JOC The Journal of Organic Chemistry

Article

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

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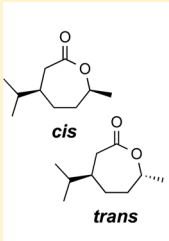
Supporting Information

ABSTRACT: 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)] provided 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 11 lactones, is encouragingly small (0.02−0.08 ppm for ^{1}H or 0.8−2.2 ppm for ^{13}C). Three pairs of *cis* versus *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 CMAE (worse fit) to the smaller CMAE (better fit). A greater match ratio value indicates better distinguishing ability. The match ratios are larger for proton data [2.4−4.0 (av = 3.2)] than for carbon [1.1−2.3 (av = 1.6)], indicating that the former provide a better basis for discriminating these diastereomers.



Corrected Mean Absolute Errors	δ^{1}H	δ^{13}C
cis_{exp} vs. cis_{comp}	0.05	1.1
cis_{exp} vs. $trans_{comp}$	0.14	2.8
$trans_{exp}$ vs. $trans_{comp}$	0.05	1.3
$trans_{exp}$ vs. cis_{comp}	0.19	1.2

INTRODUCTION

Computational approaches for 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 shows the closer/closest match leads 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 multiple isomeric compounds (CP3 parameter[6]) or for only a single isomeric compound (DP4 parameter[7]). Additionally, Sarotti has shown discrimination between experimental and computed shifts through the 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 (see 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 challenging[11] seven-membered caprolactone derivatives of known structure. We describe the use of a "match ratio"—the numerical ratio of the less closely matched data set to the more closely matched one—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 seven-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 biorenewable/sustainable polyesters.[13] These lactones constitute 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

Received: November 27, 2013
Published: December 19, 2013

   dx.doi.org/10.1021/jo402627s | J. Org. Chem. 2014, 79, 752−758

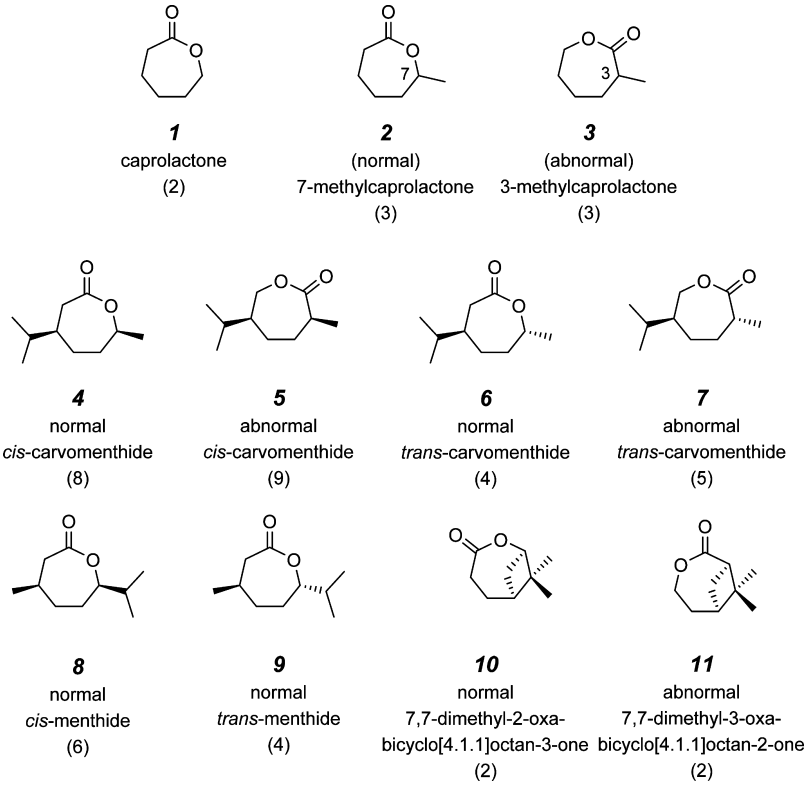
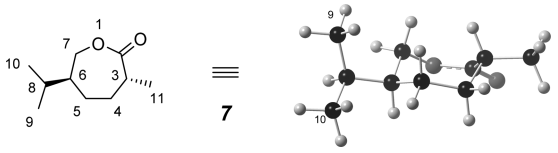


Figure 1. Seven-membered caprolactone derivatives used in this study. IUPAC compound numbering is used for **1**–**9** (i.e., the oxepane oxygen is position 1). The descriptors "normal" and "abnormal" refer to the major and minor products of Baeyer–Villiger oxidation of the precursor ketones [2-methylcyclohexanone,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

Table 1. Experimental and Computed ^{13}C and ^{1}H NMR Chemical Shifts ($CDCl_3$, 125 and 500 MHz, respectively) for Abnormal *trans*-Carvomenthide (7)



	carbon		proton				COSY
atom no.[a]	δ_{Cexp}	δ_{Ccomp}	δ_{Hexp}	δ_{Hcomp}	mult	J (Hz)	(to ^{1}H no.)
2	178.3	189.17					
3	37.2	42.59	2.72	2.80	nfom	$\sum J$ = 35.3	4*α*, Me11
4*α*	32.1	37.04	1.52–1.60	1.47	m		
4*β*			1.78	1.72	nfom	$\sum J$ = 20.1	3
5*α*	31.27	35.79	1.86	1.79	nfom	$\sum J$ = 19.7	7*α*[c]
5*β*			1.52	1.59	dddd	12, 12, 12, 3.0	
6	44.8	49.72	1.52–1.60	1.51	m		7*α*, 7*β*, 8
7*α*	71.8	76.14	4.16	4.14	ddd	12.4, 1.9, 1.9[c]	5*α*,[c] 6, 7*β*
7*β*			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 the C6 ^{i}Pr 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 $^{4}J_{HH}$ (four-bond W coupling).

of the chemical shifts of nearly all of the ^{1}H and ^{13}C resonances. These chemical shift values, δ_{Hexp} and δ_{Cexp}, respectively, (along with coupling constants and COSY correlations) are recorded in Tables S1–S11 in the Supporting Information (Table 1 shows the data for lactone **7** as a representative example). In a few instances, the chemical shifts of certain pairs of resonances

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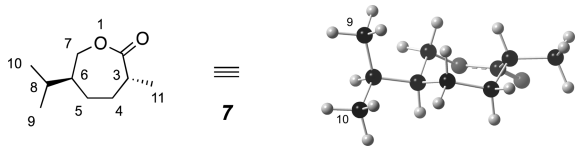
Table 2. Example (for Lactone 7) of Error Analysis and Correction of the ^{1}H NMR Data[a]



Atom number	Experimental Shift (δH_{exp})	Computed Shift (δH_{comp})	Error ($\lvert\delta H_{exp} - \delta H_{comp}\rvert$)	Scaled (Linearly Corrected) Shift	Corrected Error
3	2.72	2.80	0.08	2.79	0.07
4α	1.56	1.47	0.09	1.51	0.05
4β	1.78	1.72	0.06	1.75	0.03
5α	1.86	1.79	0.07	1.82	0.04
5β	1.52	1.59	0.07	1.63	0.11
6	1.56	1.51	0.05	1.55	0.01
7α	4.16	4.14	0.02	4.07	0.09
7β	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
			0.07 Mean Absolute Error (MAE)		0.053 Corrected Mean Absolute Error (CMAE)
	Slope 0.957 Intercept 0.104				

[a]The data from which CMAE values were extracted (for both proton and carbon chemical shifts) for the other lactones **1**–**6** and **8**–**11** are provided in the Supporting Information.

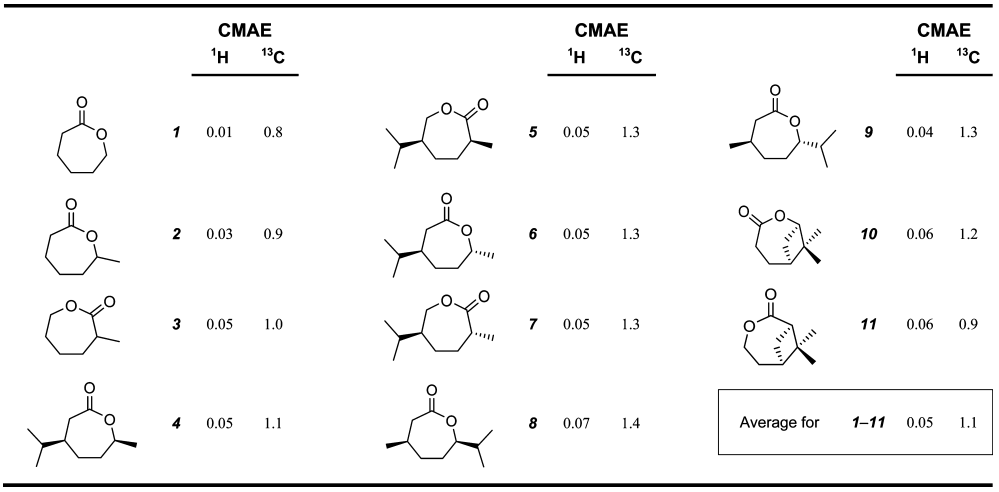


Figure 2. Corrected mean absolute errors (CMAEs) for compounds **1**–**11**.

were sufficiently similar that overlapping cross-peaks in the 2D NMR data could not be distinguished with confidence. Where relevant, these are noted by footnotes in the tables. For three of the lactones, we were not able to definitively assign two of the carbon resonances [**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 lactone chemical shifts was carried out by DFT optimization [M06-2X/6-31+G(d,p)], calculation of isotropic shielding values [B3LYP/6-311+G(2d,p)], and translation of those values to chemical shifts (see Experimental and Computational Details below). We then assessed the correlation between the 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 (δ_{Hexp} and δ_{Hcomp}) as well as the absolute error, linearly corrected computed shift, and corrected absolute error for each proton in abnormal *trans*-carvomenthide (**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 δ_{corr} = slope × δ_{comp} + intercept. Use of this correction serves to reduce the systematic error in the δ_{Hexp} values. The overall result of this correction can be discerned by

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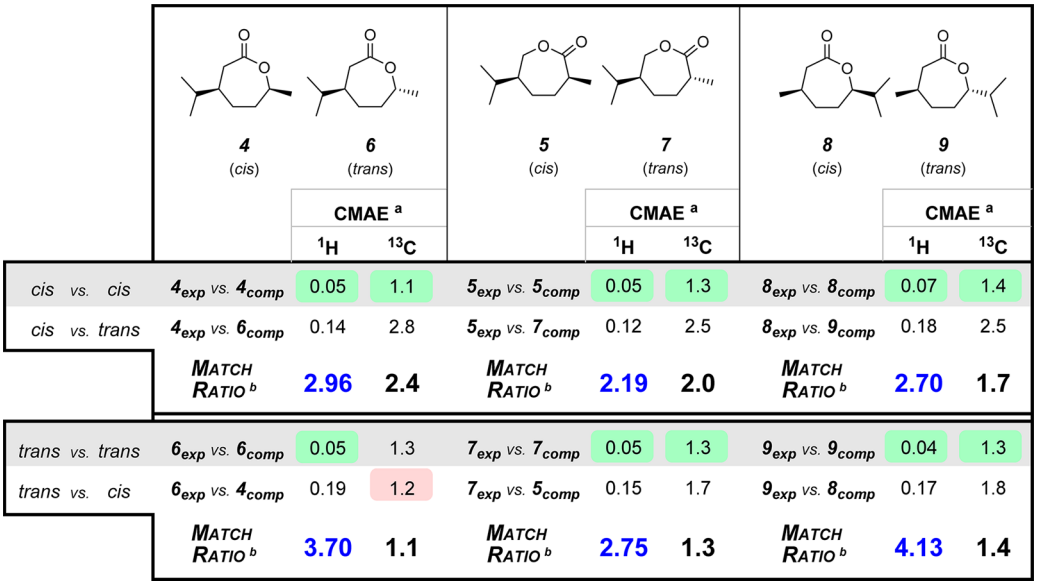


		CMAE [a] ^{1}H	CMAE [a] ^{13}C		CMAE [a] ^{1}H	CMAE [a] ^{13}C		CMAE [a] ^{1}H	CMAE [a] ^{13}C
cis vs. *cis*	4_{exp} vs. 4_{comp}	0.05	1.1	5_{exp} vs. 5_{comp}	0.05	1.3	8_{exp} vs. 8_{comp}	0.07	1.4
cis vs. *trans*	4_{exp} vs. 6_{comp}	0.14	2.8	5_{exp} vs. 7_{comp}	0.12	2.5	8_{exp} vs. 9_{comp}	0.18	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 each pair, for both the proton and the carbon chemical shift data, four comparisons are made: the CMAE value from the experimental data for the *cis* isomer is compared with the CMAE values from the computed data for both itself and its corresponding *trans* diastereomer in the top pair of rows, and the analogous comparisons for the *trans* isomer are shown in the bottom pair of rows. [a]CMAE = corrected mean absolute error. [b]Match ratio = $CMAE_{larger}/CMAE_{smaller}$.

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), which is given by eq 1:

$$\mathrm{CMAE} = \frac{1}{n}\sum_{i=1}^{n} |\delta_{\mathrm{exp}} - \delta_{\mathrm{corr}}| \qquad (1)$$

The MAE and CMAE values are shown in the bottom line of Table 2. The same form of analysis was carried out for the ^{13}C NMR data.

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

It is worth considering the question "How bad 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 ^{1}H 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 averages for the entire family of lactones **1**−**11** are 0.05 and 1.1 for ^{1}H and ^{13}C, respectively. On the basis of 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 also analyzed these data in another way, namely, by introducing the idea of a "match ratio". We define the match ratio as the larger CMAE value divided by the smaller CMAE value:

$$\text{match ratio} = \frac{\text{larger CMAE}}{\text{smaller CMAE}}$$

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.

The match ratios for the three pairs of *cis*/*trans* diastereomers (**4**/**6**, **5**/**7**, **8**/**9**) for both the proton data and the carbon data are given in Figure 3. The match ratio for the 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 revisited our earlier study of the series of methylated cyclohexanols **12**−**17** shown in Figure 4. In that work we had also concluded that the proton

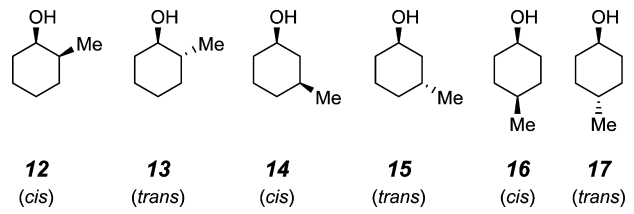
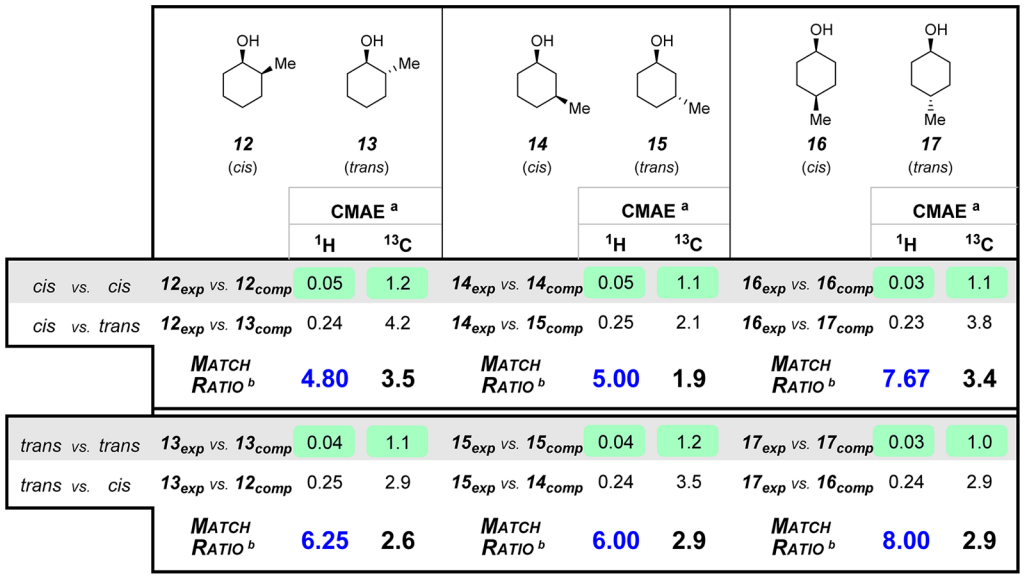


Figure 4. The series of methylcyclohexanols previously investigated.[9]

chemical shift data were more discriminating than the carbon data. We retreated the data from that study and present it here in the form of match ratios as described above (Figure 5). Again, analysis of the proton data is advantageous. The magnitudes of the match ratios in this series are significantly larger than for the lactones (Figure 3). This perhaps reflects the ability of the computational methodology to more reliably

dx.doi.org/10.1021/jo402627s | J. Org. Chem. 2014, 79, 752−758



		CMAE [a] ^{1}H	CMAE [a] ^{13}C		CMAE [a] ^{1}H	CMAE [a] ^{13}C		CMAE [a] ^{1}H	CMAE [a] ^{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 each pair, for both the proton and the carbon chemical shift data, four comparisons are made: the CMAE value from the experimental data for the *cis* isomer is compared with the CMAE values from the computed data for both itself and its corresponding *trans* diastereomer in the top pair of rows, and the analogous comparisons for the *trans* isomer are shown in the bottom pair of rows. [a]CMAE = corrected mean absolute error. [b]Match ratio = $CMAE_{larger}/CMAE_{smaller}$.

capture the conformational landscape of these six-membered compounds vis-à-vis the seven-membered compounds.

CONCLUSION

In conclusion, we have computed the ^{1}H 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 (ranging from 0.02−0.08 and 0.8−2.2 ppm for ^{1}H and ^{13}C, 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 of the CMAE for the less closely matched data to that for the more closely matched data. This has been particularly useful in highlighting the fact that ^{1}H rather than ^{13}C chemical shift data are more effective as discriminators for correct structure assignment.

EXPERIMENTAL AND COMPUTATIONAL DETAILS

Experimental Section. *General Procedures.* 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 $^{13}CDCl_3$ (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), nfom (non-first-order multiplet), and br (broad). α and β denote the orientation of the proton relative to a ring substituent as specified for each lactone that was studied. Infrared (IR) spectra were recorded on an 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 F254 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 syringe filter (0.45 μm) before injection.

Sources of the Lactones. Caprolactone (**1**) was a commercial sample. 7-Methylcaprolactone (**2**) and 3-methylcaprolactone (**3**) were prepared according to reported Baeyer−Villiger[15] and lactone enolate alkylation[16] procedures, respectively. Lactones **4**−**11** were prepared by Baeyer−Villiger oxidation (BVO) of the appropriate ketones. 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. BVO 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* ***11***[21] *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 CH_2Cl_2 (ca. 0.2 M) was added 3-chloroperoxybenzoic acid (77 wt %, 2 equiv) at ambient temperature in small portions over a period of 10 min. The reaction mixture was allowed to stir for 1 h, at which time TLC analysis indicated full consumption of the ketone. The resulting slurry was filtered, and the filtrate was 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 hexanes/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 to 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

dx.doi.org/10.1021/jo402627s | J. Org. Chem. 2014, 79, 752−758

stopped after 18 h. The conversion (GC–MS) was ca. 70%. Use of a 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 ^{1}H and ^{13}C NMR data we recorded for lactones **1**–**11** are provided in Tables S1–S11 in the Supporting Information, 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**: IR (neat): 2951, 2921, 1725, 1461, 1272, 1254, and 1175 cm^{-1}; HRMS (ESI) mass calcd for $[C_{10}H_{18}O_2Na]^+$ 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 version 9.8[24] as part of the Maestro program suite (Schrödinger Software, version 9.1.207).[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 by density functional theory (DFT) using the Gaussian 09 software package.[26] All of the DFT optimizations were performed using the M06-2X functional[27] with the 6-31+G(d,p) basis set and an "ultrafine" integration grid. The optimization was constrained to a "very-tight" cutoff. 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 the Gibbs energy (taken as the sum of electronic and thermal free energies) for each conformer.

^{1}H 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 the 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 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 ^{1}H 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}).

■ ASSOCIATED CONTENT

Supporting Information

Eleven tables containing the experimental assignments of resonances, coupling constants, and relevant COSY interactions for lacatones **1**–**11**; 11 corresponding pairs of tables containing the CMAE analyses of the ^{1}H and ^{13}C chemical shifts; copies of NMR spectra of each lactone; and 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.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported in part by awards from the U.S. Department of Health and Human Services (National Institute of General Medical Sciences, GM-65597) and the National Science Foundation (CHE-0911696 and CHE-1136607, the latter a Center for Chemical Innovation Award that supports the Center for Sustainable Polymers at the University of Minnesota). This work was carried out in part using software and hardware resources made available through the University of Minnesota Supercomputing Institute (MSI).

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