

Herein is reported the conformational analysis of four diastereomers of 2-ethyl-4-methyl-5-oxotetrahydrofuran-3-carboxylic acid (**1**–**4**), using molecular mechanics (MM3), semiempirical (AM1) and *ab initio* (HF/6-31G) methods, the last one including solvent simulation as a polarisable continuum. The effect of the rotating exocyclic groups was assessed. Results were compared with those obtained by ^{1}H NMR spectroscopy of natural and synthetic analogues in which a long aliphatic chain replaces the ethyl side chain. The aid of the combined NMR-modelling procedure for configurational assignments is discussed.



1 (2*S*, 3*S*, 4*S*) = *cis*, *trans*
2 (2*S*, 3*S*, 4*R*) = *cis*, *cis*
3 (2*S*, 3*R*, 4*S*) = *trans*, *cis*
4 (2*R*, 3*S*, 4*S*) = *trans*, *trans*

Methods

Calculations were carried out in either a Sun SparcStation 10 workstation, or a Pentium II-based PC computer. For molecular mechanics calculations, the program MM3 (92) (QCPE, Indiana University, USA), developed by Allinger and coworkers[14] was used. A relative permittivity of 3.0 was applied, and the maximum atomic movement was changed from 0.25 Å to 0.10 Å. MM3 yields free energy values calculated from the vibrational analysis of the minima. When low-frequency vibrations were present, their contributions to the free energy were calculated without any special treatment. The semiempirical calculations were carried out using the AM1 method,[15] included in the package AMPAC 5.0 (Semichem, USA). *Ab initio* calculations were performed with the Gaussian 98 program,[16] at the HF/6-31G level. The polarisable continuum model of Tomasi and coworkers[17] to emulate a chloroform solution was used through the full minimisation processes. In the three cases, the optimisations were terminated using the default criteria.

The sign of torsional angles followed the customary convention: positive sign, when the front atom in a Newman projection should rotate clockwise to be eclipsed. The Cremer and Pople puckering parameters[18] were calculated from the Cartesian

---

† Extended Tables 1–4 (Tables S-1–S-4) and coordinates for selected optimised conformers are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p2/b0/b003862h

DOI: 10.1039/b003862h

Table 1 Calculated geometries and energies for compound **1** [(2*S*,3*S*,4*S*) = *cis*,*trans*]

Method/ conformer	Puckering parameters[a] φ/°	Puckering parameters[a] q/Å	Torsion angles of side chains[b]/° χ_{38}	Torsion angles of side chains[b]/° χ_{26}	Relative energy[c]/ kJ mol^{-1}	Calculated $^3J_{H,H}$[d]/Hz $J_{H2,H3}$	Calculated $^3J_{H,H}$[d]/Hz $J_{H3,H4}$
MM3							
E_3	250	0.33	−121	57	0.0 (0.0)	7.12	12.27
E_3	248	0.33	72	58	5.6 (5.1)	7.03	12.27
E_3	249	0.34	−131	−43	8.3 (8.7)	6.96	12.48
E_3	253	0.28	−118	177	8.4 (11.1)	7.93	11.72
$^3E \rightarrow {}^3T_2$	66	0.31	−150	53	10.2 (8.9)	6.14	0.40
$^3E \rightarrow {}^3T_2$	65	0.32	−170	−57	12.8 (11.3)	5.86	0.37
AM1							
$P \rightarrow E_3$	253	0.06	−145	53	0.0	9.48	6.32
$P \rightarrow E_3$	249	0.09	−153	−39	1.1	9.52	7.18
$P \rightarrow E_3$	252	0.05	23	53	2.6	9.48	6.25
$P \rightarrow E_3$	251	0.06	24	−39	3.3	9.50	6.62
E_3/P	247	0.10	−135	164	6.8	9.52	7.40
E_3/P	247	0.11	49	168	9.7	9.49	7.89
HF/6-31G+PCM[e]							
E_3	252	0.30	−124	58	0.0	8.44	11.98
E_3	251	0.30	70	58	6.4	8.28	12.03
E_3	251	0.32	−138	−42	8.4	8.22	12.30
^3E	72	0.28	12	52	5.7	5.81	0.48
^3E	67	0.28	−149	52	6.4	5.72	0.62
^3E	72	0.30	12	−56	7.4	5.55	0.36
^3E	69	0.31	−155	−54	9.4	5.24	0.34

[a] According to Cremer and Pople.[18] [b] $\chi_{38} = \theta_{H3-C3-C8=O}$; $\chi_{26} = \theta_{H2-C2-C6-C7}$. [c] In parentheses, relative free energy. [d] Calculated with the Karplus equation using the parametrisation of Haasnoot *et al.*[19] [e] Polarisable continuum solvent model.[17]

coordinates with a program kindly provided by Dr L. Madsen (Colorado Univ.).

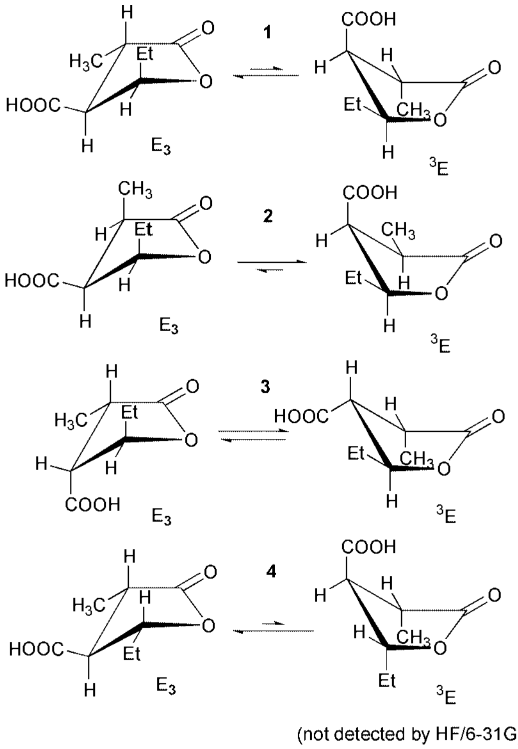
The ten possible envelope conformations of **1**–**4** were used as starting points for the MM3 and AM1 calculations. The former yielded only two final conformers, the latter just one. Those three conformers were used as starting points for the *ab initio* molecular orbital calculations, giving rise to one or two stable puckered conformers.

In the starting conformers, the exocyclic side groups (ethyl and carboxy) were arranged in a stable conformation, and later the effect of changing both of them was checked by the three calculation procedures. The acidic hydrogen was left in its stable orientation, *anti* to the ring carbon.

Vicinal coupling constants were calculated with the Karplus equation using the parametrisation of Haasnoot *et al.*[19]

Results and discussion

Four of the eight stereoisomers of 2-ethyl-4-methyl-5-oxo-tetrahydrofuran-3-carboxylic acid (**1**–**4**, one of each enantiomeric pair) were analysed by molecular mechanics (MM3, $\varepsilon = 3$). For each of the four compounds, the ten envelopes used as starting points led to just two final geometries with the maximum puckering in the atom opposing the lactone bond, as occurred in previous papers.[4,6,8,10–12] With the present numbering scheme (see structures **1**–**4**), those envelopes should be identified as E_3 and ^3E (Scheme 1). The exocyclic ethyl and carboxy side chains were rotated in order to establish all stable conformations. A similar procedure was carried out using the semiempirical method AM1, but in this instance, for the four compounds only one conformation of the ring was achieved, very close to the planar (P) form. When the MM3 conformers were minimised by an *ab initio* calculation at the HF/6-31G level, again two ring conformers were found (although only one for compound **4**). Once more, the effect of rotating the exocyclic side chains was checked, with inclusion of solvent (chloroform) by the polarisable continuum method of Tomasi and coworkers.[17] Tables 1, 2, 3 and 4 show the results obtained for the conformers of compounds **1**–**4**, respectively [a larger version of Tables 1–4 (Tables S-1–S-4) with extended geometrical data is available as supplementary data]. Compound **1** shows, by either molecular mechanics or *ab initio* calculations, the two stable envelopes E_3 and ^3E, the former being more stable: two substituents, methyl and carboxy stay in an equatorial position, while ethyl takes an axial one (Scheme 1). Similar results were obtained previously with a propyl group[12] instead of an ethyl group, without the PCM solvent model, or



Scheme 1

Table 2 Calculated geometries and energies for compound **2** [(2*S*,3*S*,4*R*) = *cis*, *cis*]

Method/ conformer	Puckering parameters[a]		Torsion angles of side chains[b]/°		Relative energy[c]/ kJ mol^{-1}	Calculated $^3J_{H,H}$[d]/Hz	
	φ/°	q/Å	χ_{38}	χ_{26}		$J_{H2,H3}$	$J_{H3,H4}$
MM3							
$E_3/{}^2T_3$	244	0.28	−112	54	9.2 (11.3)	7.45	9.27
${}^2T_3/E_3$	242	0.28	111	59	10.1 (11.8)	7.44	9.08
${}^3E$	70	0.36	−175	52	0.0 (0.0)	5.78	7.80
${}^3E$	70	0.36	174	−60	1.0 (2.6)	5.58	7.76
${}^3E$	70	0.35	2	52	3.2 (5.4)	5.89	7.95
${}^3E$	70	0.36	−1	−59	4.1 (7.4)	5.72	7.88
AM1							
$P\rightarrow{}^3T_4$	84	0.02	−179	49	0.0	9.24	11.75
$P\rightarrow{}^3E$	79	0.03	−174	−47	0.9	9.23	11.76
$P\rightarrow{}^3E$	74	0.08	−2	44	3.1	8.84	11.49
${}^3E/P$	70	0.12	3	−51	4.5	8.40	11.17
$P\rightarrow E_3/{}^2T_3$	243	0.07	−150	162	8.7	9.52	11.64
HF/6-31G+PCM[e]							
$E_3/{}^2T_3$	245	0.29	107	56	15.2	8.18	9.04
E_3	249	0.28	−107	55	15.2	8.23	8.99
${}^3E$	77	0.33	3	51	0.0	5.39	7.14
${}^3E$	76	0.33	4	−59	2.0	5.54	7.32
${}^3E$	74	0.34	−162	52	2.2	5.14	6.99
${}^3E$	74	0.34	−168	−56	4.4	5.18	6.99

[a] According to Cremer and Pople.[18] [b] $\chi_{38} = \theta_{H3\text{–}C3\text{–}C8=O}$; $\chi_{26} = \theta_{H2\text{–}C2\text{–}C6\text{–}C7}$. [c] In parentheses, relative free energy. [d] Calculated with the Karplus equation using the parametrisation of Haasnoot *et al.*[19] [e] Polarisable continuum solvent model.[17]

Table 3 Calculated geometries and energies for compound **3** [(2*S*,3*R*,4*S*) = *trans*, *cis*]

Method/ conformer	Puckering parameters[a]		Torsion angles of side chains[b]/°		Relative energy[c]/ kJ mol^{-1}	Calculated $^3J_{H,H}$[d]/Hz	
	φ/°	q/Å	χ_{38}	χ_{26}		$J_{H2,H3}$	$J_{H3,H4}$
MM3							
E_3	251	0.32	−148	56	0.4 (0.1)	0.74	8.30
E_3	251	0.32	−149	−54	2.6 (2.6)	0.79	8.22
E_3	251	0.31	14	56	4.0 (3.6)	0.84	8.47
E_3	252	0.31	13	−53	6.2 (6.0)	0.90	8.41
E_3	256	0.25	−151	−178	8.9 (10.2)	1.44	9.26
${}^3E$	67	0.33	−122	54	0.0 (0.0)	10.68	8.41
${}^3E$	68	0.30	−130	−60	2.7 (3.6)	10.41	8.79
${}^3E$	67	0.33	−122	172	5.3 (5.9)	10.78	8.51
${}^3E$	68	0.32	72	53	5.7 (5.2)	10.68	8.32
${}^3E$	68	0.30	46	−61	10.0 (10.0)	10.53	8.69
AM1							
$P\rightarrow{}^3E/{}^3T_2$	64	0.02	−144	−50	0.0	5.79	11.80
$P\rightarrow{}^3T_2/{}^3E$	62	0.05	−144	49	0.0	6.34	11.79
P	50	0.01	25	−51	2.0	5.71	11.79
$P\rightarrow{}^3T_2/{}^3E$	59	0.04	25	48	2.3	6.34	11.79
$P\rightarrow{}^3T_2/{}^3E$	60	0.05	−143	172	4.4	6.49	11.79
$P\rightarrow{}^3T_2$	57	0.04	25	171	6.7	6.43	11.79
HF/6-31G +PCM[e]							
${}^4T_3\rightarrow E_3$	262	0.27	5	56	1.6	1.62	7.99
$E_3\rightarrow{}^4T_3$	258	0.25	−150	56	4.3	1.90	8.59
${}^4T_3\rightarrow E_3$	262	0.27	4	−53	4.6	1.63	7.86
$E_3\rightarrow{}^4T_3$	258	0.24	−150	−51	7.7	2.01	8.65
${}^4T_3$	265	0.19	−150	176	9.2	2.82	9.48
${}^3E$	70	0.29	−123	54	0.0	10.47	9.23
${}^3E$	73	0.27	−130	−61	3.3	10.10	9.65
${}^3E$	71	0.29	−123	173	5.8	10.50	9.36
${}^3E$	71	0.29	71	53	5.9	10.58	8.93
${}^3E$	69	0.27	31	−62	8.6	10.35	9.57

[a] According to Cremer and Pople.[18] [b] $\chi_{38} = \theta_{H3\text{–}C3\text{–}C8=O}$; $\chi_{26} = \theta_{H2\text{–}C2\text{–}C6\text{–}C7}$. [c] In parentheses, relative free energy. [d] Calculated with the Karplus equation using the parametrisation of Haasnoot *et al.*[19] [e] Polarisable continuum solvent model.[17]

using the 6-31G* basis set.[20] Table 1 shows that though the E_3 conformer has less energy than the ${}^3E$ one, when looking at the conformers originated after rotating the side chains, the ${}^3E$ conformers have closer energy values (*i.e.*, they are entropically favoured). As occurred with model compounds cyclopentane and tetrahydrofuran,[20] MM3 gives rise to rings

Table 4 Calculated geometries and energies for compound **4** [(2*R*,3*S*,4*S*) = *trans*, *trans*]

Method/ conformer	Puckering parameters[a]		Torsion angles of side chains[b]/°		Relative energy[c]/ kJ mol^{-1}	Calculated $^3J_{H,H}$[d]/Hz	
	φ/°	q/Å	χ_{38}	χ_{26}		$J_{H2,H3}$	$J_{H3,H4}$
MM3							
E_3	252	0.32	−123	−55	0.0 (0.0)	10.46	12.14
E_3	249	0.33	125	−54	0.1 (0.5)	10.61	12.08
E_3	251	0.32	140	60	2.1 (3.6)	10.46	11.98
E_3	252	0.33	−123	−175	4.5 (5.7)	10.64	12.12
E_3	250	0.33	125	−172	5.1 (6.1)	10.71	11.99
E_3	251	0.34	0	−54	5.6 (6.1)	10.71	12.36
E_3	251	0.33	−10	60	7.2 (8.7)	10.63	12.22
$^3T_2 \rightarrow {}^3E$	59	0.21	127	−55	10.5 (10.5)	1.48	1.56
$^3T_2/^3E$	62	0.21	−128	−55	10.8 (10.7)	1.63	1.42
AM1							
$P \rightarrow E_3$	257	0.07	−152	50	0.0	6.43	6.40
$P \rightarrow E_3$	256	0.06	−136	−49	0.8	6.38	6.24
$P \rightarrow {}^3T_2$	51	0.05	107	49	1.5	4.36	3.81
P	339	0.01	107	−50	1.7	5.20	4.69
E_3/P	251	0.09	12	51	2.1	7.06	6.98
E_3/P	251	0.10	3	−48	2.5	7.09	7.00
P	285	0.01	−117	−172	4.8	5.43	4.98
P	267	0.00	105	−173	5.6	5.30	4.63
$P \rightarrow E_3$	252	0.07	3	−170	6.9	6.72	6.41
HF/6-31G+PCM[e]							
E_3	256	0.26	−113	−54	0.0	9.85	11.27
E_3	251	0.27	123	−54	0.8	10.18	11.24
E_3	253	0.26	134	61	3.3	9.91	11.04
E_3	253	0.31	−3	−54	5.1	10.47	12.02
E_3	253	0.29	−8	61	6.1	10.35	11.79
E_3	254	0.26	−114	−173	6.2	9.91	11.00
E_3	251	0.27	122	−172	6.4	10.19	11.04

[a] According to Cremer and Pople.[18] [b] $\chi_{38} = \theta_{H3-C3-C8=O}$; $\chi_{26} = \theta_{H2-C2-C6-C7}$. [c] In parentheses, relative free energy. [d] Calculated with the Karplus equation using the parametrisation of Haasnoot *et al.*[19] [e] Polarisable continuum solvent model.[17]

with a slightly higher puckering than the *ab initio* calculation procedure.

Compound **4**, in which one envelope carries the three substituents in equatorial position (Scheme 1) shows, as expected, prevalence of this envelope (E_3) by MM3 (Table 4), as well as a deformation of the other envelope towards the half chair $^3T_2$. The *ab initio* procedure leads unavoidably to the E_3 envelope, the other being a non-minimum conformation (Table 4). For compound **2** both envelopes occur (Scheme 1), ^3E being the much more stable: in this conformation, ethyl and methyl groups are equatorial, while the carboxy group is axial. The other envelope is deformed towards $^2T_3$ (Table 2). The energy difference between both envelopes is even augmented by the *ab initio* calculation procedure. Compound **3** has the most complicated conformational features of the set: according to the calculation, both envelopes carry similar energies (Table 3). MM3 and *ab initio* calculations yield the envelope with two equatorial groups (carboxy and ethyl) with slightly less energy. However, the other envelope (E_3) is entropically favoured, as shown by the analysis of different rotamers. Thus, similar populations of the two envelopes appear (Scheme 1, Table 3). The *ab initio* calculation yields the E_3 envelope deformed towards the half chair $^4T_3$.

In the four cases, AM1 gave rise to planar (P) or almost planar conformations, with a small puckering directed towards the more stable envelope (Tables 1–4). The geometrical features deduced by this semiempirical method are far from experimental facts, as previously stated for both AM1 and PM3.[6,7]

Tables 1–4 show the $^3J_{H,H}$ coupling constants expected for each conformer according to the equation of Haasnoot *et al.*[19] The calculated coupling constants were obtained by Boltzmann-averaging their contributions, leading to the data shown in Table 5. The experimental coupling constants obtained[12,21] for natural or synthetic analogues of **1**–**4** in which, instead of an ethyl chain have a long aliphatic chain (sometimes with a functionality on the other end of the chain) are also shown on Table 5. The ^1H NMR spectra leading to these data were carried out in chloroform, or sometimes in chloroform–methanol mixtures. An outstanding coincidence with the *ab initio* calculation procedure has been encountered, even for compound **3**, for which small errors in the energy calculation would lead to substantial errors in the final data. Also, a good match with the MM3 method was produced. AM1, as explained above, fails markedly; therefore its use on five-membered rings should be avoided.[6,7]

As in five-membered rings many combinations of Boltzmann-averaged rapidly interconverting conformers or even the presence of a single one can agree with experimental coupling constants, therefore their conformational analysis is difficult.[9a] For this reason, it was generally believed that NMR coupling constants of vicinal protons are of little help in the assignment of relative configurations of five-membered rings, given the lack of knowledge of their conformational features.[4b,9] However, this paper shows that with the state-of-the-art molecular modelling, the prediction of conformational features is possible and thus, when the experimental data are combined with accurate geometry calculations, an aid to the assessment of configurational features of these rings is supplied. It should be taken into account that the consideration of the exocyclic side chain conformation is not trivial, a fact well known, for instance, in carbohydrate modelling.[22] For example, studies on compound **3** yield different average coupling constants considering just the minimum energy conformer for each envelope, or the manifold of minima representing different conformations of the side chains. The latter procedure yields results

Table 5 Comparison of coupling constants (Hz) calculated[a] for compounds **1**–**4** and experimental data for analogues

Compound/method	$J_{H2,H3}$	$J_{H3,H4}$
1		
MM3	7.1	12.0
AM1	9.5	6.6
HF/6-31G+PCM	7.9	9.9
Experimental[b]	8.3	9.8
2		
MM3	5.8	7.8
AM1	9.1	11.7
HF/6-31G+PCM	5.4	7.1
Experimental[c]	5.5	7.5
3		
MM3	5.8	8.4
AM1	6.1	11.8
HF/6-31G+PCM	7.1	8.9
Experimental[d]	6.2	9.2
4		
MM3	10.4	11.9
AM1	6.0	5.8
HF/6-31G+PCM	10.0	11.3
Experimental[e]	9.5	11.5

[a] Calculated with the Karplus equation using the parametrisation of Haasnoot *et al.*[19] and averaged according to the Boltzmann population of each conformer. [b] Data[12] for (2*S*,3*S*,4*S*)-4-methyl-5-oxo-2-(14-oxopentadecyl)tetrahydrofuran-3-carboxylic acid [(−)-dihydropertusaric acid]. [c] Data[21a] for (2*S*,3*S*,4*R*)-4-methyl-5-oxo-2-(14-oxopentadecyl)tetrahydrofuran-3-carboxylic acid [(−)-dihydroallopertusaric acid]. [d] Data[21b] for (2*S*,3*R*,4*S*)-4-methyl-5-oxo-2-tridecyltetrahydrofuran-3-carboxylic acid (racemic form) [(±)-dihydroprotolichesterinic acid]. [e] Data[21c] for (2*R*,3*S*,4*S*)-4-methyl-5-oxo-2-tridecyltetrahydrofuran-3-carboxylic acid [(+)-roccellaric acid].

closer to the actual ones. Calculations by the *ab initio* procedure with the inclusion of solvent give values very close to experimental: the RMS (root-mean-square) error for the four determinations is around 0.4 Hz. However, this value is provoked by the relatively large error for the $J_{H2,H3}$ in compound **3**: the other seven data fall below or at that value. MM3 also gives rise to good results: the RMS error is around 1.0 Hz, a value slightly lower than that encountered in previous work with hydroxylated lactones.[11] It should be taken into account that the higher error found when working with MM3 is mostly produced by geometry considerations (too puckered rings) and not by energy calculations which are calculated fairly well by this force-field. AM1, on the other hand gives calculated values which would lead straight to wrong configurational assignments.

Acknowledgements

Both authors are Research Members of the National Research Council of Argentina (CONICET). This work was supported by a grant from the UBA. We are indebted to Dr G. Burton (UBA) for allowing us the operation of the Gaussian 98 program.

References

1 J. E. Kilpatrick, K. S. Pitzer and R. Spitzer, *J. Am. Chem. Soc.*, 1947, **69**, 2483.

2 (*a*) C. Altona and M. Sundaralingam, *J. Am. Chem. Soc.*, 1972, **94**, 8205; (*b*) B. Fuchs, *Top. Stereochem.*, 1978, **10**, 1; (*c*) E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational analysis*, ACS, Washington, DC, 1981, ch. 4.

3 (*a*) D. Cremer and J. A. Pople, *J. Am. Chem. Soc.*, 1975, **97**, 1354; (*b*) S. A. M. T. Hussain, W. D. Ollis, C. Smith and J. F. Stoddart, *J. Chem. Soc.*, *Perkin Trans. 1*, 1975, 1480.

4 (*a*) G. Dana, J. Gharbi-Benarous, J. Vaisserman, M. Philoche-Levisalles and C. Bois, *Tetrahedron*, 1988, **44**, 6357; (*b*) A. S. Serianni and R. Barker, *J. Org. Chem.*, 1984, **49**, 3292.

5 D. Cremer, *Isr. J. Chem.*, 1983, **23**, 72.

6 S.-Y. Han, M. M. Joullié, V. V. Fokin and N. A. Petasis, *Tetrahedron: Asymmetry*, 1994, **5**, 2535.

7 D. M. Ferguson, I. R. Gould, W. A. Glauser, S. Schroeder and P. A. Kollman, *J. Comput. Chem.*, 1992, **13**, 525.

8 T. Angelotti, M. Krisko, T. O'Connor and A. S. Serianni, *J. Am. Chem. Soc.*, 1987, **109**, 4464.

9 (*a*) A. Gaudemer, in *Stereochemistry: Fundamentals and methods*, ed. H. B. Kagan, G. Thieme Pub, Stuttgart, 1977, vol. 1, p. 44; (*b*) O. Jardetzki, *Biochem. Biophys. Acta*, 1980, **621**, 227.

10 (*a*) D. Horton and Z. Walaszek, *Carbohydr. Res.*, 1982, **105**, 95; (*b*) D. Horton and Z. Walaszek, *Carbohydr. Res.*, 1982, **105**, 111; (*c*) Z. Walaszek and D. Horton, *Carbohydr. Res.*, 1982, **105**, 131.

11 (*a*) C. Jaime, C. Segura, I. Dinarés and J. Font, *J. Org. Chem.*, 1993, **58**, 154; (*b*) I. Dinarés, A. Entrena, C. Jaime, C. Segura and J. Font, *Electron. J. Theor. Chem.*, 1997, **2**, 160.

12 M. S. Maier, D. I. González Marimón, C. A. Stortz and M. T. Adler, *J. Nat. Prod.*, 1999, **62**, 1565.

13 (*a*) K. B. Wiberg and R. F. Waldron, *J. Am. Chem. Soc.*, 1991, **113**, 7697; (*b*) R. J. Abraham, A. Ghersi, G. Petrillo and F. Sancassan, *J. Chem. Soc.*, *Perkin Trans. 2*, 1997, 1279.

14 N. L. Allinger, Y. H. Yuh and J. H. Lii, *J. Am. Chem. Soc.*, 1989, **111**, 8551.

15 M. J. S. Dewar, E. G. Zoebich, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.

16 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle and J. A. Pople, Gaussian 98, Revision A.3, Gaussian, Inc., Pittsburgh, PA, 1998.

17 V. Barone, M. Cossi and J. Tomasi, *J. Comput. Chem.*, 1998, **19**, 404.

18 D. Cremer and J. A. Pople, *J. Am. Chem. Soc.*, 1975, **97**, 1358.

19 C. A. G. Haasnoot, F. A. A. M. de Leeuw and C. Altona, *Tetrahedron*, 1980, **36**, 2783.

20 C. A. Stortz and M. S. Maier, unpublished work.

21 (*a*) S. Huneck, T. Tønsberg and F. Bohlmann, *Phytochemistry*, 1986, **25**, 453; (*b*) P. K. Mandal and S. C. Roy, *Tetrahedron*, 1999, **55**, 11395; (*c*) S. Huneck and I. Yoshimura, *Identification of lichen substances*, Springer-Verlag, Berlin, 1996, p. 153.

22 C. A. Stortz, *Carbohydr. Res.*, 1999, **322**, 77.