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Analysis of 7-Membered Lactones by Computational NMR Methods. Proton NMR Chemical Shift Data are More Discriminating than Carbon

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Abstract

	Corrected Mean Absolute Errors	
	$\delta^1\text{H}$	$\delta^{13}\text{C}$
<i>cis</i>		
<i>cis_{exp}</i> vs. <i>cis_{comp}</i>	0.05	1.1
<i>cis_{exp}</i> vs. <i>trans_{comp}</i>	0.14	2.8
<i>trans</i>		
<i>trans_{exp}</i> vs. <i>trans_{comp}</i>	0.05	1.3
<i>trans_{exp}</i> vs. <i>cis_{comp}</i>	0.19	1.2

We report an NMR chemical shift study of conformationally challenging seven-membered lactones (**1–11**); computed and experimental data sets are compared. The computations involved full conformational analysis of each lactone, Boltzmann-weighted averaging of the chemical shifts across all conformers, and linear correction of the computed chemical shifts. DFT geometry optimizations [M06-2X/6-31+G(d,p)] and GIAO NMR chemical shift calculations [B3LYP/6-311+G(2d,p)] provide the computed chemical shifts. The corrected-mean absolute error (CMAE), the average of the differences between the computed and experimental chemical shifts for each of the eleven lactones, is encouragingly small (0.02–0.08 ppm for ^1H or 0.8–2.2 ppm for ^{13}C). Three pairs of *cis* vs. *trans* diastereomeric lactones were used to assess the ability of the method to distinguish between stereoisomers. The experimental shifts were compared with the computed shifts for each of the two possible isomers. We introduce the use of a “match ratio”—the ratio of the larger (worse fit) to the smaller (better fit) CMAE. A greater match ratio value indicates better distinguishing ability. The match ratios are larger for proton data [2.4–4.0 (ave = 3.2)] than for carbon [1.1–2.3 (ave = 1.6)], indicating that the former provide a better basis for discriminating these diastereomers.

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Author Contributions

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Notes

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ASSOCIATED CONTENT

Supporting Information. Eleven tables containing the experimental assignment of resonances, coupling constants, and relevant COSY interactions for each of **1–11**; eleven corresponding pairs of tables containing the CMAE analysis of the ^1H and ^{13}C chemical shifts; copies of NMR spectra of each lactone; Cartesian coordinates, computed isotropic shielding values, and derived chemical shifts for each conformer of each lactone. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Introduction

Computational approaches to deducing the structure of organic compounds are growing in importance and reliability.^{1–5} One common method involves computing the set of chemical shifts, typically both proton and carbon, for each candidate structure (e.g., **A** and **B**) and then comparing the results with experimental data for the compound of interest (e.g., **X**). This is particularly valuable in the context of comparing and distinguishing between diastereomeric structures, which can otherwise be quite challenging. The set of shifts that show the closer/closest match lead to an assignment (or validation) of the structure in question. Methods for analyzing the “goodness of fit” have been further developed by Smith and Goodman through statistical treatments that provide numerical probabilities for analyzing various fits.^{6,7} Their parameters have been developed to handle situations when experimental data are available for a multiple isomeric compounds (CP3 parameter⁶) or for only a single isomeric compound (DP4⁷ parameter). Additionally, Sarotti has shown discrimination between experimental and computed shifts through application of a training set as an artificial neural network to guide pattern recognition.⁸ We have used a “goodness of fit” analysis to study an array of diastereomeric six-membered methylcyclohexanol compounds (Figure 4).⁹ Among other things, we made the observation that proton data sets provide for a greater degree of discrimination among the possibilities than do carbon chemical shift data.^{9,10} It is clear that the ability to reliably map the conformational landscape of each given structure of interest is essential in this approach. We report here a similar study of some conformationally more challenging¹¹ seven-membered caprolactone derivatives of known structure. We describe the use of a “match ratio”—the numerical ratio between the less vs. the more closely matched data sets—to judge the merit of each pair of possible fits (i.e., **A** vs. **X** vs. **B** vs. **X**).

In the course of studying the ring-opening transesterification polymerization (ROTEP) of various terpene-derived lactones, we have prepared the series of 7-membered caprolactone derivatives **1–11** shown in Figure 1. We have assigned the NMR spectra of these compounds in a more thorough manner than had been reported previously for most.¹² These compounds are of growing interest as reactive monomers for the preparation of bio-renewable/sustainable polyesters.¹³ These lactones comprised an attractive set for study by the NMR methods outlined above.

RESULTS AND DISCUSSION

NMR Spectroscopic Data Collection, Interpretation, and Assignment for Lactones 1-11

A complete battery of NMR spectral data (1D-proton, 1D-carbon, COSY, and HMQC) was collected for each of lactones **1–11**. NOESY spectra were recorded for **10** and **11** in order to confirm the assignments of certain protons within the methylene pairs. Cumulative analysis of these spectra permitted the assignment of the chemical shifts of nearly all ¹H and ¹³C resonances. These chemical shift values, δ_{Hexp} and δ_{Cexp} , respectively, (along with coupling constant and COSY correlations) are recorded in Tables S1–S11 (a representative example is given below for lactone **7**, Table 1). In a few instances the chemical shifts of certain pairs of resonances were sufficiently similar that overlapping cross-peaks in the 2D NMR data could not be distinguished with confidence. Where appropriate, these are noted by footnotes in the table. For three of the lactones we were not able to definitively assign two of the carbon resonances in each [**1** (C4 vs. C5), **8** (C5 vs. C6), and **9** (C4 vs. C8)]. In those instances, the chemical shift value most closely matching that of the computed value was used in the goodness of fit analysis (below).⁷

Comparison of Experimental and Computed Chemical Shifts for Lactones 1-11

Briefly, computation of the lactones was carried out by DFT optimization [M06-2X/6-31+G(d,p)], and calculation of isotropic shielding values [B3LYP/6-311+G(2d,p)] and their translation to chemical shifts (see Experimental and Computational Details below). We then assessed the correlation between experimental and computed chemical shifts for each of the lactones **1** – **11**. Discussed here is one representative example of the method we used. Specifically, the chemical shift data (δH_{exp} and δH_{comp}) as well as the absolute error, linearly correct computed shift, and the corrected absolute error for each proton in abnormal *trans*-carvomenthine (**7**) are shown in Table 2. Linear correction is the scaling of each computed shift to an equation for a straight line obtained by least-squares regression analysis of all the experimental (y-axis) versus computed (x-axis) chemical shifts of the same compound. The correction takes the form of the equation $\delta_{\text{corr}} = \text{slope} * \delta_{\text{comp}} + \text{intercept}$. Use of this correction serves to reduce systematic error in the δH_{comp} values. The overall result of this correction can be discerned by comparing the mean absolute error (MAE, the average absolute error compared against experimental data across all resonances [proton or carbon] for those of any one computed structure) with the corrected mean absolute error (CMAE, eq 1) values shown in the bottom line of Table 2. The same form of analysis was carried out for the ^{13}C NMR data.

$$\text{CMAE} = \frac{1}{n} \sum_{i=1}^n |\delta_{\text{exp}} - \delta_{\text{corr}}| \quad (\text{eq 1})$$

This analysis was carried out for each of the lactones and the final CMAE values are compiled in Figure 2. Notice that the CMAE values for the ^1H NMR data range from 0.01 to 0.07 ($\mu = 0.05$, $\sigma = 0.01$). The magnitudes of these deviations are consistent with what we have observed previously.^{9,10,14}

It is worth considering the question of “How bad of a fit can be achieved?” The worst case arises by comparing the experimental shifts arranged from smallest to largest with the computed shifts arranged from largest to smallest. In the case of, for example, lactone **7**, these worst case CMAEs for ^1H and ^{13}C are 0.62 and 30.0, respectively. Indeed, across the entire family of lactones **1–11**, the average worst case CMAEs are 0.46 and 29.3, respectively. A complementary analysis involves determining the best possible match of the data by comparing the experimental and computed chemical shifts, both organized from smallest to largest. These CMAE values for **7** are 0.05 and 1.3, while the average for the entire family of lactones **1–11** is 0.05 and 1.1 for ^1H and ^{13}C respectively. Given these upper and lower numerical bounds for the goodness of fit, the CMAEs reported in Figure 2 can be judged to be quite good.

We have also analyzed these data in another way – namely, by introducing the idea of a “match ratio”. We define this as the value of the larger corrected mean absolute error (CMAE) divided by the value of the smaller CMAE. This ratio is an indicator of the extent to which computed data sets for two different structural isomers match the experimental data. A match ratio of 1.0 means that there is no preference for one computed data set over the other when compared to the experimental data.

$$\frac{\text{CMAE}_{\text{larger}}}{\text{CMAE}_{\text{smaller}}}$$

The match ratios for the three pairs of *cis/trans* diastereomers (**4/6**, **5/7**, **8/9**) for each of proton and carbon data are given in Figure 3. The match ratio for proton data (in blue) in each case is larger than that for the carbon data. That is, comparison of computed versus experimental proton shifts results in a higher degree of discrimination between stereoisomers. Accordingly, proton-based analysis would appear to be more reliable for assigning the stereostructure of an unknown. To further underscore that idea we have revisited our earlier study of the series of methylated cyclohexanols (**17** – **22**) shown in Figure 4.

In that work we had also concluded that the proton chemical shift data were more discriminating compared with carbon. We have re-treated the data from that study and present it here in the form of the match ratio as described above (Figure 5). Again, analysis of the proton data is advantageous. Notice that the magnitude of the match ratios in this series is significantly larger than for the lactones (Figure 3). This perhaps reflects the ability of the computational methodology to more reliably capture the conformational landscape of these six- vis-à-vis the seven-membered compounds.

Conclusion

In conclusion, we have computed the ^1H and ^{13}C NMR chemical shifts for a series of seven-membered lactones (**1**–**11**) and compared them with the experimental data. The corrected-mean absolute errors (CMAEs) were small (^1H and ^{13}C ranged from 0.02–0.08 and 0.8–2.2 ppm, respectively), indicating a high degree of agreement between the computed and experimental data. The ability to distinguish between diastereomeric lactones was evaluated utilizing a “match ratio”, the numerical ratio between the less vs. the more closely matched data sets. This has been particularly useful in highlighting the fact that ^1H rather than ^{13}C chemical shift data are more effective at discriminators for correct structure assignment.

EXPERIMENTAL AND COMPUTATIONAL DETAILS

Experimental Section

Glassware for moisture-sensitive experiments (e.g., enolate alkylation) was dried in an oven at 150 °C prior to use. These experiments were carried out under an atmosphere of dry nitrogen. Anhydrous dichloromethane (DCM) and tetrahydrofuran (THF) were obtained by passing the commercial grade solvent through an activated alumina column. All other solvents and reagents from the commercial sources were used as received. NMR spectra were recorded on a 500 or 300 MHz NMR spectrometer in CDCl_3 . Proton chemical shifts are referenced to internal TMS (δ 0.00). Carbon chemical shifts are referenced to $^{13}\text{CDCl}_3$ (δ 77.23) for spectra recorded in CDCl_3 . The following abbreviations are used to describe multiplets: s (singlet), d (doublet), t (triplet), q (quartet), pent (pentet), m (multiplet), nfm (non-first order multiplet), and br (broad). α/β correspond to the orientation of the proton relative to a ring substituent as specified for each lactone that was studied. Infrared (IR) spectra were recorded on a FT-IR spectrometer in ATR mode (Zn-Se). Only the most intense and/or diagnostic peaks are reported. GC-MS experiments using electron impact ionization (EI) were performed at 70 eV using a mass selective detector. MPLC refers to medium pressure liquid chromatography (25–60 psi) using hand-packed columns of silica gel (18–32 μm , 60 Å), an HPLC pump, and a differential refractive index detector. Analytical TLC was performed using TLC plastic sheets with F_{254} indicator and detection was performed by UV-light or potassium permanganate, *p*-anisaldehyde, or phosphomolybdic acid staining. High-resolution mass spectra were recorded on an ESI-TOF mass spectrometer using PEG or PPG as an internal calibrant. Samples were filtered through a PTFE (0.45 μm) syringe filter before injection.

Source of the Lactones—Caprolactone (**1**) was a commercial sample. 7-Methylcaprolactone (**2**) and 3-methylcaprolactone (**3**) were prepared according to reported Baeyer-Villiger¹⁵ and lactone enolate alkylation¹⁶ procedures, respectively. Lactones **4–11** were prepared by Baeyer-Villiger oxidation (BVO) of the appropriate ketone. Each of the *cis*- and *trans*-carvomenthones upon treatment with *m*-chloroperoxybenzoic acid (*m*CPBA) gave the normal/abnormal lactones **4/5** and **6/7**, respectively. The BVO of each of *cis*- and *trans*-menthone gave (only) the normal lactones **8** and **9**, respectively. The bicyclic lactones **10** and **11** were prepared from the β -pinene-derived ketone nopinone.

General procedure for Baeyer-Villiger Oxidation

Preparation of lactones 4 (1263400-98-1),¹⁷ 5, 6 (141538-90-1),¹⁸ 7 (141538-91-2),¹⁸ 8 (68330-68-7),¹⁹ 9 (499-54-7),²⁰ 10,²¹ and 11²¹ from *cis*-carvomenthone,¹⁷ *trans*-carvomenthone,¹⁷ *cis*-menthone, *trans*-menthone, and nopinone.^{22,23} To a stirred solution of ketone (1 equiv) and trifluoroacetic acid (1 equiv) in CH₂Cl₂ (ca. 0.2 M) was added 3-chloroperoxybenzoic acid (77 wt %, 2 equiv) at ambient temperature in small portions over a period of 10 minutes. The reaction mixture was allowed to stir for 1 hour, at which time TLC analysis indicated full consumption of the ketone. The resulting slurry was filtered and the filtrate cooled to 0 °C to give an additional amount of precipitate, which was removed via a second filtration. The resulting filtrate was washed sequentially with saturated sodium bisulfite, saturated sodium bicarbonate, and saturated sodium chloride solution. The organic layer was dried (sodium sulfate), filtered, and concentrated. The residue was purified by MPLC (silica gel, 10–12:1 Hex:EtOAc) to afford a mixture of the abnormal and normal lactones in the case of **5/4** (1:50) or **7/6** (1:19) or the pure lactone in the case of **8** or **9**, each as a colorless oil. The isolated yields at this stage ranged from 50–80%. The mixture of **5/4** or **7/6** was subjected to a second chromatographic separation (MPLC), now using a less polar eluent (16–20:1 hexanes:EtOAc) to obtain the sample of each lactone used for the NMR studies. For the case of lactones **10** and **11**, the reaction was performed in the absence of TFA at 80 °C and was stopped after 18 h. The conversion (GC/MS) was ca. 70%. Use of longer reaction time was observed to lead to competitive destruction of the abnormal lactone **11**. These products were separated using 6:1 hexanes:EtOAc as the MPLC eluent.

Spectroscopic Data for Lactones—The ¹H and ¹³C NMR data we recorded for lactones **1–11** is provided in Tables S1–S11, respectively. Copies of these spectra have been included in the Supporting Information because many are of higher quality than those reported for these (often long-known) compounds. The only one of these lactones that has not been previously reported in the literature is the **abnormal *cis*-carvomenthide (5)**. Additional characterization data for **5** are: IR (neat): 2951, 2921, 1725, 1461, 1272, 1254, and 1175 cm^{–1}. HRMS (ESI) mass calc. for [C₁₀H₁₈O₂Na]⁺ 193.1199, found 193.1209.

Computational Section

For each candidate structure, a molecular mechanics multiconformational search was performed using the static Merck Molecular Force Field (MMFFs) implemented in MacroModel (v9.8)²⁴ as part of the Maestro program suite (Schrödinger Software, v9.1.207).²⁵ All minima lying within 5.04 kcal•mol^{–1} of the energy of the global minimum were saved and then individually subjected to geometry optimization using density functional theory (DFT) using the Gaussian 09 software package.²⁶ All DFT optimizations were performed using the M06-2X²⁷ functional with the 6-31+G(d,p) basis set. The was constrained to a “very-tight” cutoff, and an “ultrafine” integration grid. Reoptimization was performed on each initial structure to ensure complete convergence to a local minimum. Geometry optimization was followed by a frequency calculation to obtain Gibbs energy (taken as the sum of electronic and thermal free energies) for each conformer.

^1H and ^{13}C NMR chemical shift values were then computed for each conformer using Gaussian 09; the default gauge independent atomic orbital (GIAO) method,^{28–32} the B3LYP^{33–36} functional, and 6-311+G(2d,p) basis set were used. Solvation modeling in chloroform for both geometry optimization and NMR computation was achieved using the integral equation formalism of the polarizable continuum method (IEF-PCM) and Bondi radii.³⁷ Isotropic shielding values obtained from the computation were referenced relative to the hydrogen or carbon isotropic shielding values of tetramethylsilane (TMS) computed at the same level of theory.

The number of discrete conformers following DFT optimization for each of lactones **1–11** varied between two and nine (see Figure 1). Each member of each set of conformers for each lactone was Boltzmann weighted according to its relative Gibbs energy. Each ^1H and ^{13}C chemical shift value was then weighted according to the mole fraction of that conformer. Finally, each of these contributions was summed across the entire set of conformers to arrive at the final, Boltzmann-averaged NMR chemical shift (δ_{comp}).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

7-Membered caprolactone derivatives used in this study. IUPAC compound numbering for 1–9 is used (i.e., the oxepane oxygen is position 1). The descriptors “normal” and “abnormal” refer to the major and minor products of Baeyer-Villiger oxidation of the precursor ketones [2-methylcyclohexanone, *cis*- or *trans*-carvomenthone (from dihydrocarvone), *cis*- or *trans*-menthone, and nopinone (from β -pinene)], respectively. The number of conformational isomers identified and used for the computation of (Boltzmann weighted) chemical shifts (see text) is shown in parentheses.

		CMAE				CMAE				CMAE	
		¹ H	¹³ C			¹ H	¹³ C			¹ H	¹³ C
1	0.01	0.8		5	0.05	1.3		9	0.04	1.3
2	0.03	0.9		6	0.05	1.3		10	0.06	1.2
3	0.05	1.0		7	0.05	1.3		11	0.06	0.9
4	0.05	1.1		8	0.07	1.4	<div style="border: 1px solid black; padding: 5px; display: inline-block;"> Average for 1 – 11 </div>			
										0.05	1.1

Figure 2.
Corrected mean absolute errors (CMAEs) for compounds **1–11**.

4 (cis)	6 (trans)	5 (cis)	7 (trans)	8 (cis)	9 (trans)				
CMAE ^a		CMAE ^a		CMAE ^a					
¹ H ¹³ C		¹ H ¹³ C		¹ H ¹³ C					
cis vs. cis	4_{exp} vs. 4_{comp}	0.05	1.1	5_{exp} vs. 5_{comp}	0.05	1.3	8_{exp} vs. 8_{comp}	0.07	1.4
cis vs. trans	4_{exp} vs. 6_{comp}	0.14	2.8	5_{exp} vs. 7_{comp}	0.12	2.5	8_{exp} vs. 9_{comp}	0.18	2.5
	MATCH RATIO ^b	2.96	2.4	MATCH RATIO ^b	2.19	2.0	MATCH RATIO ^b	2.70	1.7
trans vs. trans	6_{exp} vs. 6_{comp}	0.05	1.3	7_{exp} vs. 7_{comp}	0.05	1.3	9_{exp} vs. 9_{comp}	0.04	1.3
trans vs. cis	6_{exp} vs. 4_{comp}	0.19	1.2	7_{exp} vs. 5_{comp}	0.15	1.7	9_{exp} vs. 8_{comp}	0.17	1.8
	MATCH RATIO ^b	3.70	1.1	MATCH RATIO ^b	2.75	1.3	MATCH RATIO ^b	4.13	1.4

Figure 3.

CMAE values and the derived “match ratios” for the diastereomeric pairs **4** vs. **6**, **5** vs. **7**, and **8** vs. **9**. For any one pair, four comparisons are made for each of the proton and the carbon chemical shift data. Namely, the CMAE values for the experimental data of each *cis* isomer with the computed data for both itself and its corresponding *trans* diastereomer are given (top pair of rows). Likewise, the analogous values for each *trans* isomer are given (bottom pair of rows).

^a CMAE = corrected mean absolute error

^b Match Ratio = CMAE_{larger}/CMAE_{smaller}

Figure 4.
The series of methylcyclohexanols previously investigated.⁹

		12 (cis) 13 (trans)		14 (cis) 15 (trans)		16 (cis) 17 (trans)			
		CMAE ^a		CMAE ^a		CMAE ^a			
		¹ H	¹³ C	¹ H	¹³ C	¹ H	¹³ C		
cis vs. cis	12_{exp} vs. 12_{comp}	0.05	1.2	14_{exp} vs. 14_{comp}	0.05	1.1	16_{exp} vs. 16_{comp}	0.03	1.1
cis vs. trans	12_{exp} vs. 13_{comp}	0.24	4.2	14_{exp} vs. 15_{comp}	0.25	2.1	16_{exp} vs. 17_{comp}	0.23	3.8
		MATCH RATIO ^b	4.80 3.5	MATCH RATIO ^b	5.00 1.9	MATCH RATIO ^b	7.67 3.4		
trans vs. trans	13_{exp} vs. 13_{comp}	0.04	1.1	15_{exp} vs. 15_{comp}	0.04	1.2	17_{exp} vs. 17_{comp}	0.03	1.0
trans vs. cis	13_{exp} vs. 12_{comp}	0.25	2.9	15_{exp} vs. 14_{comp}	0.24	3.5	17_{exp} vs. 16_{comp}	0.24	2.9
		MATCH RATIO ^b	6.25 2.6	MATCH RATIO ^b	6.00 2.9	MATCH RATIO ^b	8.00 2.9		

Figure 5.

CMAE values and the derived “match ratios” for the diastereomeric pairs **12** vs. **13**, **14** vs. **15**, and **16** vs. **17**. For any one pair, four comparisons are made for each of the proton and the carbon chemical shift data. Namely, the CMAE values for the experimental data of each *cis* isomer with the computed data for both itself and its corresponding *trans* diastereomer are given (top pair of rows). Likewise, the analogous values for each *trans* isomer are given (bottom pair of rows).

^a CMAE = corrected mean absolute error. ^b Match Ratio = CMAE_{larger}/CMAE_{smaller}

Table 1

Experimental and computed ^{13}C and ^1H NMR chemical shifts (CDCl_3 , 125 and 500 MHz, respectively) for abnormal *trans*-carvomenthine (**7**).

Atom number ^a	Carbon		Proton		COSY (to ^1H -#)
	δ_{exp}	δ_{comp}	δ_{Hexp}	δ_{Hcomp}	
2	178.3	189.17			
3	37.2	42.59	2.72	2.80	Sum of Js = 35.3 4 α , Me11
4 α	32.1	37.04	1.52–1.60	1.47	m
4 β			1.78	1.72	nform Sum of Js = 20.1 3
5 α			1.86	1.79	nform Sum of Js = 19.7 7 α^c
5 β	31.27	35.79	1.52	1.59	dddd 12, 12, 12, 3.0
6	44.8	49.72	1.52–1.60	1.51	m
7 α			4.16	4.14	ddd 12.4, 1.9, 1.9 ^c 5 α^c , 6, 7 β
7 β	71.8	76.14	4.09	4.23	dd 12.4, 8.4 6, 7 α
8	31.31	37.76	1.68	1.62	dqq 4.0, 6.9, 6.9 6, Me9, Me10
Me9	19.6 ^b	20.14	0.91 ^b	0.88	d 6.9 8
Me10	19.4 ^b	20.88	0.90 ^b	0.87	d 6.9 8
Me11	18.6	20.25	1.20	1.07	d 6.7 3

^a α (= *trans*) and β (= *cis*) relative to C6 ^1Pr group.

^b the proton and carbon chemical shifts for each of the isopropyl Me groups have been correlated by HMQC; however, the assignment to the pro-*S* and pro-*R* C9 and C10 is arbitrary.

^c protons 5 α and 7 α experience $^4J_{\text{HH}}$ (4 bond W-coupling)

Table 2

Example (for lactone **7**) of error analysis and correction of the ^1H NMR data.^a

Atom number	Experimental Shift ($\delta\text{H}_{\text{exp}}$)	Computed Shift ($\delta\text{H}_{\text{comp}}$)	Error ($ \delta\text{H}_{\text{exp}} - \delta\text{H}_{\text{comp}} $)	Scaled (Linearly Corrected) Shift	Corrected Error
3	2.72	2.80	0.08	2.79	0.07
4 α	1.56	1.47	0.09	1.51	0.05
4 β	1.78	1.72	0.06	1.75	0.03
5 α	1.86	1.79	0.07	1.82	0.04
5 β	1.52	1.59	0.07	1.63	0.11
6	1.56	1.51	0.05	1.55	0.01
7 α	4.16	4.14	0.02	4.07	0.09
7 β	4.09	4.23	0.14	4.16	0.07
8	1.68	1.62	0.06	1.66	0.02
Me9	0.91	0.88	0.04	0.94	0.03
Me10	0.90	0.87	0.02	0.94	0.04
Me11	1.20	1.07	0.13	1.13	0.07
<div> <div>Slope</div> <div>Intercept</div> <div>0.957</div> <div>0.104</div> </div>				<div> <div>0.07</div> <div>Mean Absolute Error (MAE)</div> </div>	<div> <div>0.053</div> <div>Corrected Mean Absolute Error (CMAE)</div> </div>

^aThe data from which CMAE values were extracted (for both proton and carbon chemical shifts) for the other lactones **1–6** and **8–11** is provided in the Supplementary Information.