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Conformational analysis of 8-oxabicyclo[3.2.1]oct-6-en-3-one derivatives by NMR and theoretical calculations

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Abstract

This work describes the conformational analysis of alcohols 2α,4α-dimethyl-6,7-*exo*-isopropylidenedioxy-8-oxabicyclo[3.2.1]octan-3α-ol (**5**) and –3β-ol (**6**) and of alcohols 1,2α,4α,5-tetramethyl-6,7-*exo*-isopropylidenedioxy-8-oxabicyclo[3.2.1]octan-3α-ol (**7**) and -3β-ol (**8**). Based on NMR data and AM1, HF/6-31G* and DFT/B3LYP/6-31G* geometry optimization, the pyran ring of compounds (**5**) to (**7**) is found to have a chair conformation. In the case of (**8**), NMR data indicate the presence of a boat conformer ($\mathbf{8}_{\mathrm{boat}}$). However, the chair conformer ($\mathbf{8}_{\mathrm{chair}}$) is predicted to have smaller relative energy as given by calculations employing different basis sets for either calculations on isolated molecules or including the solvent used in the NMR analyses ($CDCl_3$). In contradistinction to thermodynamic results, DFT/B3LYP/6-31G* calculations of hydrogen (δ_H) and carbon (δ_C) chemical shifts of ($\mathbf{8}_{\mathrm{boat}}$) were concordant with NMR experimental data of (**8**). Therefore, the chemical shift calculations agree better with the experimental results than does the quantum chemical calculations leading to the conformational analysis of (**8**).

Keywords: Herbicidal activity; 8-Oxabicyclo[3.2.1]octan-3-ols; NMR conformational analysis; DTF

1. Introduction

Endeavour in the agrochemical sector is the province of modern chemical industry, whereas academia concentrates on the discovery of new prototypes either based on natural products or those that are designed. We have been involved in a research program geared to the develop studies of new herbicides and plant growth regulating compounds derived from the easily available 8-oxabicyclo[3.2.1]oct-6-en-3-one (**1**, Fig. 1), which has served as a building block for the synthesis of cyclic and acyclic targets [1–4]. We have discovered that compounds with the general structure 3-aryl-6,7-*exo*-isopropylidenedioxy-8-oxabicyclo[3.2.1]octan-3-ol (**2**, Fig. 1) show strong herbicidal activity against several crops and weeds [1,5].

As part of our research on the synthesis of compounds with herbicidal and/or plant growth regulating activity [6], we have recently published the synthesis and biological activities of the new compounds: 2α,4α-dimethyl-6,7-*exo*-isopropylidenedioxy-8-oxabicyclo[3.2.1]octan-3α-ol (**5**) and -3β-ol (**6**), as well as 1,2α,4α,5-tetramethyl-6,7-*exo*-isopropylidenedioxy-8-oxabicyclo[3.2.1]octan-3α-ol (**7**) and -3β-ol (**8**), obtained from the reduction of 2α,4α-dimethyl- and 1,2α,4α,5-tetramethyl-6,7-*exo*-isopropilidenodioxy-8-oxabicyclo[3.2.1]octan-3-one (**3**) and (**4**), respectively [7]. To unravel the structure–biological activity relationship of alcohols (**5**) to (**8**), it is interesting to develop studies of their conformational properties as these compounds may show different activities. These studies may be performed by combining experimental NMR data and theoretical calculations as we previously reported for other compounds [8]. As will be shown later, NMR (^{1}H and ^{13}C) studies and theoretical calculations using the semi-empirical (AM1), ab initio Hartree–Fock (HF) and density functional theory (DFT) quantum chemical methods for compounds (**6**) to (**8**) yielded very interesting information on their conformational analysis.

2. Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 400 Advance spectrometers using tetramethylsilane (TMS) as

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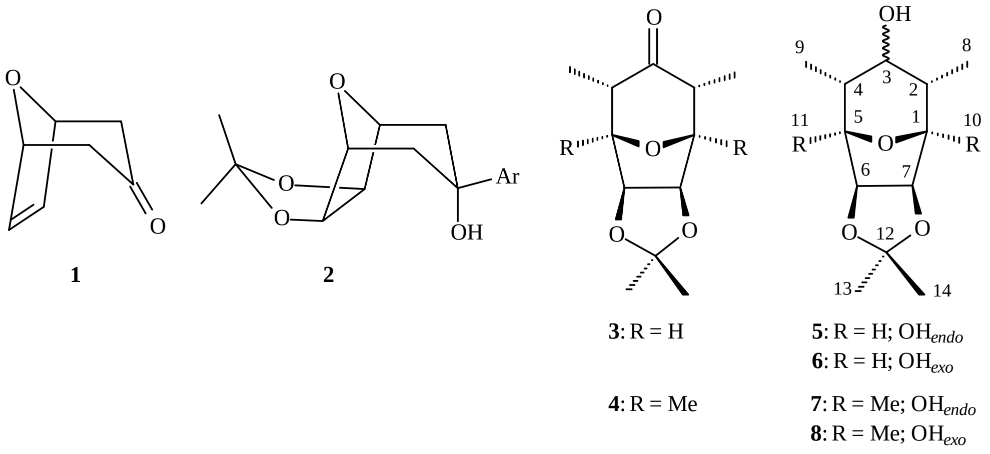


1

2

3: R = H

4: R = Me

5: R = H; OH*endo*
6: R = H; OH*exo*

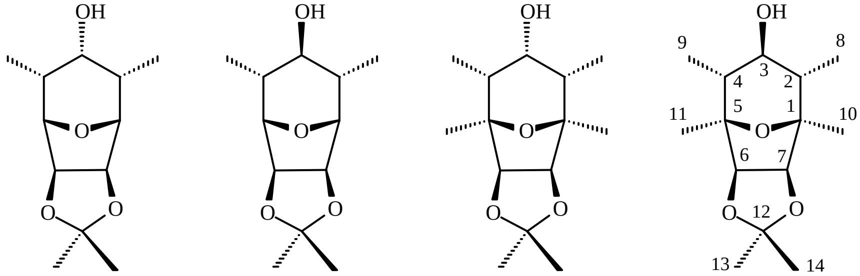
7: R = Me; OH*endo*
8: R = Me; OH*exo*

Fig. 1. Structure of 8-oxabicyclo[3.2.1]octane derivatives.

internal standard. The samples (15 mg) were dissolved in 0.5 mL of $CDCl_3$ and set into 5.0 mm NMR tubes. Chemical shifts are given in ppm (δ units) and coupling constants (*J*) are given in Hertz. Typical procedure described in the literature was used for the preparation of alcohols (**5**) to (**8**) [7]. 2α,4α-Dimethyl-6,7-*exo*-isopropylidenedioxy-8-oxabicyclo[3.2.1]octan-3α-ol (**5**): ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 111.05 (C-12), 83.13 (C-6/7), 80.91 (C-1/5), 71.08 (C-3), 37.40 (C-2/4), 26.13 (C-14), 24.53 (C-13), and 12.68 (C-8/9); ^1H NMR data are shown in Table 1. 2α,4α-Dimethyl-6,7-*exo*-isopropylidenedioxy-8-oxabicyclo[3.2.1]octan-3α-ol (**6**): ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 111.53 (C-12), 84.16 (C-6/7), 79.80 (C-1/5), 75.62 (C-3), 40.99 (C-2/4), 25.98 (C-14), 24.52 (C-13), and 13.31 (C-8/9); ^1H NMR data are shown in Tables 1 and 3. 1,2α,4α,5-Tetramethyl-6,7-*exo*-isopropylidenedioxy-8-oxabicyclo[3.2.1]octan-3α-ol (**7**): ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 111.32 (C-12), 83.92 (C-6/7), 83.04 (C-1/5), 73.37 (C-3), 43.1 (C-2/4), 26.46 (C-14), 25.30 (C-13), 19.31 (C-10/11), and 13.26 (C-8/9); ^1H NMR data are shown in Table 1. 1,2α,4α,5-Tetramethyl-6,7-*exo*-isopropylidenedioxy-8-oxabicyclo[3.2.1]octan-3β-ol (**8**): ^1H and ^{13}C NMR data are shown in Tables 1 and 4.

Theoretical studies were carried out using the GAUSSIAN 03W software package [9].The geometry optimizations were performed using the semi-empirical method AM1 [10], ab initio Hartree–Fock (HF) [11] and density functional theory (DFT) [12] with the BLYP functional, employing the standard Pople's split valence 6-31G* basis set [13]. The optimized geometries were characterized as true minima on the potential energy surface (PES) with all harmonic frequencies being real.

Table 1
^1H NMR data of alcohols (**5**) to (**8**) using $CDCl_3$ as solvent and TMS as internal standard (δ in ppm and coupling constants *J* in H_2)



Hydrogen	**5**, δ(*J*)	**6**,δ(*J*)	**7**, δ(*J*)	**8**, δ (*J*)
1/5	3.95 ($J_{1,2}=J_{5,4}=3.7$)	4.04 ($J_{1,2}=J_{5,4}=3.9$)	–	–
2/4	2.04 ($J_{2,8}=J_{4,9}=7.3$, $J_{2,1}=J_{4,5}=3.7$, $J_{2,3}=J_{4,3}=3.6$)	1.72 ($J_{2,3}=J_{4,3}=10.1$, $J_{2,8}=J_{4,9}=7.0$, $J_{2,1}=J_{4,5}=3.9$)	1.83 ($J_{2,8}=J_{4,9}=7.2$, $J_{2,3}=J_{4,3}=3.7$)	1.82 ($J_{2,8}=J_{4,9}=7.2$, $J_{2,3}=J_{4,3}=3.9$)
3	3.67 ($J_{3,2}=J_{3,4}=J_{3,OH}=3.6$)	2.71 ($J_{3,2}=J_{3,4}=10.1$)	3.63 ($J_{3,2}=J_{3,4}=3.7$)	3.67 ($J_{3,2}=J_{3,4}=J_{3,OH}=3.6$)
6/7	5.00 (s)	4.50 (s)	4.82 (s)	4.82 (s)
10/11	–	–	1.26 (s)	1.26 (s)
8/9	1.01 ($J_{8,2}=J_{9,4}=7.3$)	1.05 ($J_{8,2}=J_{9,4}=7.0$)	1.02 ($J_{8,2}=J_{9,4}=7.2$)	1.02 ($J_{8,2}=J_{9,4}=7.2$)
13	1.32 (s)	1.32 (s)	1.33 (s)	1.33 (s)
14	1.48 (s)	1.49 (s)	1.49 (s)	1.49 (s)
OH	1.58 ($J_{OH,3}=3.6$)	1.60 (b.s.)	1.61 (s)	1.43 ($J_{OH,3}=3.6$)