Experimental and Theoretical Investigation of Epoxide Quebrachitol Derivatives Through Spectroscopic Analysis

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ABSTRACT
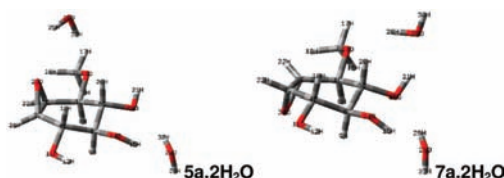
Two synthetic epoxide derivatives, important intermediates in organic synthesis, were obtained from L-quebrachitol, and their conformations were proposed based on spectroscopic analysis. Density functional theory (DFT) calculations of infrared and NMR spectra were shown to be reliable enough for organic chemistry applications. The observed structures were determined with the aid of the DFT spectroscopic data, stressing the relevance and utility of combined experimental/theoretical studies and also the usefulness of the ^{13}C NMR B3LYP/6-31G(d,p) calculations.

The precise determination of the molecular structure of chemical species that can be detected in a given reaction media, for example, in a specific synthetic route passing through various intermediate structures leading to a desired product, is very important in organic chemistry applications. The relative energy values for various possible equilibrium and transition state structures, that can be obtained using computational chemistry methods, can be very helpful to decide between plausible reaction mechanisms. An expected goal of such studies is an understanding of chemical reactivity at a molecular level, through the evaluation of the effect of the molecular structure and local chemical environment on a given chemical reaction, which can be of fundamental or applied interest (such as organic catalysis or biochemical process). The synthesis of azide derivatives from L-quebrachitol **1** can be cited as an example, where a combination of theoretical and experimental data led to the determination of the reaction mechanism.[1] In conformational analysis, another important area, a combination of experimental spectroscopic data and theoretical ab initio results can lead to the determination of the conformational population in equilibrium at a given temperature, such as for example reported for tetramethylimidazolidine compounds.[2] In many organic chemistry applications, substituted six-membered ring species are present, usually in condensed media, with spectroscopic methods being used routinely for experimental structural determination. Unfortunately, in such cases where an adequate crystalline solid sample is not available X-ray diffraction experiments cannot be used. Therefore, the use of theoretical methods turns out to be of great utility for the determination of molecular structure.

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The structure of distinct chemically useful aminoglycoside antibiotics, such as neomycin, kanamycin, and gentamycin, contains the amino cyclitol moiety deoxy-streptamine **2**.[3a,b] Conduritol epoxides and aminoconduritols are inhibitors of glycosidases.[3c] Inositols are also present in several substances of biological interest such as pancrastitatin[4a] and inositol phosphates, a group of phosphorylated inositols which control and modulate vital physiological processes, such as cell growth and apoptosis.[4b,c] Therefore, the biological importance of cyclitols and inositols has strongly stimulated the investigation of new methods to synthesize their enantiomerically pure and differentially protected derivatives. It is also important to mention that the well-established accessibility and versatility of epoxides have made them one of the key intermediates of modern organic synthesis. Not only are these compounds easily prepared from a variety of starting materials but also the inherent polarity and strain of their three-membered ring make them susceptible to reaction with a large number of reagents: electrophiles, nucleophiles, acids, bases, reducing agents, and some oxidizing agents. Thus, the understanding of the mechanisms of reaction of these synthetic intermediates is an important task;[5] therefore, the use of quantum chemistry methods is justified.

In a previous work,[1a] we reported the preparation of mesylated **3** from L-quebrachitol and its transformation to the azido compound **4** with total retention of the configuration (Scheme 1), which was confirmed by theoretical calculations.[1b] Epoxide
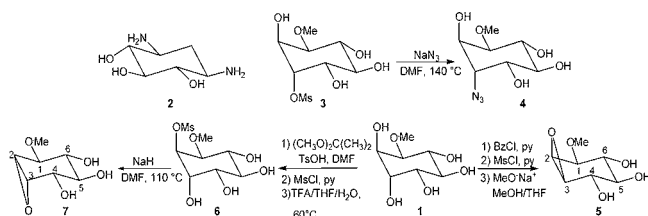
5, which was previously proposed as an intermediate in the mechanism for the reaction between a quebrachitol derivative and sodium azide,[1b] was now synthesized in three steps from L-quebrachitol **1** (Scheme 1).[6] The parent epoxide **7** was prepared in 62% yield by reaction of mesylate **6** with sodium hydride in dimethylformamide (DMF) at 110 °C (Scheme 1).[6] Infrared (IR) and nuclear magnetic resonance (NMR) data were used for characterization.[6]

In the present work, we carried out a detailed structural analysis for the two epoxides **5** and **7** using the Density Functional Theory (DFT) method.[7] Theoretical IR spectra and ^{13}C NMR chemical shifts were calculated for the determination of the molecular structure through comparison with experimental spectroscopic data. First place, we conducted an evaluation of how trustable is the popular B3LYP functional for the calculation of the IR spectra and NMR chemical shifts as compared with post-Hartree−Fock (post-HF) ab initio results, using as reference data Møller−Plesset second-order perturbation theory (MP2) calculations and also experimental spectroscopic data. The aim here is to reaffirm, on sound basis, the great utility of DFT calculations of spectroscopic quantities, such as NMR and IR spectra, to complement experimental studies in the area of organic chemistry, corroborating experimental assignments and also providing new insights into the molecular structure.

The structures proposed for epoxides **5** and **7** shown in Scheme 1 (qualitative 2D representation), having the OH and MeO substituent groups in the equatorial position, were fully optimized without any geometrical constraint at the DFT (B3LYP functional)[8] and MP2 level using the 6-311+G(2d,p) basis set.[9a,b] To assess the effect of structural modifications on the NMR spectra, a search for local minima on the potential energy surface (PES) was carried out, with eight isomeric structures optimized for each epoxide (named a−h). The 2D view of the optimized structures is shown in Figure 1 with the carbon where the OH group changed with respect
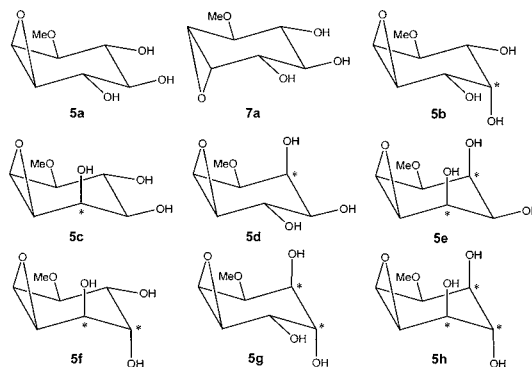

Figure 1. Structures of epoxides **5a**, **7a**, and the seven **5a** isomers.

to **5a** is marked with an asterisk. All fully optimized structures for epoxides **5** and **7** are given as Supporting Information (Figures S6 and S7). Harmonic frequency calculations were performed for the characterization of each structure as true minima (all frequencies are real), which also yield directly the

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IR spectra (vibrational frequencies and intensities of normal modes). The NMR technique is known as very useful to experimental characterization of organic compounds; an example was shown recently for the camphorquinone biotransformation products.[10] In this work the gauge-independent atomic orbital (GIAO) method[11] was applied for the calculation of the ^{13}C and ^{1}H magnetic shielding constants (σ) and the chemical shift (δ) for selected atoms obtained on the δ-scale relative to the TMS at the B3LYP/6-311+G(2d,p) level, as previously described in the anhydrotetracycline−platinum dichloride complex study reported by our group.[12] The solvent effect on the calculation of chemical shifts was also evaluated using a polarizable continuum model (PCM),[13] followed by ^{13}C NMR calculations. The changes in the chemical shifts are more pronounced for water ($\varepsilon = 78.39$), DMF ($\varepsilon = 36.70$), and methanol ($\varepsilon = 32.63$) but not very sizable (see Supporting Information: Table S1) showing a maximum average deviation (AD) value of 2.8% (1.8 ppm). For solvents with small dielectric constants (ε), such as THF and pyridine (used in the experimental part of this work), the solvent effect can be ignored. All calculations were carried out with the Gaussian-03 program.[14]

A comparison between B3LYP with post-HF MP2 values using various basis sets was done. A summary of the ^{13}C NMR results for epoxide **5a** are given as Supporting Information (see Table 1), along with average deviation (AD). It can be seen that the agreement is very good. Therefore, the use of the B3LYP/6-311+G(2d,p) level of calculation, which is much more computationally affordable than MP2, is justified showing a small AD value with reference to MP2 result of 1.3% (0.8 ppm), which can be considered small enough for experimental determination. Enlarging the basis set to a quadruple-ζ quality leads to larger AD values (Supporting Information: Figures S8, S9, Table S2).

B3LYP/6-311+G(2d,p) ^{13}C NMR results (TMS scaled factor: 0.985) are shown in Figure 2 along with experimental and B3LYP/6-31G(d,p) data. It can be seen that the two sets of B3LYP results are practically the same showing exactly the same NMR profile and a nice agreement with the experimental ^{13}C NMR data, so the B3LYP/6-31G(d,p) level is sufficient. This result leaves no doubt that the epoxide **5a** is definitively the molecular structure present in the experimental sample handled in the NMR measurements. In addition, it is showed that an average uncertainty in the theoretical ^{13}C NMR results of 5% (or 3 ppm) can be attained in DFT calculations and also that this is good enough for
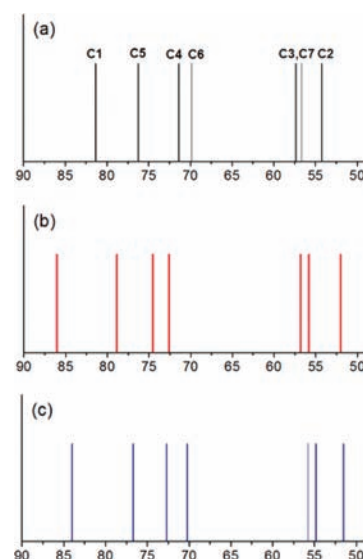

Figure 2. Epoxide **5**: Comparison between experimental and B3LYP NMR data. (a) Experimental ^{13}C NMR data (ppm): C1, 81.4; C2, 54.3; C3, 56.7; C4, 69.9; C5, 71.4; C6, 76.3; C7, 57.4. (b) B3LYP/6-311+G(2d,p) TMS Scaled (0.985): (4.1%; 2.9 ppm). (c) B3LYP/6-31G(d,p): (4.2%; 2.8 ppm).

structural elucidation of organic compounds. A similar analysis was performed for epoxide **7**, and the conclusions are the same (see Supporting Information Figure S10).

The B3LYP/6-311+G(2d,p) calculated chemical shifts for the eight epoxides **5** (**5a−5h**, see Figure 1) given as Supporting Information (Figures S11 and S12 for epoxide **7**) show that there are sizable variations in the ^{13}C NMR profiles with structure **5a** exhibiting the best agreement with experiment, reproducing precisely the observed NMR profile. It can be seen that the nuclear magnetic shielding on the carbon atoms is sensitive to structural changes, and therefore, the match of theoretical ^{13}C NMR patterns with the experimental profile is a good criterion to identify a plausible molecular structure present in the sample handled in the NMR experiment. This is indeed a very welcome and important result that can stimulate further theoretical/experimental joint research projects.

Regarding the analysis of the IR spectrum, a series of calculations for structure **5a**, using the DFT B3LYP functional and the correlated MP2 level of theory employing various basis sets, were performed to assess the credibility of the B3LYP IR spectra calculation (see Supporting Information Figure S13). Theoretical band spectra are shown, which were simulated using a fitting to a Lorentzian distribution function to mimic the experimental spectrum profile,[15] with 15 cm^{-1} for average width of the peaks at half height and 2×10^{-6} mol cm^{-3} for sample concentration. It was shown that a good match between B3LYP and MP2 spectra is always observed. A comparison between the experimental spectrum recorded for epoxide **5** (in KBr)[6] and B3LYP/6-311+G(2d,p) spectra reported in Figures 3a−c is very informative and shows a good overall agreement between theory and experiment for the main assigned bands

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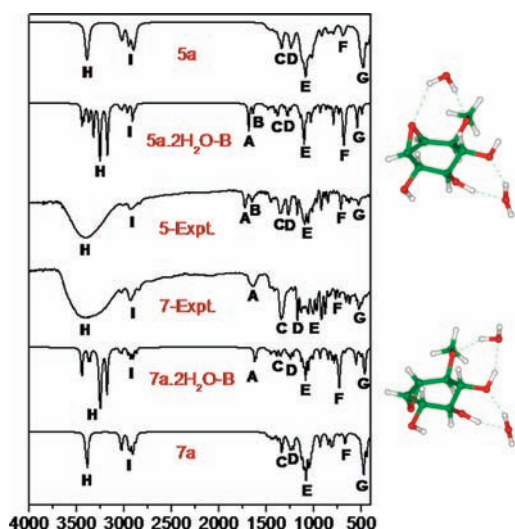
Figure 3. Experimental and B3LYP/6-311+G(2d,p) IR spectra for **5** and **7**. (a) B3LYP: **5a**. (b) B3LYP: **5a·2H₂O-B**. (c) Expt.: **5**. (d) Expt.: **7**. (e) B3LYP: **7a·2H₂O-B**. (f) B3LYP: **7a**. The experimental IR spectra for epoxides **5** and **7** were recorded in the 4000−230 cm^{-1} region (measured in KBr). The B3LYP IR spectra were scaled using the following progressive scaling factors in the respective spectral region: 4000−3250, **0.89**; 3250−2000, **0.97**; 2000−800, **0.99**; 800−600, **1.10**; 600−400 cm^{-1}, **1.25**.

within acceptable deviations. The B3LYP frequencies were scaled to be comparable with experiment, a very useful procedure that enables the assignments of experimental IR bands (Supporting Information Table S3), as reviewed recently by Radom and collaborators.[16] The only serious disagreement between theoretical and experimental IR spectra for epoxide **5a** is in the 1800−1600 cm^{-1} region, where two close absorption bands are missing in the theoretical spectra, which could be attributed to humidity in the experimental sample. To confirm this assumption, IR spectra were calculated for dihydrated, tetrahydrated, and pentahydrated structures (Supporting Information Figures S14, S15), and new intense bands just above 1600 cm^{-1} appeared (Figures 3b and 3e) due to the presence of water (experimentally observed at 1595 cm^{-1} for H₂O vapor).

The presence of well-resolved A, B, C, D, F, and G bands in the theoretical IR spectrum, in the 2000−400 cm^{-1} region, is strong evidence in favor of the **5a** isomer having the OH groups at the equatorial position as proposed and expected experimentally.[6] It is important to mention that the absence of an intense absorption band in the theoretical spectrum, which is present in the observed spectrum, is a strong argument to rule out a given molecular structure from a list of probable candidates, as has also been shown for the characterization of metal complexation sites.[17]

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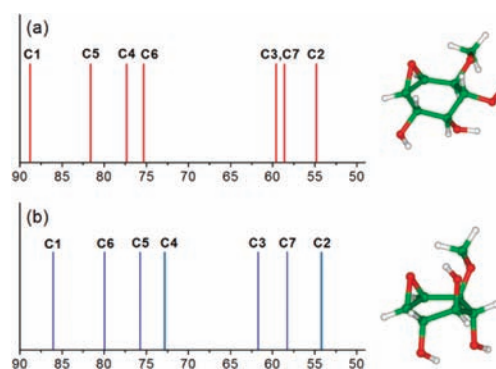(17) Dos Santos, H. F.; Zerner, M. C.; De Almeida, W. B. *J. C.hem. Soc., Perkin Trans. II* **1998**, *11*, 2519.

Figure 4. B3LYP/6-311+G(2d,p) ^{13}C NMR chemical shifts (in ppm) for the possible conformers for epoxide **5**. (a) **5**^{a}. (b) **5a′** conformer.

The best agreement with the experimental IR spectra for epoxide **5** is achieved with a dihydrated structure named B (**5a·2H₂O-B**; see Figure 3b), where one of the water molecules is H-bonded to the OCH₃ group and close to the epoxide moiety, providing information on the structure of the hydrated epoxide species.

To corroborate the presence of hydration waters in the epoxide compounds, thermogravimetry experiments were conducted using the same samples handled in the measurements of IR spectra (see Supporting Information; Figure S5). The analysis of the TG and DTA curves enabled us to conclude that the correct stoichiometry for both epoxides should be **5·2H₂O** and **7·2H₂O**.

We have performed a search for possible conformers of epoxide **5a** and found only one additional conformer named **5a′** (see Figure 4b), which is however approximately 5 kcal mol^{-1} above **5a**. It can be seen from Figure 4 that conformational changes lead to sizable modification in the ^{13}C NMR spectra (Figure 4b), showing that NMR chemical shifts can be useful in conformational analysis and conformer **5a′** can be ruled out from a possible conformational equilibrium based on the comparison of ^{13}C NMR profiles (see also Supporting Information: IR data, Figure S16). Therefore, a single conformer **5a** (or **5a·2H₂O**) is present.

A very important and welcome result of this work was to show the usefulness of ^{13}C NMR B3LYP calculations to differentiate a series of inositol compounds, having substituent groups at equatorial/axial positions, which are substances of biological interest and of great relevance to the area of organic synthesis.

Supporting Information Available: Experimental and theoretical IR and ^{13}C NMR spectra, B3LYP optimized Cartesian coordinates, and total energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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