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Theoretical Study of Anthracycline Antibiotic Analogues—III. Conformational Analysis on Different 2,6-Dideoxy-2-halo-α-L-hexopyranoses by Molecular Mechanics and Semiempirical Methods

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Abstract—Conformational analysis of 2,6-dideoxy-2-halo-α-L-hexopyranoses (compounds **1–11**) has been performed by molecular mechanics and molecular orbital calculations including solvation effects. The numerical results obtained and those obtained from the electrostatic potential calculation have been used together to interpret theoretically the influence of the introduction of the halogen atom at the C-2 position of the sugar moiety.

Introduction

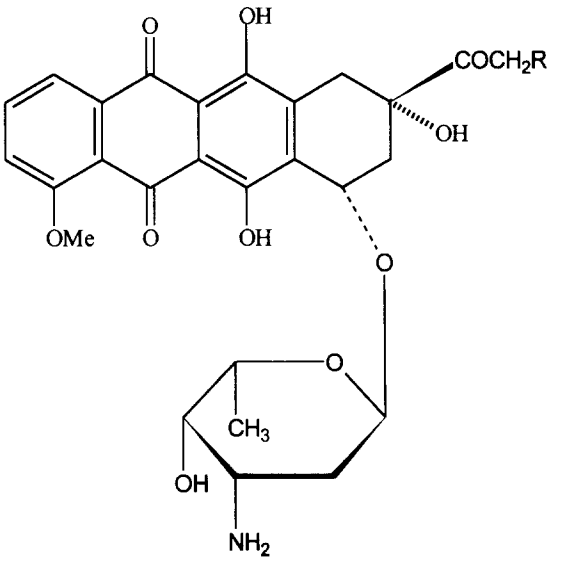
The recognized high activity of daunomycin[1] and adriamycin[2] (see Fig. 1) against various types of human cancer,[3] tempered by various undesirable side effects,[3a,4] has motivated a search for analogues of greater efficiency and decreased cardiotoxicity.

Reviews on different aspects of anthracycline antibiotics are available.[5] Additionally, structural studies including X-ray,[6] NMR,[7,8] molecular mechanics (MM)[9,10] and molecular orbital (MO) calculations have been published. Papers describing the conformational study by using MM and MO calculations on different sugar derivatives have been recently presented by our group.[11]

Previous studies[12] on anthracycline antibiotic analogues modified in the sugar ring proved that substitution by a halogen atom in the position 2 of the sugar moiety leads to an antibiotic with higher activity and lower toxicity than the parent compound when the halogen is axial, and to loss of activity when it is equatorial.

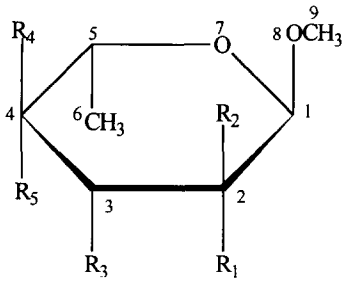
In our department, experimental research on anthracycline antibiotic analogues has been performed, with special emphasis on the synthesis of the sugar moiety.[13] Our group is involved in the theoretical study of anthracycline antibiotic analogues. Results are presented on the calculations of 3,6-dideoxy-α-L-hexopyranoses branched at C-3[14] and 2,3,6-trideoxy-3-amino-α-L-hexopyranose derivatives.[15]

This paper presents MM and MO calculations on different 2,6-dideoxy-2-halo-α-L-hexopyranoses in order to study the influence of the halogen at C-2 in different (axial or equatorial) dispositions. Solvation effects have been taken into account in the optimization of these model compounds in order to extract conclusions applicable to the anthracycline glycosides which will be investigated in the next paper. The structures of the compounds studied are depicted in Scheme 1.



R = H Daunomycin.
R = OH Adriamycin.

Figure 1. Structures of anthracycline antibiotics daunomycin and adriamycin.



Compounds	R_1	R_2	R_3	R_4	R_5
1	I	H	OAc	OAc	H
2	Br	H	OAc	OAc	H
3	Cl	H	OAc	OAc	H
4	F	H	OAc	OAc	H
5	H	I	OAc	OAc	H
6	H	Br	OAc	OAc	H
7	H	Cl	OAc	OAc	H
8	H	F	OAc	OAc	H
9	H	H	OAc	OAc	H
10	H	F	NH_2	H	OH
11	F	H	OH	H	OH

Scheme 1. Structures of compounds **1–11**, showing the skeleton numbering.

Methodology

Molecular modeling of the studied compounds was performed using the PCMODEL program,[16] running on PC and SGI computer workstations. The MM[17] calculations were performed with the PCMODEL program by using the MMX force field, which was a modification by Gajewski and Gilbert of Allinger's MM2[18] and MMP1[19] programs. The conformational search for the minimum energy conformations was performed with the MULTOR option. The description of the force field and the procedure followed in the conformational analysis was described elsewhere.[14] Among the characteristics of the PCMODEL codes[14] we mention the use of the point charges for the electrostatic calculations which are derived from the bond dipoles programmed into MM2. H-Bonds are also taken into account through a $1/r^2$ attractive term.

The MO calculations were performed with the MOPAC version 6 program,[20] using the AM1[22] Hamiltonian. The electrostatic potentials were calculated over the electronic density surface of 0.002 $e \times au^{-3}$, which corresponds approximately to the van der Waals surface, with the standard procedure inside the Spartan program.[21] Solvation effects have been performed using the $AM1_{aq}$ and $AM1_{hd}$ models of Dixon et al.[23] which simulate the solvation on water and hexadecane, respectively. The molecular optimization with the $AM1_{aq}$ and $AM1_{hd}$ models have been done following the procedure included in the Spartan program.

Theoretical $^3J_{HH}$ calculations were calculated by the $^3J_{HH2}$ program (QCPE Program number 591) which is setup with the use of an extended multiparametric Karplus equation.[24]

Calculations

Calculations were performed for structures **1–11** (see Scheme 1). These compounds have a methyl--6-deoxy-α-L-hexopyranoside configuration with different substituents at the 2, 3 and 4 positions. For all the compounds studied, both ring conformations $^1C_4$ and $^4C_1$ have been considered.

Molecular mechanics calculations

The MM calculations (PCMODEL) on structures **1–11** have been performed for each ring conformation ($^1C_4$ and $^4C_1$). Conformational analysis considering the different substituents has been performed by means of the MULTOR option. The numerical results are summarized in Tables **1–3**.

Table 1 shows the steric energy and the dipole moment for the most stable conformation of both $^1C_4$ and $^4C_1$

Table 1. Steric energies, dipole moments, and energy differences between the most stable $^1C_4$ and $^4C_1$ ring conformations for compounds **1–11**, obtained by MM calculations

Compd	Conformations	Steric energy (kcal mol^{-1})	ΔE (kcal mol^{-1})	Dipole moment (debye)
1	$^1C_4$	5.79		1.96
			5.16	
	$^4C_1$	10.95		1.94
2	$^1C_4$	3.79		2.33
			4.98	
	$^4C_1$	8.77		1.87
3	$^1C_4$	2.40		2.45
			5.02	
	$^4C_1$	7.42		1.90
4	$^1C_4$	−3.52		2.40
			5.68	
	$^4C_1$	2.16		1.86
5	$^1C_4$	5.16		1.94
			7.01	
	$^4C_1$	12.17		3.27
6	$^1C_4$	3.12		2.28
			7.33	
	$^4C_1$	10.45		3.71
7	$^1C_4$	1.86		2.36
			7.25	
	$^4C_1$	9.11		3.84
8	$^1C_4$	−3.40		2.26
			6.69	
	$^4C_1$	3.29		3.85
9	$^1C_4$	9.93		1.54
			5.85	
	$^4C_1$	15.78		2.58
10	$^1C_4$	3.17		2.02
			6.50	
	$^4C_1$	9.67		3.45
11	$^1C_4$	−0.1		3.90
			3.28	
	$^4C_1$	3.18		1.35

ring geometries obtained by MM. The energy difference between the most stable conformations of the two rings disposition is also included. Table 2 lists the geometrical parameters for the most stable ring conformation ($^1C_4$ and $^4C_1$) of structures **1–11**.

Table 2. Geometrical parameters (distances in Å and angles in degree) of the acetalic group for compounds **1–11** in the most stable $^1C_4$ and $^4C_1$ ring conformation, obtained by MM calculations

Compd	Conf	d_1[a]	d_2[b]	d_3[c]	d_4[d]	α[e]	θ_1[a]	θ_2[g]
1	$^1C_4$	1.424	1.427	1.422	1.425	113.9	−62.6	−67.7
	$^4C_1$	1.426	1.427	1.423	1.422	109.5	−179.9	−70.3
2	$^1C_4$	1.424	1.425	1.422	1.425	113.7	−63.1	−67.9
	$^4C_1$	1.426	1.427	1.423	1.423	109.5	−179.8	−70.8
3	$^1C_4$	1.424	1.426	1.422	1.426	113.9	−62.8	−68.0
	$^4C_1$	1.425	1.427	1.422	1.423	109.7	179.9	−71.1
4	$^1C_4$	1.424	1.425	1.422	1.426	114.2	−63.9	−67.5
	$^4C_1$	1.425	1.427	1.423	1.423	109.9	−179.1	−71.3
5	$^1C_4$	1.425	1.426	1.422	1.426	113.4	−61.9	−69.2
	$^4C_1$	1.423	1.426	1.423	1.424	111.7	174.1	−68.8
6	$^1C_4$	1.425	1.426	1.422	1.426	113.4	−62.0	−69.3
	$^4C_1$	1.423	1.426	1.423	1.424	111.7	175.1	−68.7
7	$^1C_4$	1.425	1.425	1.422	1.426	113.6	−62.3	−68.9
	$^4C_1$	1.423	1.426	1.423	1.424	111.6	175.7	−67.9
8	$^1C_4$	1.424	1.425	1.422	1.426	113.7	−61.6	−69.3
	$^4C_1$	1.423	1.425	1.422	1.424	112.0	177.6	−67.3
9	$^1C_4$	1.424	1.426	1.422	1.426	114.1	−63.7	−68.0
	$^4C_1$	1.425	1.427	1.423	1.424	110.8	179.2	−69.3
10	$^1C_4$	1.425	1.426	1.422	1.427	113.5	−62.7	−69.7
	$^4C_1$	1.424	1.426	1.422	1.425	111.8	178.6	−68.0
11	$^1C_4$	1.425	1.426	1.422	1.426	113.8	−64.6	−68.0
	$^4C_1$	1.426	1.427	1.422	1.424	109.9	−179.5	−71.7

[a]d_1 = C1-O7; [b]d_2 = C1-O8; [c]d_3 = O8-C9; [d]d_4 = O7-C5; [e]α = O7-C1-O8; [f]θ_1 = C5-O7-C1-O8; [g]θ_2 = O7-C1-O8-C9. (For numbering see Scheme 1).

The ring puckering[25] parameters can be used to obtain a quantitative conformational description of the ring system. These puckering parameters are calculated with the COMPUC program,[26,27] the results are summarized in Table 3. Cartesian coordinates obtained by MM of all of the minimum energy conformations in both $^1C_4$ and $^4C_1$ ring dispositions for structures **1–11** are available as supplementary material.

Molecular orbital calculations

On the MM minimum energy conformations of structures **1–11**, the MO calculations were performed with the MOPAC program using the AM1 Hamiltonian, for both ring conformations $^1C_4$ and $^4C_1$, with full geometry optimization. Full geometry optimization was also performed in the $AM1_{aq}$ and the $AM1_{hd}$ models in order to predict solvation on water and hexadecane, respectively, using the Spartan program. Comparisons of the numerical results are summarized in Tables 4–6.

Table 4 shows the heat of formation of the different minimum energy conformations obtained by the AM1, $AM1_{aq}$ and $AM1_{hd}$ calculations in the $^1C_4$ and $^4C_1$ ring dispositions. For the minimum energy conformations of compounds **1–11** ($^1C_4$ and $^4C_1$) the geometrical parameters of the anomeric center are listed in Table 5, and the ring puckering parameters for AM1 minimum energy are shown in Table 6.

From the mixture of the minimum energy conformations $^1C_4$ and $^4C_1$, $^3J_{HH}$ calculations have been performed for the AM1, $AM1_{aq}$ and $AM1_{hd}$ geometries taking into account the coordinates and the

Table 3. Puckering parameters and coordinates[a] for compounds **1–11** in the $^1C_4$ and $^4C_1$ ring conformation, obtained by MM calculations

Compounds	Φ (2)	Θ	Q	q_2	q_3	z_1	z_2	z_3	z_4	z_5	z_6
$^1C_4$ conformation											
1	201.90	179.40	0.5688	0.006	−0.569	−0.2354	0.2349	−0.2317	0.2290	−0.2295	0.2327
2	103.01	179.14	0.5655	0.009	−0.565	−0.2319	0.2272	−0.2261	0.2297	−0.2344	0.2355
3	106.03	179.92	0.5681	0.001	−0.568	−0.2321	0.2316	−0.2314	0.2318	−0.2323	0.2324
4	18.13	178.80	0.5728	0.012	−0.573	−0.2272	0.2286	−0.2352	0.2404	−0.2390	0.2324
5	241.66	177.85	0.5757	0.022	−0.575	−0.2408	0.2473	−0.2414	0.2289	−0.2224	0.2283
6	275.79	178.04	0.5816	0.020	−0.581	−0.2361	0.2466	−0.2478	0.2385	−0.2280	0.2268
7	280.94	178.61	0.5811	0.014	−0.581	−0.2356	0.2433	−0.2449	0.2387	−0.2310	0.2295
8	259.99	178.33	0.5780	0.017	−0.578	−0.2375	0.2450	−0.2433	0.2342	−0.2267	0.2284
9	8.58	179.13	0.5723	0.009	−0.572	−0.2287	0.2305	−0.2354	0.2386	−0.2367	0.2318
10	275.41	176.91	0.5674	0.031	−0.567	−0.2297	0.2457	−0.2474	0.2330	−0.2169	0.2153
11	29.83	179.15	0.5592	0.008	−0.559	−0.2241	0.2242	−0.2283	0.2324	−0.2324	0.2283
$^4C_1$ conformation											
1	60.00	5.36	0.5431	0.051	0.541	0.2354	−0.2500	0.2354	−0.2061	0.1914	−0.2061
2	63.83	5.67	0.5540	0.054	0.541	0.2347	−0.2520	0.2383	−0.2073	0.1900	−0.2037
3	61.84	6.02	0.5431	0.057	0.540	0.2360	−0.2534	0.2379	−0.2050	0.1876	−0.2031
4	61.94	6.38	0.5414	0.060	0.538	0.2360	−0.2544	0.2380	−0.2033	0.1850	−0.2013
5	43.48	11.94	0.5289	0.109	0.517	0.2571	−0.2719	0.2260	−0.1654	0.1507	−0.1965
6	43.56	10.31	0.5287	0.095	0.520	0.2519	−0.2648	0.2252	−0.1728	0.1599	−0.1995
7	45.94	10.24	0.5310	0.094	0.523	0.2512	−0.2662	0.2883	−0.1754	0.1605	−0.1984
8	56.51	8.54	0.5369	0.080	0.531	0.2422	−0.2627	0.2373	−0.1914	0.1708	−0.1962
9	56.44	7.44	0.5403	0.07	0.536	0.2411	−0.2591	0.2367	−0.1964	0.1784	−0.2007
10	78.36	5.66	0.5556	0.055	0.553	0.2321	−0.2558	0.2494	−0.2193	0.1957	−0.2021
11	57.56	5.23	0.5493	0.05	0.547	0.2388	−0.2522	0.2367	−0.2078	0.1944	−0.2099

[a]All coordinates and puckering amplitudes in Å and angles in degrees.

corresponding energies. The numerical results are presented in Table 7 in which a comparison of theoretical $^3J_{HH}$ and experimental data when available[28] are shown.

Results and Discussion

From MM minimum energy conformations, the PLUTO drawing[29] shows the structures **1–11** as having a $^1C_4$ ring disposition (Fig. 2). It was observed in all the structures that this disposition is more stable than the $^4C_1$ ring disposition, by more than 3.3 kcal mol^{-1} (see Table 1). This ΔE between the two conformations is large enough to justify that conformation $^1C_4$ is the most dominant in the conformational mixture at room temperature. The conformations shown in Figure 2 are the minimum energy ones, reached by using the MULTOR option analysis, considering all the side chains of the two ring dispositions for each of the compounds studied. This conformational study yields a mixture of conformations with different dispositions of

Table 4. Heat of formation (H_f, kcal mol^{-1}), calculated by AM1, $AM1_{aq}$ and $AM1_{hd}$ for the most stable $^1C_4$ and $^4C_1$ ring conformations for compounds **1–11**, and the energy differences between them

Compd	Conf	AM1		$AM1_{AQ}$		$AM1_{hd}$	
		H_f	ΔH_f	H_f	ΔH_f	H_f	ΔH_f
1[a]	$^1C_4$	−251.90		—		—	
			2.81		—		—
	$^4C_1$	−249.09		—		—	
2	$^1C_4$	−265.13		−275.09		−276.36	
			3.01		2.04		2.86
	$^4C_1$	−262.12		−273.05		−273.51	
3	$^1C_4$	−278.97		−291.73		−290.06	
			3.00		1.96		2.83
	$^4C_1$	−275.97		−289.77		−287.23	
4	$^1C_4$	−318.51		−324.78		−326.67	
			2.37		1.42		2.15
	$^4C_1$	−316.14		−323.36		−324.52	
5	$^1C_4$	−251.65		—		—	
			5.30		—		—
	$^4C_1$	−246.35		—		—	
6	$^1C_4$	−265.01		−274.14		−276.17	
			5.74		4.86		5.75
	$^4C_1$	−259.27		−269.28		−270.42	
7	$^1C_4$	−278.90		−290.69		−289.84	
			5.62		4.80		5.49
	$^4C_1$	−273.28		−285.89		−284.35	
8	$^1C_4$	−318.70		−324.38		−326.87	
			5.32		4.29		5.26
	$^4C_1$	−313.38		−320.09		−321.61	
9	$^1C_4$	−276.95		−284.06		−285.84	
			3.34		2.19		3.25
	$^4C_1$	−273.52		−281.87		−282.59	
10	$^1C_4$	−197.44		−213.62		−206.12	
			5.21		3.91		4.99
	$^4C_1$	−192.23		−209.71		−201.13	
11	$^1C_4$	−251.19		−266.58		−257.87	
			5.17		5.74		5.13
	$^4C_1$	−246.02		−260.84		−252.74	

[a]Iodine is not parametrized in Spartan program for solvation.

Table 5. Geometrical parameters (distances in Å and angles in degrees) of the acetalic group, for the most stable conformation, $^1C_4$ and $^4C_1$ of compounds **1-11** obtained by MO calculations[a]

Compd	d_1	d_2	d_3	d_4	α	θ_1	θ_2
$^1C_4$			**AM1**				
1	1.411	1.419	1.420	1.430	106.5	−64.1	−72.1
2	1.410	1.418	1.421	1.430	106.6	−63.8	−73.3
3	1.409	1.417	1.421	1.430	106.8	−64.5	−72.8
4	1.408	1.414	1.421	1.431	107.2	−64.1	−72.4
5	1.414	1.415	1.421	1.431	106.2	−60.3	−74.4
6	1.414	1.414	1.421	1.431	106.3	−59.7	−77.7
7	1.413	1.414	1.421	1.431	106.5	−59.9	−77.7
8	1.410	1.411	1.422	1.432	107.3	−60.2	−75.7
9	1.413	1.417	1.420	1.430	106.7	−64.9	−70.8
10	1.408	1.415	1.421	1.432	106.9	−64.5	−74.2
11	1.410	1.414	1.422	1.435	107.1	−64.3	−72.4
			$AM1_{aq}$				
2	1.407	1.426	1.419	1.430	108.0	−64.1	−70.7
3	1.407	1.425	1.420	1.430	108.1	−64.9	−71.0
4	1.407	1.422	1.419	1.429	108.5	−64.7	−70.2
6	1.414	1.420	1.420	1.430	107.3	−58.6	−81.4
7	1.414	1.419	1.420	1.431	107.5	−58.6	−80.8
8	1.410	1.418	1.420	1.430	108.6	−59.4	−73.7
9	1.412	1.424	1.419	1.429	108.1	−64.9	−68.3
10	1.410	1.418	1.419	1.430	108.2	−62.5	−75.0
11	1.410	1.420	1.420	1.432	108.2	−64.0	−71.7
			$AM1_{Hd}$				
2	1.409	1.420	1.421	1.430	106.8	−64.0	−73.0
3	1.409	1.419	1.421	1.430	106.9	−64.5	−73.0
4	1.408	1.415	1.421	1.430	107.3	−64.3	−72.7
6	1.414	1.415	1.421	1.431	106.4	−59.8	−79.2
7	1.413	1.415	1.421	1.431	106.6	−59.9	−79.4
8	1.410	1.413	1.421	1.431	107.5	−60.2	−75.9
9	1.413	1.418	1.420	1.430	106.9	−64.9	−70.8
10	1.408	1.415	1.421	1.432	107.1	−64.2	−74.5
11	1.410	1.415	1.421	1.435	107.3	−64.4	−72.3
$^4C_1$			**AM1**				
1	1.426	1.414	1.422	1.422	101.1	−174.9	−70.8
2	1.425	1.413	1.422	1.422	101.2	−175.0	−72.2
3	1.425	1.412	1.422	1.422	101.5	−174.8	−73.1
4	1.421	1.410	1.422	1.423	102.3	−175.7	−71.2
5	1.421	1.411	1.422	1.424	103.2	177.3	−65.7
6	1.420	1.410	1.422	1.424	103.5	176.9	−65.5
7	1.423	1.426	1.423	1.424	111.6	175.7	−67.8
8	1.419	1.409	1.422	1.424	103.3	−179.1	−65.3
9	1.424	1.413	1.421	1.423	102.4	−175.3	−67.1
10	1.422	1.410	1.422	1.424	102.5	−174.0	−67.1
11	1.420	1.410	1.422	1.425	102.3	−175.8	−70.4
			$AM1_{aq}$				
2	1.428	1.420	1.421	1.416	100.4	177.2	−86.7
3	1.428	1.419	1.422	1.417	100.8	−176.7	−84.9
4	1.424	1.418	1.421	1.417	101.8	−177.9	−80.7
6	1.420	1.419	1.422	1.418	103.4	175.3	−73.4
7	1.420	1.418	1.422	1.419	103.5	176.5	−72.6
8	1.421	1.418	1.421	1.417	103.0	178.0	−74.7
9	1.428	1.421	1.421	1.417	102.2	−178.0	−75.6
10	1.422	1.416	1.420	1.420	102.4	−176.3	−75.5
11	1.423	1.417	1.421	1.420	101.9	−177.2	−78.6
			$AM1_{Hd}$				
2	1.426	1.414	1.422	1.421	101.1	−175.5	−74.2
3	1.425	1.414	1.422	1.421	101.5	−175.4	−73.5
4	1.421	1.411	1.422	1.422	102.2	−176.2	−72.8
6	1.421	1.411	1.422	1.422	103.6	−175.4	−66.4
7	1.421	1.411	1.422	1.422	103.4	178.3	−65.8
8	1.419	1.410	1.422	1.422	103.2	−179.5	−66.9
9	1.425	1.415	1.421	1.421	102.5	−175.9	−68.5
10	1.422	1.411	1.422	1.423	102.5	−174.3	−68.4
11	1.420	1.411	1.422	1.424	102.3	−176.1	−72.2

[a]For geometrical definition and numbering see Table 2 and Scheme 1.

Table 6. Puckering parameters and coordinates[a] obtained by AM1 calculations for compounds **1–11** in the $^1C_4$ and $^4C_1$ ring conformation

Compounds	Φ (2)	Θ	Q	q_2	q_3	z_1	z_2	z_3	z_4	z_5	z_6
$^1C_4$ conformation											
1	45.98	175.33	0.5319	0.043	−0.050	−0.1990	0.1922	−0.2095	0.2338	−0.2406	0.2233
2	38.13	175.12	0.5351	0.046	−0.533	−0.197	0.1933	−0.2139	0.2383	−0.2420	0.2214
3	54.49	174.52	0.5320	0.051	−0.530	−0.1992	0.1870	−0.2041	0.2332	−0.2454	0.2284
4	72.74	173.82	0.5352	0.058	−0.532	−0.2074	0.1848	−0.1974	0.2271	−0.2497	0.2398
5	295.24	177.03	0.5522	0.029	−0.551	−0.2181	0.2346	−0.2416	0.2322	−0.2157	0.2087
6	294.89	176.93	0.557	0.030	−0.556	−0.2198	0.2370	−0.2443	0.2343	−0.2172	0.2099
7	291.38	177.48	0.5538	0.024	−0.553	−0.2207	0.2347	−0.2398	0.2310	−0.2171	0.2120
8	347.41	178.26	0.5575	0.017	−0.557	−0.2180	0.2246	−0.2341	0.2370	−0.2304	0.2209
9	44.62	171.81	0.5431	0.077	−0.538	−0.1877	0.1764	−0.2082	0.2512	−0.2625	0.2307
10	359.66	171.17	0.5817	0.089	−0.575	−0.1831	0.2092	−0.2607	0.2862	−0.2602	0.2086
11	85.77	170.75	0.5446	0.088	−0.538	−0.2157	0.1739	−0.1777	0.2232	−0.2649	0.2612
$^4C_1$ conformation											
1	85.83	10.83	0.4238	0.098	0.514	0.2142	−0.2612	0.2570	−0.2059	0.1589	−0.1630
2	84.67	10.75	0.5269	0.098	0.518	0.2166	−0.2629	0.2576	−0.2061	0.1598	−0.1650
3	82.16	10.73	0.5259	0.098	0.517	0.2187	−0.2633	0.2556	−0.2032	0.1586	−0.1663
4	73.05	11.46	0.5269	0.105	0.516	0.2285	−0.2697	0.2521	−0.1932	0.1519	−0.1695
5	47.63	19.53	0.4881	0.163	0.460	0.2513	−0.2798	0.2164	−0.1243	0.0958	−0.1593
6	54.61	19.44	0.4958	0.165	0.468	0.2460	−0.2857	0.2306	−0.1357	0.096	−0.1512
7	45.92	10.16	0.5314	0.094	0.523	0.2512	−0.2660	0.2284	−0.1759	0.1611	−0.1987
8	44.51	14.89	0.4965	0.128	0.480	0.2484	−0.2669	0.2143	−0.1434	0.1249	−0.1774
9	55.94	11.74	0.4978	0.101	0.487	0.2317	−0.2573	0.2246	−0.1662	0.1406	−0.1734
10	139.51	4.07	0.5539	0.039	0.553	0.2083	−0.2297	0.2470	−0.2429	0.2214	−0.2041
11	44.22	5.30	0.5388	0.050	0.537	0.2397	−0.2467	0.2261	−0.1984	0.1914	−0.2120

[a]All coordinates and puckering amplitudes in Å and angles in degrees.

the substituents for both $^1C_4$ and $^4C_1$ ring conformations. The data and structures shown in the different Tables and Figures correspond to the most stable disposition for each ring conformation obtained from this conformational analysis. The ΔE between conformers for the different compounds can be rationalized as shown in Table 8. This Table summarizes the presence of different conformational effects (anomeric effect, gauche effect, and 1,3-diaxial interaction) for the $^1C_4$ and $^4C_1$ conformation of compounds **1–11**. The energy increment between these conformations for each compound is also shown for comparison.

It is well known that the anomeric effect prefers an axial electronegative substituent on the anomeric carbon.[30] Stabilizing gauche interactions are also present when two electronegative substituents in adjacent atoms are in gauche orientation. The 1,3-diaxial interaction is always a destabilizing one, and increases with the size of the groups. For all the compounds studied, the preferred conformation is always the $^1C_4$ which is compatible with the anomeric effect, giving the methoxyl group in the axial disposition. The ΔE between ring conformations for compounds **1–4** and **5–8** can be explained by looking at other interactions existing in both the $^1C_4$ and the $^4C_1$ conformations. In compounds **1–4**, there exists one more 1,3-diaxial X....Y interaction in the $^4C_1$ conformation than in $^1C_4$. In compounds **5–8** however, there exists two more 1,3-diaxial X....Y interactions in the $^4C_1$ conformation than in $^1C_4$. This demonstrates a higher ΔE for compounds **5–8** than for compounds **1–4**. The only difference between compounds **1–4** is in the nature of the halogen at C-2 (I, Br, C, and F, respectively). When we compare the ΔE for these compounds, we observe that these energies decrease with increasing size of the halogen due to the steric effect in the axial disposition of the halogen in the $^1C_4$ ring conformation. This is true when passing from F, Cl and Br (ΔE = 5.68, 5.02 and 4.98 kcal mol^{-1}; see Table 8), but when the halogen is iodine, the ΔE is higher than that obtained in bromine and chlorine derivatives. The same phenomena can be observed in the case of compounds **5–8**. These compounds are epimers at C-2 of compounds **1–4**, having a halogen in the axial disposition when the $^4C_1$ conformation is adopted, and therefore, increasing the size of the halogen should destabilize this ring conformation. This destabilization can be observed by looking at the ΔE when passing from compounds with a fluorine, to the chlorine or bromine atom (6.69, 7.25, and 7.33 kcal mol^{-1}, respectively), but again, the iodine derivative **5** shows a ΔE = 7.01 kcal mol^{-1} that signifies a stabilization of the $^4C_1$ conformation in comparison with compounds **6** and **7**.

This anomaly observed in iodine compounds can be explained by looking at Table 9. This Table shows the 1,3-diaxial X—H and X—O interaction distances observed in compounds **1–8** in the ring conformation with the halogen in the axial disposition. The addition of van der Waals radii RW(X)+RW(H) and RW(X)+RW(O) and the differences (Δr) between the distances and the corresponding RW is also shown. This difference (Δr) increases on passing from X = F to Cl or Br; but a small decrease is observed in iodine in comparison with the bromine derivative, giving a smaller steric interaction of the iodine in the axial disposition.

In general, the ΔEs observed for the compounds studied are compatible with the number and the types of the different conformational effects presented in the different ring conformations (Table 8). The one discrepancy is the ΔE observed for compound **11**. If we look at Table 8, there is one more stabilizing gauche effect and anomeric effect present in the $^1C_4$ than in the $^4C_1$ ring conformation. A similar situation is observed for compound **10**, however, the $^4C_1$ ring conformation of compound **11** is stabilized at least 2 kcal mol^{-1}, and may perhaps be due to the possibility of the hydrogen bond formation between the hydroxy at C-3 and the fluorine in this conformation. This H-bond is not possible in the $^1C_4$ disposition (H3−F = 3.71 and 2.52 Å in the $^1C_4$ and the $^4C_1$ conformations).

Most of the tendencies observed from the MM calculations are also reproduced in semiempirical methods. AM1, $AM1_{aq}$, and $AM1_{hd}$ calculations give larger energy differences between ring conformers for compounds **5–8** than for compounds **1–4**. Using the semiempirical methods, compounds **1–4** and **5–8** always showed the $^1C_4$ ring conformation as stabilized when increasing the size of the halogen (Table 4). The iodine derivatives (**1** and **5**) also show an anomalous behavior in AM1 calculation. Table 4 shows the comparison of the heats of formation between AM1

Table 7. Calculated and experimental $^3J_{HH}$ values for compounds **1-11**

Compd	Methods	$J_{1,2}$ (Hz)	$J_{2,3}$ (Hz)	$J_{3,4}$ (Hz)	$J_{4,5}$ (Hz)
	Exp.[28a]	1.0	4.5	9.2	9.2
1	AM1	1.18	4.85	8.60	9.24
	$AM1_{aq}$				
	$AM1_{Hd}$				
	Exp.[28b]	1.5	2.3	*	9.3
2	AM1	1.17	4.40	8.73	9.17
	$AM1_{aq}$	1.27	4.26	9.08	9.18
	$AM1_{Hd}$	1.18	4.35	8.79	9.17
	Exp.[28c]	1.0	3.5	10.0	10.0
3	AM1	1.27	4.32	8.59	9.28
	$AM1_{aq}$	1.35	3.89	9.07	9.19
	$AM1_{Hd}$	1.19	4.01	8.76	9.24
	Exp.				
4	AM1	1.75	3.82	8.16	923
	$AM1_{aq}$	1.99	3.68	9.24	9.14
	$AM1_{Hd}$	1.65	3.50	8.82	9.25
	Exp.				
5	AM1	2.59	10.19	7.70	9.22
	$AM1_{aq}$				
	$AM1_{Hd}$				
	Exp.[28b]	3.3	11.0	9.2	9.4
6	AM1	2.48	10.06	8.04	9.18
	$AM1_{aq}$	2.51	9.96	8.29	9.23
	$AM1_{Hd}$	2.49	10.03	8.07	9.18
	Exp.[28c]	3.5	10.0	10.0	9.5
7	AM1	2.79	9.55	7.82	9.25
	$AM1_{aq}$	2.75	9.44	8.19	9.24
	$AM1_{Hd}$	2.65	9.66	8.02	9.19
	Exp.				
8	AM1	3.23	8.45	7.93	9.33
	$AM1_{aq}$	3.04	8.85	8.41	9.33
	$AM1_{Hd}$	3.03	8.73	8.19	9.28
	Exp.[28a]	1.2 3.7	5.7 11.7	9.6	9.8
	AM1	1.94 3.39	5.99 9.49	8.04	9.34
		(1–2eq) (1–2ax)	(2eq-3) (2ax, 3)		
9	$AM1_{aq}$	2.07 3.69	5.98 9.69	8.38	9.44
		(1–2eq) (1–2ax)	(2eq-3) (2ax, 3)		
	$AM1_{Hd}$	1.94 3.45	6.01 9.53	8.06	9.33
		(1–2eq) (1–2ax)	(2eq-3) (2ax, 3)		
	Exp.				
10	AM1	3.10	10.35	1.72	0.88
	$AM1_{aq}$	2.86	10.29	1.90	1.28
	$AM1_{Hd}$	2.93	10.33	1.88	1.24
	Exp.				
11	AM1	1.49	3.53	2.74	0.71
	$AM1_{aq}$	1.56	3.51	2.67	0.66
	$AM1_{Hd}$	1.50	3.51	2.73	0.71

*These coupling constants could not be measured by the author because of overlapping of the signals.

isolated, solvated in water ($AM1_{aq}$), and solvated in hexadecane ($AM1_{hd}$) for compounds **1–11** in both $^1C_4$ and $^4C_1$ conformations (data for compounds **1** and **5** are not shown because iodine is not parametrized in Spartan for solvation). The $^1C_4$ conformation is always more stable than the $^4C_1$. But the energy difference

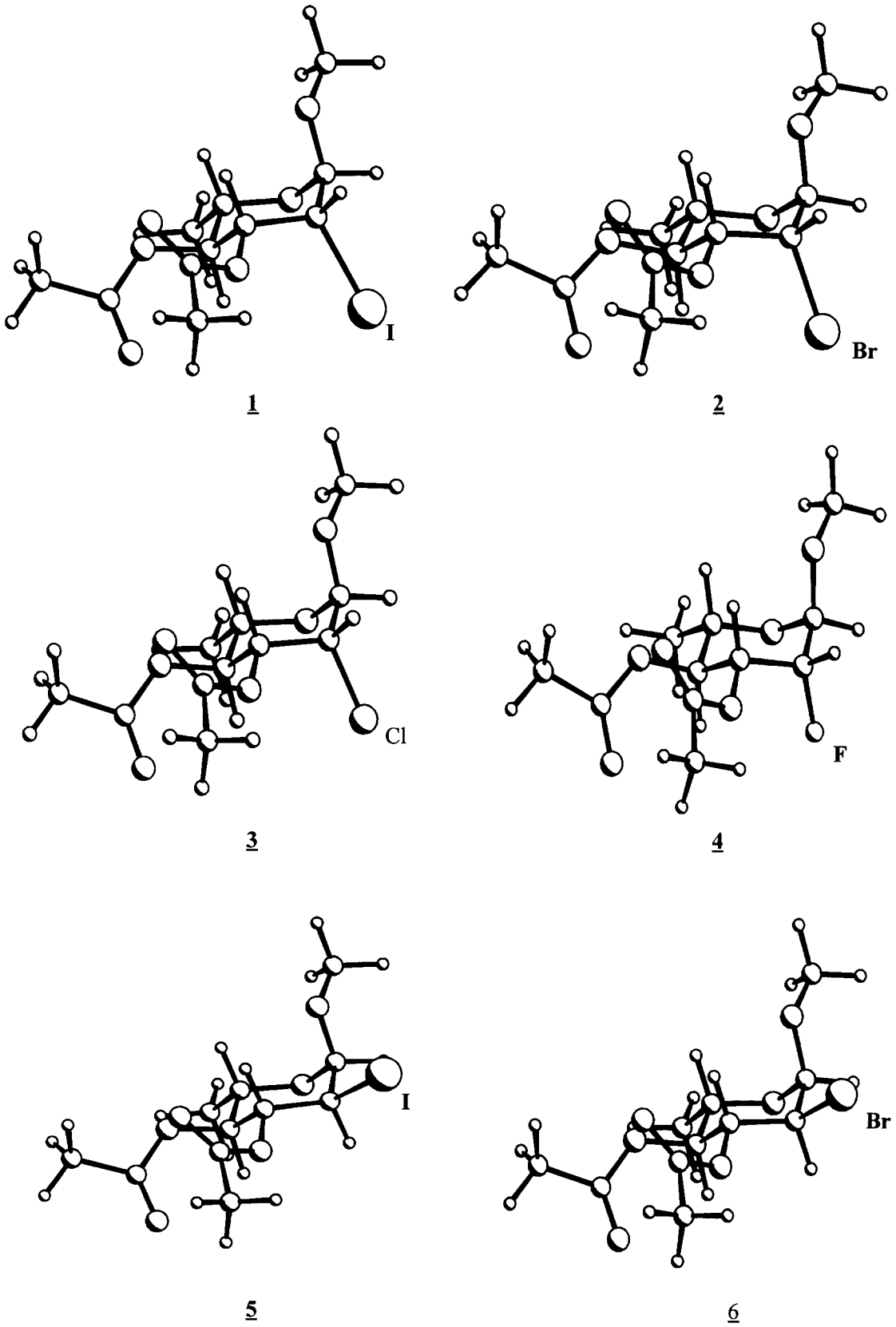
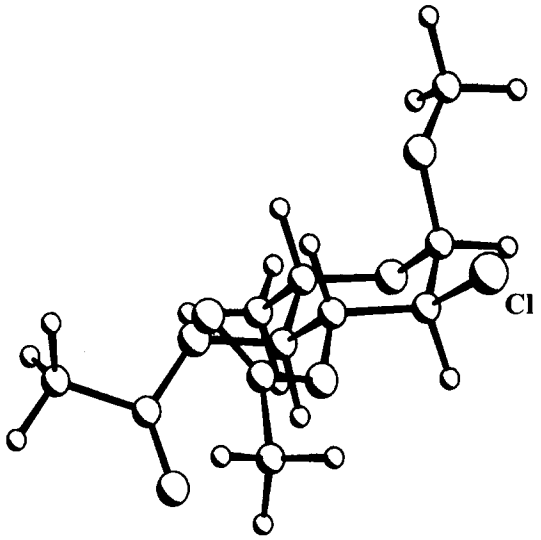


Figure 2. PLUTO DRAWING of the MMX optimized structures for compounds **1–11** in the $^1C_4$ conformation.



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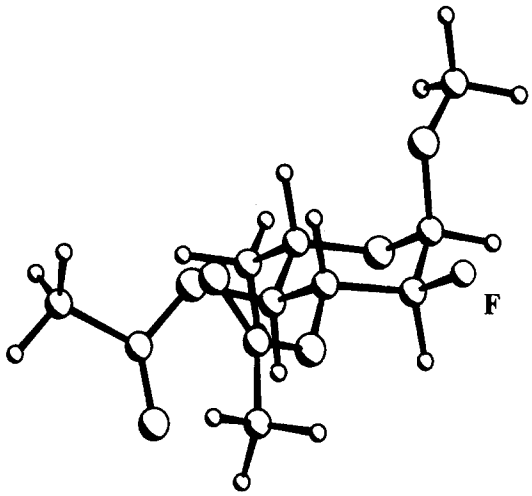

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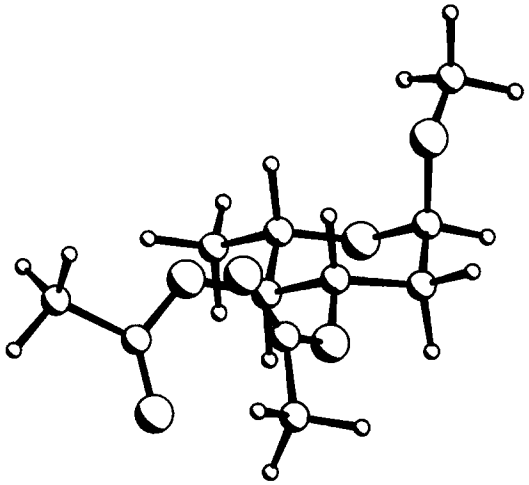

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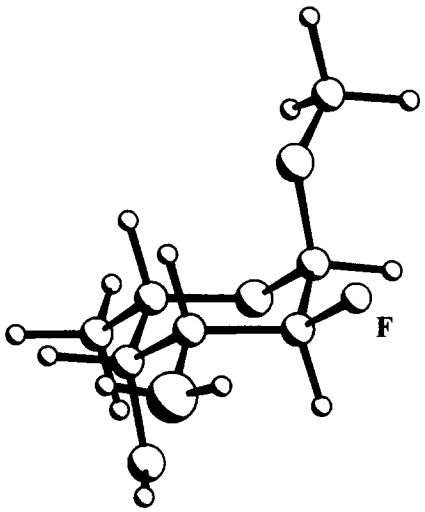

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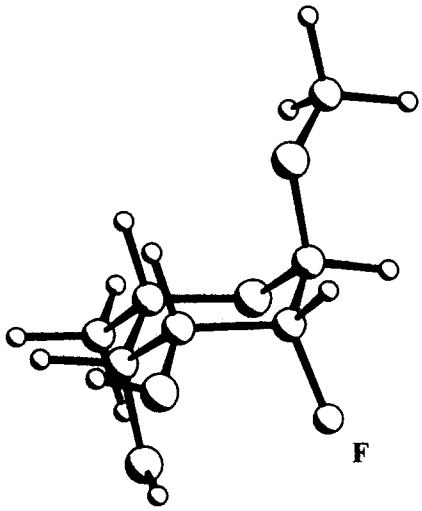


11

Figure 2. continued.

between the two conformations decreases for the structures solvated in water. The energy difference for solvation in hexadecane is of almost the same magnitude as in the case of unsolvated structures. This is in agreement with the experimental finding that the anomeric effect decreases in polar solvents.

Compound **11** shows a behavior opposite to that of compounds **1–10**, showing a higher energy difference in the water-solvated structures than in the hexadecane-solvated or unsolvated ones. This can be explained from its structure which presents three axial substituents in the $^1C_4$ conformation, giving a higher dipole moment (AM1 calculations give: 3.11 debye for $^1C_4$ and 1.25 debye for $^4C_1$).

Table 8. Conformational effects present in both $^1C_4$ and $^4C_1$ ring conformation of compounds **1–11**

Compd	Conf	Anomeric effect	Gauche interaction	1,3-interaction		ΔE (kcal mol^{-1})
				X..Y	X..H	
1	$^1C_4$	Yes	3	0	3	5.16
	$^4C_1$	No	3	1	3	
2	$^1C_4$	Yes	3	0	3	4.98
	$^4C_1$	No	3	1	3	
3	$^1C_4$	Yes	3	0	3	5.02
	$^4C_1$	No	3	1	3	
4	$^1C_4$	Yes	3	0	3	5.69
	$^4C_1$	No	3	1	3	
5	$^1C_4$	Yes	3	0	2	7.01
	$^4C_1$	No	3	2	2	
6	$^1C_4$	Yes	3	0	2	7.33
	$^4C_1$	No	3	2	2	
7	$^1C_4$	Yes	3	0	2	7.25
	$^4C_1$	No	3	2	2	
8	$^1C_4$	Yes	3	0	2	6.69
	$^4C_1$	No	3	2	2	
9	$^1C_4$	Yes	1	0	2	5.85
	$^4C_1$	No	1	1	3	
10	$^1C_4$	Yes	4	0	3	6.50
	$^4C_1$	No	3	1	3	
11	$^1C_4$	Yes	4	1	2	3.28
	$^4C_1$	No	3	1	2	

The geometrical parameters obtained from MM and MO calculations are in good agreement. Figures available as supplementary material, show a fitting using the ring atoms and those directly bonded to it, between the minimum energy structures obtained from MM and MO (AM1) calculations. The RMS values for the positions of these atoms are also shown. The ring fitting is very good although there are some discrepancies in the side chains, mainly in the OAc group in position 3.

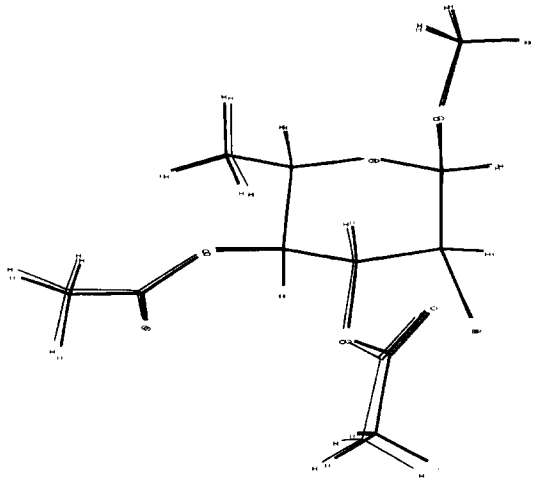
On the other hand, the structures obtained from isolated or solvated compounds are very similar, as can be seen in Figure 3, in which fitting between the minimum energy conformations for compounds **1–11** as obtained by AM1 and $AM1_{aq}$ is shown together with the RMS values for the position of ring atoms and those directly bonded to it. These RMS values are always less than 0.065 Å. From this finding, we can conclude that the solvation has a larger influence on the energies of the structures studied than on the geometries.

The C1 atom is an anomeric center. Therefore, the anomeric effect must play an important role in the conformational behavior of the compounds considered. Both MM and MO calculations give a minimum energy conformation for each compound which is in accordance with the anomeric conformational preferences. Then for all the compounds studied, the $^1C_4$ ring conformation is the most stable one with an axial disposition of the methoxy group at C1. The minimum energy conformations obtained also follow the exoanomeric effect (see Fig. 2). This affirmation can be confirmed numerically from Tables 2 and 5 in both MM and MO calculations. The pyranose ring conformation that follows the anomeric and the exoanomeric effect, should give Θ_1 and Θ_2 values around $|60°|$;[30] MM values are around $-61°$ and $-69°$ for Θ_1 and Θ_2. The AM1 values are almost the same as obtained by MM and compatible with the anomeric and exoanomeric preferences. In the $^4C_1$ ring

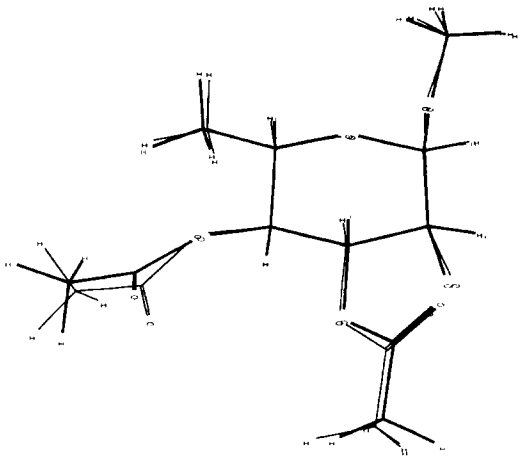
Table 9. 1,3-Diaxial interaction distances in Å (X...H and X...O), calculated in compounds **1–8** when the halogen is axial

Compd	Conf	X—H	X—O	RW(H)+RW(X)[a]	RW(X)+RW(O)[a]	Δr
1	$^1C_4$	3.17		3.82		0.65
2	$^1C_4$	3.02		3.68		0.66
3	$^1C_4$	2.91		3.53		0.62
4	$^1C_4$	2.68		3.15		0.47
5	$^4C_1$		3.40		4.06	0.66
6	$^4C_1$		3.24		3.92	0.68
7	$^4C_1$		3.13		3.77	0.64
8	$^4C_1$		2.86		3.39	0.53

[a]From MM2 van der Waals parameters.



2
RMS = 0.031Å



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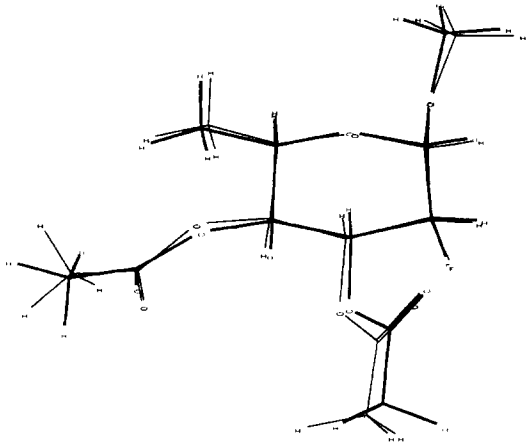
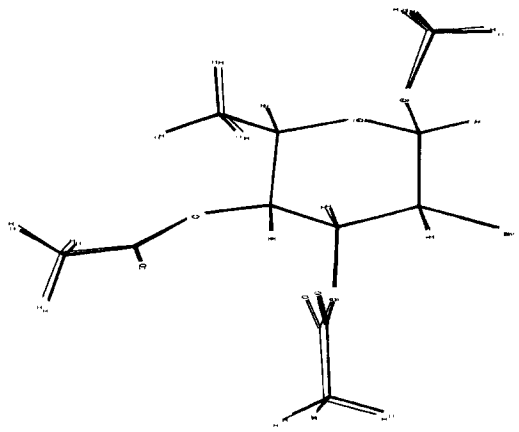
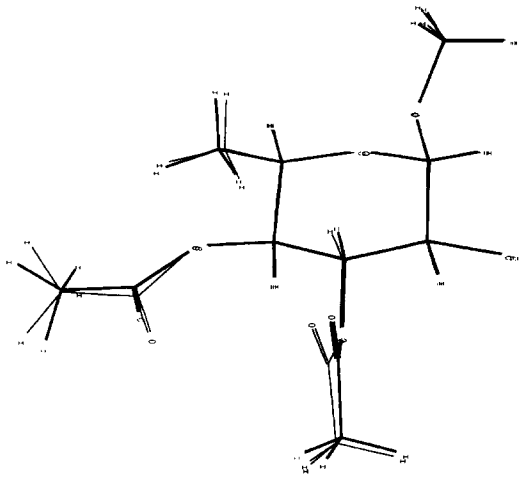


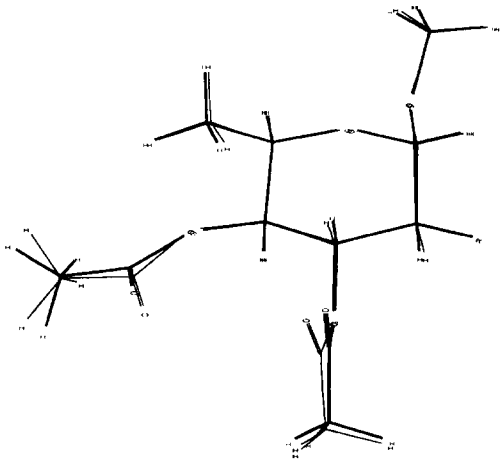
4
RMS = 0.065 Å



6
RMS = 0.019 Å



7
RMS = 0.025 Å

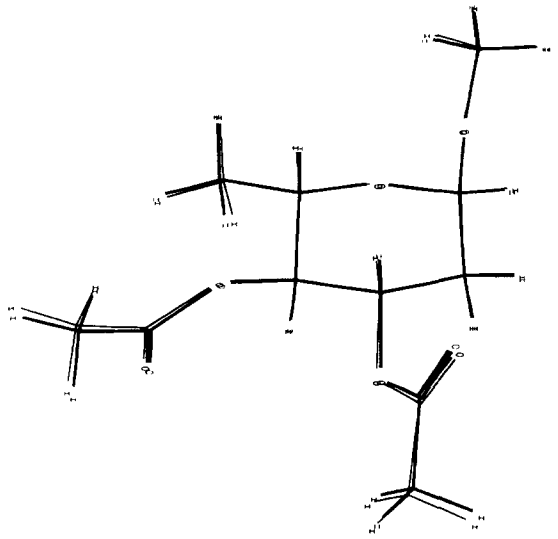


8
RMS = 0.036 Å

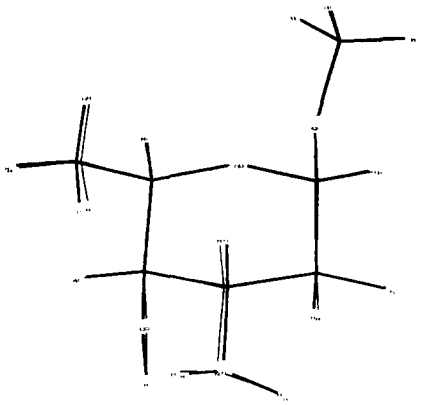
Figure 3. Computer-generated representations of the fitting between the geometry of compounds **2–4** and **6–11** as obtained by AM1 (thin line) and $AM1_{aq}$ (thick line) calculations, and the corresponding root means squares (RMS) values.

conformation, the methoxy group at C1 should adopt an equatorial disposition giving values of Θ_1 near 180°. However, this conformation gives Θ_2 values compatible with exoanomeric effects around −70° for MM and somewhat higher for semiempirical calculations (see Tables 2 and 5).

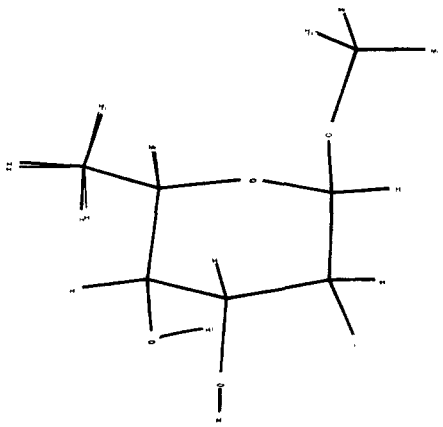
Because of the anomeric effect, the geometry of the acetalic group presents interesting bond lengths and angle tendencies. Elsewhere,[31] the average values for bond lengths and angles of the acetalic groups for methyl D-glucopyranosides obtained from crystallographic averaged structures are shown. From that, we can observe that the values of d_1 and d_2 are more than 0.02 Å smaller than d_3 and d_4 for the axial disposition. However, when the methoxy is equatorial, d_1 increases to almost the same value as d_3 or d_4 and d_2 decreases in 0.02 Å with respect to the axial disposition (see Table 2 and Scheme 1 for definition of d_1–d_4 and other geometrical parameters). The acetalic angle O—C—O (α) also changes when passing from the axial to the equatorial disposition of the methoxy group, decreasing by almost 5°. These tendencies observed from the experimental values have also been predicted theoretically by both ab initio[32] (for dimethoxymethane) and MM[11a] (for 2-alcoxytetrahydropyran) methods. In Tables 2 and 5, the geometrical parameters obtained for both $^1C_4$ and $^4C_1$ dispositions (compounds **1–11**) by MM and MO calculations are shown. As can be seen in Table 2, there are no significant changes in the d_1–d_4 values for a ring conformation and there are no changes when



9
RMS = 0.030 Å



10
RMS = 0.022 Å



11
RMS = 0.016 Å

Figure 3. continued.

passing from the $^1C_4$ to the $^4C_1$ ring disposition. This may be due to the lack of anomeric effect parametrization in MM2 and MMP1 in which MMX are based. Nevertheless, the decreasing tendency in the α angles is observed with values of around 114° and more than 109° for the $^1C_4$ and $^4C_1$ ring disposition. The MO calculations reproduce the geometrical tendency of the acetalic group better than MM calculations as can be seen in Table 5. Thus, in AM1 calculations d_1 and d_2 for compounds with $^1C_4$ ring dispositions (methoxy axial) give values smaller by 0.01 or 0.02 Å than d_3 and d_4, respectively, and when a $^4C_1$ conformation is adopted, a rise in d_1 (with similar values of d_3 and d_4) is observed. A variation in the α angle is also observed when changing from the $^1C_4$ to the $^4C_1$ conformations. These findings are modified when solvation is taken into account, especially in water with an increase of d_2 to almost the same values as d_3 and d_4, when the $^1C_4$ conformation is adopted. This d_2 increase is also observed in the $^4C_1$ conformation together with a small decrease in d_4. The effects in hexadecane are smaller, giving almost the same results as unsolvated compounds. This discrepancy could be explained if we consider a better solvation of the glycosidic oxygen than the ring oxygen. The analysis of the ring disposition in structures **1–11** can be performed by using the Cremer and Pople[25] ring puckering parameters in the $^1C_4$ and $^4C_1$ conformations. Structures **1–11** are methylpyranosides with a six-membered ring, so three puckering parameters are needed to describe the ring conformation. The parameters used are: the puckering amplitude Q, the polar angle θ, and phase angle $\Phi(2)$. The numerical results are shown in Tables 3 and 6 for MM and AM1 calculations. The adopted $^1C_4$ ring conformation is compatible with Θ values of about 178° and 171° for MMX and MO calculations, respectively. The puckering amplitude Q is also compatible with chair conformation with values higher than 0.5 Å, and $|q_3|$ is always much greater than q_2 and negative, indicating a $^1C_4$ ring conformation. The values observed for the $^4C_1$ minimum energy conformation of structures **1–11** are also compatible with a normal chair ring conformation (small Θ, $q_3 \gg q_2$ and positive).

As was pointed out in the Introduction, the substitution in position 2 of the sugar moiety by a halogen leads to an antibiotic with higher activity and lower toxicity than the parent compound when the halogen is in the axial position. When the halogen is equatorial, a loss of activity and the increase in toxicity appear. Elsewhere,[12] it was stated that this different behavior is due to the different facility of hydrolysis of the glycosidic bond. The susceptibility of the glycosidic linkage to hydrolysis may correlate with values of electrostatic potentials obtained by the Spartan program from the AM1 wave function over the electron density surface = 0.002 $e \times au^{-3}$ of the different oxygen atoms of the studied compounds. Looking at Table 10 we can observe that the electrostatic potentials over the O8 atom have higher[33] values when the halogen is in equatorial position than when it is in axial position. Moreover, for compounds with the halogen axial, the electrostatic potential decreases with the increase of the electronegativity of the halogen (compounds **1–4** and **11**), showing the minimum values for compound **11**. When the halogen is equatorial the electrostatic potential increases with the electronegativity of the halogen, to give the maximum values for compound **8**. When there is no halogen at C-2, the value for compound **9** is almost as high as the one for compounds **7** and **8**.

Table 10. Values of electrostatic potential (kcal mol^{-1}), calculated over the electronic density surface of 0.002 $e \times au^{-3}$ of compounds **1–11** from the AM1 hamiltonian

Compd	Electrostatic potential (kcal mol^{-1})			
	O7	O3[a]	O4	O8
1	−52.15	−44.00	−40.34	−52.78
2	−52.91	−45.26	−40.79	−51.19
3	−53.24	−49.80	−40.26	−51.06
4	−51.68	−49.50	−39.84	−50.37
5	−50.01	−42.38	−47.15	−52.77
6	−49.35	−42.90	−43.82	−55.15
7	−49.29	−42.56	−43.45	−56.35
8	−49.25	−42.23	−43.54	−56.74
9	−54.51	−44.35	−42.73	−57.84
10	−57.96	−52.21	−61.87	−53.64
11	−48.15	−57.68	−55.97	−43.76

[a]N3 for compound 10.

All these considerations can explain the increase in the activity of anthracycline antibiotic when a halogen group is introduced in the axial disposition at C-2. It is also of great interest to point out the usefulness of the electrostatic potential study in the structure–activity relationship investigation.

As pointed out before, comparison of geometrical optimization by semiempirical methods was studied on isolated molecules, and solvation in water and hexadecane was also taken into account. Furthermore, all these geometry optimizations have been done on model structures in order to obtain conclusions to be applied to the bioactive anthracycline antibiotics. From the calculations performed in this paper, we can surmise that the solvated geometries are very close to the unsolvated one, so, in the study of the whole antibiotic, the geometry optimization at the solvation level will not be necessary.

Another interesting point is to know the accuracy of the semiempirical calculations. For that, theoretical $^3J_{HH}$ coupling constants have been calculated in order to be compared with the experimental ones where available. In Table 7, comparison of theoretical and experimental coupling constants (solvated and unsolvated) are shown. As can be seen, there exists a good agreement between the results obtained and the experimentally available data (compounds: **1**, **2**, **3**, **6**, **7** and **9**). The higher discrepancies are for $J_{2,3}$ of compound **2**, and could possibly be due to a bad experimental assignment.

Supplementary Material

Supplementary material available: a listing of MM optimized geometries for compounds **1–11** in the $^1C_4$ and $^4C_1$ conformations (six pages) and Figures (two pages). This supplementary material is available from the authors upon request.

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