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Theoretical prediction and assignment of vicinal $^{1}H-^{1}H$ coupling constants of diastereomeric 3-alkoxy-6,7-epoxy-2-oxabicyclo[3.3.0]octanes

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Spin–spin coupling constants between nuclei in NMR spectroscopy reflect their spatial arrangement. A number of calculation methods, applying different levels of theory, have been developed to support the stereochemical assignment of novel compounds. Nevertheless, revisions of the assignment of structures in the literature are not rare. In the present work, the reliability of the calculation methods amenable for a theoretical prediction of spin–spin coupling constants of vicinal protons to support correct stereochemical assignment of substitution at five-membered rings of 3-alkoxy-6,7-epoxy-2-oxabicyclo[3.3.0]octanes was studied. Experimental ^{3}J(H,H) coupling constants were compared with the coupling constants calculated for all possible diastereomers. The fully quantum chemical approach provided theoretical ^{3}J(H,H) coupling constants with an absolute deviation of no more than 1.1 Hz for 91% of the experimentally studied coupled spins, whereas the methods without quantum chemical geometry optimization resulted in completely unreliable predictions. Consequently, for a reliable stereochemical assignment of small and medium size molecules, the protocol for calculating the coupling constants based on the results of the quantum chemical geometry optimization is recommended.

Supporting information may be found in the online version of this article.

Keywords: NMR; ^{1}H; ^{13}C; computational chemistry; ^{3}J(H,H) coupling constants; five-membered rings; relative configuration

Introduction

The analysis of NMR data has often proven to be complex and it is challenging to get the correct chemical structure assignments. It is well recognized that the determination of the relative configuration of the substituents in a five-membered ring by NMR spectroscopy is a complicated task,[1] due to the possibility of several energetically close conformations. In such cases, it would be highly appreciated by chemists if one could rely on the predicted NMR spectra to draw a final conclusion about the structure. There are different ways to approach the prediction of NMR signals: full quantum chemical (QC), full empirical and combined methods.[2] In recent years, a vast majority of assignments applying quantum chemistry have been made on the basis of chemical shift calculations (some recent examples are given in Ref.[3]), while some workers still remain skeptic regarding prediction capability of the calculation methods available. However, there are only a few studies involving vicinal proton–proton coupling constants obtained by QC calculations.[4] The evident hesitations on picking the most reliable theoretical approach in this field prompted us to undertake the current investigation in order to contribute to the clarification of the situation.

During our work on the stereoselective synthesis of 9,11-secosterols[5] starting from oxabicyclo[3.3.0]octenes,[6] we were faced with a misinterpretation of the relative configuration in 6,7-epoxy-3-methoxy-2-oxabicyclo[3.3.0]octanes (Fig. 1). The formation of all four possible diastereomers **1–4** was observed and our NMR data of the major products were in good agreement with the previously published data of Kitahara *et al*.[7] However, the authors stated the selective formation of only the *exo*-epoxides **1** and **2**. We took the problem of stereochemical assignment of the epoxides **1–4** (and additionally **5–7** to extend the test set) as an incentive to carry out an investigation of the theoretical prediction of vicinal proton–proton coupling constants applying methods on different levels of theory, in order to provide the guidelines for achieving reliable results.

In the present research, the epoxides **1–7** were considered to represent in themselves a good model set of compounds for testing the methods amenable to the assignment of stereochemistry of 2-oxabicyclo[3.3.0]octanes because the model set consists of diastereomers, for which all changes in the coupling constants are caused just only by the modification of the stereochemical orientation of the substituents. In addition, up to 11 vicinal spin–spin coupling constants can be detected in every bicyclic core which gives a reliable set of data to be compared with the results of calculations.

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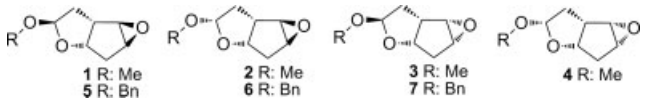

Figure 1. 3-Alkoxy-6,7-epoxy-2-oxabicyclo[3.3.0]octanes.

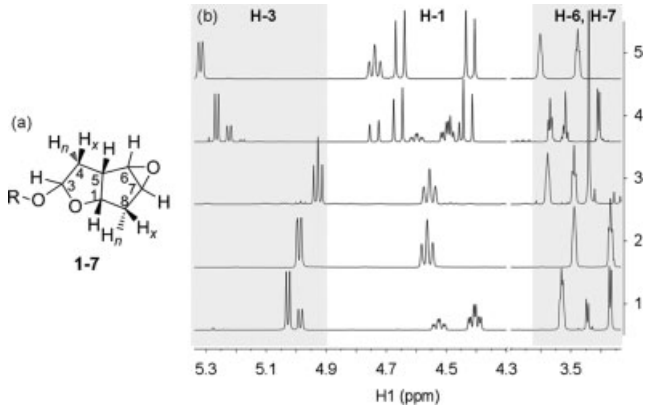

Figure 2. (a) Numeration of atoms in epoxides **1–7**; (b) ^{1}H-NMR spectra fragments (3.3–3.7 and 4.3–5.3 ppm, see Tables 1 and 2) of the epoxides measured at 400 MHz in $CDCl_3$. (**1**) Methoxy *exo*-epoxide **1** and *exo*-epoxide **2**; (**2**) methoxy *endo*-epoxide **3**; (**3**) methoxy *endo*-epoxide **4**; (**4**) benzyloxy *exo*-epoxide **5** and *exo*-epoxide **6**; (**5**) benzyloxy *endo*-epoxide **7**.

Results and Discussion

NMR analysis

The epoxidation of the mixture of 3-*exo*-methoxy-2-oxabicyclo [3.3.0]oct-6-ene and 3-*endo*-methoxy-2-oxabicyclo[3.3.0]oct-6-ene afforded two main fractions of the products after flash chromatography on silica gel. (See Sup. Info.) the characteristic NMR signals reported previously[7] were in good agreement with those recorded for the products in the current work. However, the interpretation of the NMR data in our case resulted in somewhat unexpected results. The less polar epoxide fraction has previously been assigned[7] as epoxide **2** and the more polar fraction as epoxide **1**. In the current work, the less polar fraction obtained was found to consist of a mixture of two epoxides **1** + **2** (4 : 1) and the more polar fraction only of the epoxide **3**. The ^{1}H-NMR spectra of the sample with the less polar methoxy epoxides had the characteristic signals for two H-1 (Fig. 2 and Table 1) in the region of 4.35–4.55 ppm (td, $J = 3$ and 2×7 Hz) and for two H-3 in the region of 4.95–5.05 ppm (d, $J = 5$ Hz). The more polar product had a signal of H-1 at 4.5 ppm (t, $J = 7$ Hz) and for H-3 at 5.0 ppm (dd, $J = 1$ and 5 Hz; Table 1). As a result of a careful examination of the crude product, we also succeeded in isolating a minor amount of the most polar diastereomeric epoxide **4**.

The diastereomeric benzyloxy epoxides **5–7** were prepared and isolated in two fractions, **5**+**6** and **7**. The characteristic NMR signals corresponding to the atoms of the bicyclic core were similar to those determined for the methoxy compounds.

The descriptive signals of the epoxy groups configuration were distinguished from this corresponding to H-6 proton (Fig. 2 and Tables 1 and 2). *Exo*-epoxides **1, 2, 5** and **6** all had signals for H-6 as *doublets* in the 3.4–3.5 ppm region, with coupling constants ^3J(H-6,H-7) = 2.5–2.6 Hz. *Endo*-epoxides **3, 4** and **7** had, in the same region, a *multiplet* due to additional coupling of *cis*-oriented H-5 and H-6 protons – ^3J(H-6,H-5) = 2.3–2.4 Hz. On the other hand, H-3 protons, describing the stereo-orientation of the acetal functional group, had much less conclusive multiplets. All isomers had one coupling ^3J(H-3,H-4) = 5 Hz, with one of the hydrogen atoms at C-4, and only the epoxide **4** had an additional distinguishing coupling, ~5 Hz with the second hydrogen attached to C-4 (Fig. 2 and Tables 1 and 2).

To distinguish between stereoisomers by the orientation of the alkoxy group, a single diastereomer, 3-*exo*-benzyloxy-2-oxabicyclo[3.3.0]oct-6-ene[8] was epoxidized, affording two separable products: *exo*-epoxide **5** and *endo*-epoxide **7**. The configuration of the epoxy-group was followed by the H-6 multiplicity. The NMR signals recorded for the *exo*-benzyloxy-*endo*-epoxide **7**, synthesized starting from a single alkene diastereomer, were found to be identical to the signals derived for this compound from the spectrum of the diastereomeric mixture of the epoxides, synthesized starting from the mixture of *exo*- and *endo*-benzyloxy alkenes. Also the representative peaks of *exo*-benzyloxy-*exo*-epoxide **5** corresponded to the major isomer found in the mixture of **5** + **6**, leading us to the conclusion that compound **6** was *endo*-benzyloxy-*exo*-epoxide. As previously mentioned, the signals of the bicyclic core of methoxy and benzyloxy compounds were very similar, allowing the complete assignment of the relative configuration of methoxy epoxides **1, 2** and **3**. Additionally compounds **3** and **4** were previously synthesized by a different method[6g,9] and our ^{1}H-NMR signals for H-1 and H-3 matched the assignment of Newton *et al*.[9a]

It is well known that coupling constants of the nuclei of vicinal hydrogen atoms reflect the relative configuration of the molecule. Every compound shown in Fig. 1 has nine non-equivalent protons in the bicyclic core and a total of 75 vicinal coupling constants were extracted from the ^{1}H-NMR spectra. On the basis of the obtained set of ^3J(H,H) values, the reliability of different prediction methods for vicinal coupling constants for the prediction of stereoisomers in substituted five-membered rings was studied.

QC calculation of ^3J(H,H) coupling constants and evaluation of prediction capability

The applied methods of the theoretical prediction of vicinal spin–spin couplings can be categorized by the level of empirical data involved in the calculations. The computationally most demanding is the full QC approach. For epoxides **1, 2, 3, 5, 6** and **7**, conformational analysis involving an optimization of structures with B3LYP/6-31G(d) as the final highest level resulted in identification of one distinct low-energy conformation for each compound. However, in the case of epoxide **4**, geometry optimization resulted in three close-lying low-energy conformations. Therefore, a B3LYP optimization of molecular geometry of **4** applying a higher quality basis set (6-311+G(d,p)) was performed, which provided the two low-energy conformers **4a** and **4b** with only a negligible energy difference (1.0 kJ/mol) (Fig. 3).

Calculations of NMR spin–spin coupling constants of these low-energy conformers were performed using the gauge-including atomic orbitals (GIAO) method. The calculation of coupling constants as implemented in Gaussian03[10] is based on the approach developed by Helgaker *et al*.[11] and Sychrovski *et al*.[12] The comparison of the experimental ^3J(H,H) constants with the constants calculated for the protons of the bicyclic core using full QC approach are presented in Chart A (for the compounds **1, 2, 3, 5, 6, 7**) and in Chart B (for the two low-energy conformers of the epoxide **4**) (Fig. 4).

Table 1. ^{1}H and ^{13}C chemical shifts (ppm) and $^{1}H-^{1}H$ coupling constants (Hz) of epoxides **1–4**

	Compound							
	1		2		3		4	
Atom no.	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1	4.40 (td, 2.7, 2 × 6.9)	82.91	4.52 (td, 2.5, 2 × 7.0)	85.30	4.56 (t, 7.3)	83.06	4.55 (t, 7.8)	83.48
3	5.03 (d, 4.7)	106.72	4.99 (d, 5.1)	106.60	4.97 (dd, 1.0, 5.3)	106.95	4.93 (dd, 5.9, 5.5)	108.00
4	1.65*n* (ddd, 4.7, 9.2, 12.9); 2.04*x* (dd, 9.1, 12.9)	34.87	1.86*n* (dd, 2.6, 13.6); 2.11*x* (ddd, 5.2, 11.0,13.6)	35.31	1.89*x* (ddd, 1.3, 9.5, 13.2); 2.12*n* (dt, 5.1, 13.2)	33.56	2.01*n* (m, 4.6, 5.3, 13.3); 2.25*x* (ddd, 5.9, 10.1, 13.2)	32.85
5	3.04 (td, 6.9, 2 × 9.2)	43.92	2.85 (ddd, 2.6, 6.7, 10.9)	44.41	2.75 (dddd, 2.1, 4.7, 7.2, 9.6)	42.93	2.69 (dddd, 2.3, 4.6, 7.7, 10.0)	42.88
6	3.37 (d, 2.5)	60.70	3.45 (d, 2.6)	62.15	3.37 (m, 2 × 2.4)	61.15	3.49 (m, 2 × 2.4)	61.25
7	3.52–3.54 (m)	58.53	3.52–3.54 (m)	58.79	3.35–3.40 (m)	61.50	3.55–3.63 (m)	61.22
8	1.79*n* (dt, 2 × 2.515.3); 2.36*x* (dd, 6.9, 15.3)	35.78	1.92*n* (dt, 2 × 2.4, 15.4); 22.33*x* (dd, 7.3, 15.4)	37.57	1.93*x* (ddd, 1.8, 7.4, 15.7); 2.13*n* (d, 15,6)	34.15	2.04*x* (ddd, 1.9, 7.7, 15.6); 2.28*n* (dd, 1.4, 15.8)	35.21
Me	3.25 (s)	54.37	3.30 (s)	54.79	3.18 (s)	54.29	3.44 (s)	56.70

Table 2. ^{1}H and ^{13}C chemical shifts (ppm) and $^{1}H-^{1}H$ coupling constants (Hz) of epoxides **5–7**

	Compound					
	5		6		7	
Atom no.	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1	4.50 (td, 2.7, 6.9 × 2)	83.11	4.61 (td, 2.2, 6.8 × 2)	85.66	4.73 (t, 7.2)	83.44
3	5.27 (d, 4.7)	104.84	5.22 (d, 5.1)	104.56	5.31 (dd, 1.4, 5.3)	105.40
4	1.70*n* (ddd, 4.7, 9.3, 12.8); 2.15*x* (dd, 9.0 Hz, 12.8)	34.96	1.98–2.0*n* (m); 2.13–2.19*x* (m)	35.43	2.24*n* (dt, 5.1 × 2, 13.2); 2.10*x* (ddd, 1.4, 9.5, 13.3)	33.78
5	3.14 (td, 6.9, 9.1 × 2)	44.07	2.91 (ddd, 2.6, 6.7, 10.8)	44.59	2.88 (dddd, 2.2, 4.8, 7.5, 9.6)	43.18
6	3.41 (d, 2.5)	60.75	3.51–3.54 (m)	62.37	3.46–3.49 (m, 2.3 × 2)	61.41
7	3.57 (t, 2.4)	58.59		58.94	3.59–3.61 (m)	61.77
8	1.84*n* (dt, 2.5x2, 15.3); 2.41*x* (dd, 6.9, 15.4)	35.81	1.98–2.03*n* (m); 2.37*x* (dd, 7.0, 15.8)	37.63	2.26*n* (d, 15.7); 2.06*x* (ddd, 1.8, 7.4, 15.8)	34.30
$PhCH_2$	4.66 (d, 11.9);4.43 (d, 11.9)	68.61	4.74 (d, 12.0); 4.47 (d, 12.0)	68.92	4.65 (d, 11.7); 4.42 (d, 11.7)	68.88
i-Ph	–	138.12	–	138.04	–	138.18
o-Ph	7.24–7.36 (m)	128.51	7.24–7.36 (m)	128.51	7.25–7.33 (m)	128.47
m-Ph		127.95		127.72		128.07
p-Ph		127.69		127.69		127.68

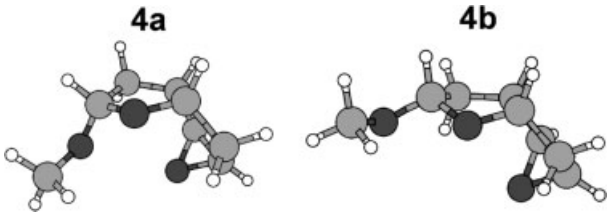

Figure 3. Low-energy conformers **4a** and **4b**.

The ^{3}J(H,H) spin–spin coupling constants calculated for the conformer **4a** deviated significantly from the experimental values ($R^2 = 0.74$). Since the coupling values calculated for conformer **4b** were in better agreement with the experiment ($R^2 = 0.92$), they were used for the evaluation of the prediction capability. This choice was done as an *ad hoc* simplification in the current work to be overcome in the further development of the theoretical approach under investigation.

The full QC approach resulted in very good theoretical prediction of the vicinal coupling constants. The mean absolute deviation (AD) for all related diastereomers was 0.4 Hz. Ninety-one percent of all coupling constants had deviations from the experimental values between 0 and 1.1 Hz, and only 3% of the deviations had values between 1.5 and 1.9 Hz. However, epoxide diastereomers (Fig. 1) bearing *endo*-substituents show somewhat more significant deviation between experimental and calculated coupling constants (Tables 3 and 4). In a few cases, in which coupling constants' values are up to 2.6 Hz,

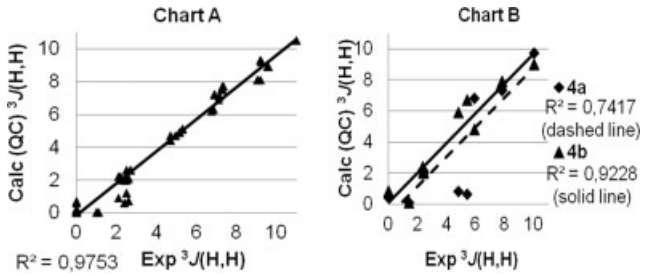

Figure 4. Correlation of vicinal spin–spin coupling constants calculated by full QC with experimental ones. Chart A: compounds **1, 2, 3, 5, 6, 7** (64 points); Chart B: conformers **4a** and **4b** (11 points).

the relative deviation exceeds 50%. A probable explanation to this phenomenon is in line with the above discussed different deviations found for the more favored two conformers (**4a** and **4b**) of bis-*endo*-substituted epoxide **4**. As to these larger deviations between experimental and calculated coupling constants, they seem to be related to intramolecular steric repulsions between *endo*-substituents and other parts of the molecule; this point needs further investigation on higher levels of theory. Another probable source of deviations can generally be seen in the fact that the present calculations were performed for isolated molecules, while appropriate NMR measurements were performed in $CDCl_3$ solution – that always makes some difference. The current evaluation of the methods amenable to the theoretical prediction of the spin–spin coupling constants is based on a simple statistical approach (considering the MAD values) and a few shortcomings can be considered of secondary importance with respect to the overall positive results gained by using full QC calculations.

The ability of the applied methods (QC, combined, empirical) to distinguish between related diastereomers was assessed as follows: for all possible combinations of diastereomers (epoxides **1**–**4** and **5**–**7**), a complete set of ADs involving each pair of corresponding coupling constants, $AD^{a,b} = |^3J(H^a,H^b)_{calc} - {}^3J(H^a,H^b)_{exp}|$, was calculated. From these values, the mean absolute deviations (MAD) were obtained. Tables 5 and 6 list the results for coupling constants $^3J(H,H)_{calc}$ obtained by the full QC approach (B3LYP/6-31G(d) geometry optimization followed by B3LYP/6-311+G(d,p) GIAO NMR ^3J(H,H) calculation).

The MAD values for each pair of corresponding compounds are shown in the Tables 5–12. The lowest value in a row (exp.) bisecting with the correct corresponding diastereomer in a column (calc.), i.e. in the diagonal of table reflects the prediction capability. In each case, the correct stereoisomer was predicted by the full QC approach. The MAD values of non-related diastereomers presented comparatively in the Tables 5 and 6 are significantly higher than that of related diastereomers. This demonstrates that for a theoretical prediction of ^3J(H,H) spin–spin coupling constants, the used full QC method is highly reliable and has good prediction capability.

Further, we tested whether it is necessary to invest those much computational resources for reliable theoretical prediction of coupling constants. In order to do that, the low-energy conformations from the QC calculation were combined with the widely used empirical Karplus-type equation of Haasnoot, DeLeeuw and Altona (HLA),[13] resulting in the ''combined QC'' approach in this case (See Sup. Info.). The coupling constants calculated by the combined QC method deviated from the experimental results more than it was found for the full QC approach. Whereas the full QC approach was able to predict 91% of the coupling constants with ADs up to 1.1 Hz, the combined QC approach yielded only 31% of the deviations within this range. Here, 91% of the ADs covered the range of 0–3.7 Hz. The highest deviation was 4.9 Hz.

According to data presented in Tables 7 and 8, comparison of the MAD values allows the unambiguous assignment for all diastereomers except for compound **4**, where MAD for pairs $\mathbf{4}_{exp}-\mathbf{3}_{calc}$ and $\mathbf{4}_{exp}-\mathbf{4}_{calc}$ was very close, as there was a significant increase in the ADs (average MAD 1.8) compared with the full QC approach (average MAD 0.4) between related diastereomers, which makes combined QC prediction less reliable.

Next, we considered a low-level force field method for geometry optimization in combination with the Karplus-type coupling constant calculation. There are several NMR-prediction software programs available for the calculation of the ^{1}H-NMR spectra from a 2D structural drawing. Firstly, the non-commercial software SPINUS[14] was used, which incorporates 3D structure generation by a molecular mechanics approach and the prediction of ^3J(H,H) couplings by a Karplus equation (See Sup. Info.). The coupling constants calculated with SPINUS had in some cases even higher AD values for related diastereoisomers than for non-related diastereomers. Only 29% had values up to 1.1 Hz, and 92% of the AD were up to 5.7 Hz; the highest deviation being 7.9 Hz.

The prediction capability of the SPINUS software was unreliable (Tables 9 and 10). This approach resulted in four correct predictions (for **3**, **4**, **6** and **7**); in the case of compound **2** the MAD was equal for the two isomers $\mathbf{2}_{calc.}$ and $\mathbf{4}_{calc}$ and in the case of compounds **1** and **5** the prediction was incorrect.

The commercial software NMRPredict[15] applies Abraham's approach. It optimizes the 3D structures of the compounds with a molecular mechanics force field and calculates vicinal ^3J(H,H) couplings by a modified Karplus equation (including parameters for cyclopentanes).[16] We applied the algorithm BEST for coupling constant calculations (See Sup. Info.). Twenty percent of the ADs for related diastereomers had values up to 1.1 Hz, 92% of the deviations were between 0 and 6.1 Hz, and the highest deviation was 7.4 Hz. It was stated that only compound **1** was predicted correctly.

Finally, using the quite popular ACD software,[17] the prediction resulted in exactly identical ^3J(H,H)coupling constants for all the diastereomers. This software relies on an empirical NMR database. Despite a large variety and number of different compounds incorporated into this database, the prediction algorithm is still quite helpless for diastereomer differentiation as one cannot expect it to contain data for every possible compound. That is also the case with oxabicyclo[3.3.0]octanes, for which reliable spectral information cannot be deduced.

Conclusions

The current study was aimed at the unambiguous assignment of the relative configurations of 3-alkoxy-6,7-epoxy-2-oxabicyclo[3.3.0]octanes on the basis of 75 experimental vicinal ^3J(H,H) coupling constants. A procedure for testing the prediction capability of the applied methods for distinguishing the related diastereomers has been proposed.

The method relying on empirical NMR data (ACD/NMR Predictor) was unable to yield any useful information about the relative configurations. Molecular mechanical approaches, combined with the Karplus-type equation (SPINUS, NMRPredict), resulted in

Table 3. Experimental *versus* calculated by full QC approach ^3J(H,H) spin–spin coupling constants of methoxy epoxides **1–4**, their absolute deviations (AD)[a] and mean absolute deviations (MAD)[b]

	Compound									
	1		2		3		4a		4b	
Coupled ^{1}H	$^3J_{exp}$ ($^3J_{calc}$)[c]	AD	$^3J_{exp}$ ($^3J_{calc}$)	AD	$^3J_{exp}$ ($^3J_{calc}$)	AD	$^3J_{exp}$ ($^3J_{calc}$)	AD	$^3J_{exp}$ ($^3J_{calc}$)	AD
1–5	6.9 (7.2)	0.3	6.9 (6.3)	0.6	7.3 (7.5)	0.2	7.8 (7.4)	0.4	7.8 (7.7)	0.1
1–8*n*	2.7 (2.6)	0.0	2.5 (1.2)	1.3	0.0 (0.7)	0.7	0.0 (0.4)	0.4	0.0 (0.8)	0.8
1–8*x*	6.9 (7.2)	0.3	7.2 (7.1)	0.1	7.3 (7.7)	0.4	7.8 (7.3)	0.5	7.8 (7.9)	0.1
3–4*n*	4.7 (4.4)	0.3	0 (0.0)	0.0	5.3 (5.1)	0.2	5.4 (0.6)	4.8	5.4 (6.7)	1.3
3–4*x*	0[d] (0.0)	0.0	5.1 (4.9)	0.3	1.0 (0.0)	1.0	5.9 (6.8)	0.9	5.9 (4.8)	1.1
4*n*–5	9.2 (9.3)	0.1	2.6 (0.7)	1.9	4.7 (4.7)	0.0	4.6 (0.8)	3.8	4.6 (5.9)	1.3
4*x*–5	9.2 (8.1)	1.1	11.0 (10.5)	0.5	9.6 (8.9)	0.7	10.0 (9.7)	0.3	10.0 (9.0)	1.0
5–6	0 (0.2)	0.2	0 (0.1)	0.1	2.1 (2.2)	0.1	2.4 (2.2)	0.2	2.4 (2.4)	0.0
6–7	2.5 (2.0)	0.5	2.6 (2.1)	0.5	2.4 (2.0)	0.4	2.4 (2.1)	0.3	2.4 (2.0)	0.4
7–8*n*	2.5 (2.0)	0.5	2.5 (2.1)	0.4	ND[e] (0.1)	ND	1.4 (0.1)	1.3	1.4 (0.1)	1.3
7–8*x*	0 (0.2)	0.2	0 (0.1)	0.1	ND (2.0)	ND	2.3 (2.0)	0.3	2.3 (2.1)	0.2
MAD		0.3		0.5		0.4		1.3		0.7

[a] In Hz, $|^3J$(H,H)calc $- {}^3J$(H,H)exp$|$.
[b] In Hz, $(1/n)\Sigma|^3J$(H,H)calc $- {}^3J$(H,H)exp$|$, where *n* is the number of compared coupling constants.
[c] Absolute values.
[d] All experimental coupling constants below 1 Hz were set to 0.
[e] Not determined.

Table 4. Experimental *versus* calculated by full QC approach ^3J(H,H) spin–spin coupling constants of benzyloxy epoxides **5–7** and their AD and MAD

	Compound					
	5		6		7	
Coupled ^{1}H	$^3J_{exp}$ ($^3J_{calc}$)	AD	$^3J_{exp}$ ($^3J_{calc}$)	AD	$^3J_{exp}$ ($^3J_{calc}$)	AD
1–5	6.9 (7.2)	0.3	6.8 (6.2)	0.6	7.3 (7.5)	0.2
1–8*n*	2.7 (2.6)	0.1	2.1 (0.9)	1.2	0 (0.6)	0.6
1–8*x*	6.9 (7.2)	0.3	7.1 (6.9)	0.2	7.4 (7.7)	0.3
3–4*n*	4.7 (4.4)	0.3	0 (0.0)	0.0	5.3 (5.1)	0.2
3–4*x*	0 (0.0)	0.0	5.2 (4.9)	0.3	1.1 (0.0)	1.1
4*n*–5	9.3 (9.2)	0.1	2.4 (0.6)	1.8	5.0 (4.7)	0.3
4*x*–5	9.1 (8.1)	1.0	11.1 (10.2)	0.9	9.6 (8.9)	0.7
5–6	0 (0.2)	0.2	0 (0.1)	0.1	2.2 (2.2)	0.0
6–7	2.5 (2.0)	0.5	2.6 (2.2)	0.4	2.5 (2.0)	0.5
7–8*n*	2.4 (2.0)	0.4	2.5 (2.6)	0.1	0 (0.1)	0.1
7–8*x*	0 (0.1)	0.1	0 (0.1)	0.1	2.2 (2.0)	0.2
MAD		0.3		0.5		0.4

Table 5. MAD of full QC calculated ^3J(H,H) coupling constants from experimental values of methoxy isomers **1–4**. (Minimum MAD values shown in bold in Tables 5–12)

	$\mathbf{1}_{calc}$	$\mathbf{2}_{calc}$	$\mathbf{3}_{calc}$	$\mathbf{4b}_{calc}$
$\mathbf{1}_{exp}$	**0.3**	2.1	1.4	1.9
$\mathbf{2}_{exp}$	1.9	**0.5**	2.2	2.1
$\mathbf{3}_{exp}$	1.5	2.1	**0.4**	1.1
$\mathbf{4}_{exp}$	2.0	1.8	1.0	**0.7**

Table 6. Mean absolute deviation of full QC calculated ^3J(H,H) coupling constants from experimental values of benzyloxy isomers **5–7**

	$\mathbf{5}_{calc}$	$\mathbf{6}_{calc}$	$\mathbf{7}_{calc}$
$\mathbf{5}_{exp}$	**0.3**	2.0	1.4
$\mathbf{6}_{exp}$	2.0	**0.5**	2.2
$\mathbf{7}_{exp}$	1.5	2.1	**0.4**

ambiguous assignments. One reason behind it may be the lack of total conformational analysis by which a more thorough scan of the potential energy surface can be achieved. Therefore, the output geometries of these programs are not in good agreement with the most abundant conformation of a compound studied in the NMR experiment. The second reason lies evidently in the concept of empirical generalizations: they often rely on the collection of experimental data that is sometimes loosely connected to the compound of interest. QC geometry optimization combined with the Karplus-type HLA equation allows the correct stereochemical assignment for all stereoisomers. However, the calculated coupling constants deviated still considerably from the experimental values.

We realized that the best way to confirm the relative configuration of diastereomeric compounds is to use a full QC approach. Thorough conformational analysis to identify the most abundant conformation of the compound, followed by an *ab initio* geometry optimization and subsequent spin–spin coupling QC calculation could predict ^3J(H,H) coupling constants with an AD of no more than 1.1 Hz for 91% of the coupling constants.

Due to the fact that the quantum chemistry related software has become more user-friendly and aimed towards an "average experimental chemist", besides considering the increase in the

Table 7. MAD of combined QC calculated ^{3}J(H,H) coupling constants from experimental values of methoxy isomers **1–4**

	$\mathbf{1}_{calc}$	$\mathbf{2}_{calc}$	$\mathbf{3}_{calc}$	$\mathbf{4b}_{calc}$
$\mathbf{1}_{exp}$	**1.9**	3.0	2.4	3.0
$\mathbf{2}_{exp}$	3.3	**1.8**	3.0	3.1
$\mathbf{3}_{exp}$	2.5	2.9	**1.7**	2.6
$\mathbf{4}_{exp}$	2.7	2.4	1.8	**1.7**

Table 8. MAD of combined QC calculated ^{3}J(H,H) coupling constants from experimental values of benzyloxy isomers **5–7**

	$\mathbf{5}_{calc}$	$\mathbf{6}_{calc}$	$\mathbf{7}_{calc}$
$\mathbf{5}_{exp}$	**1.9**	3.0	2.4
$\mathbf{6}_{exp}$	3.4	**1.8**	3.0
$\mathbf{7}_{exp}$	2.4	3.0	**1.7**

Table 9. MAD of combined MM (SPINUS) calculated ^{3}J(H,H) coupling constants from experimental values of methoxy isomers **1–4**

	$\mathbf{1}_{calc}$	$\mathbf{2}_{calc}$	$\mathbf{3}_{calc}$	$\mathbf{4}_{calc}$
$\mathbf{1}_{exp}$	3.6	3.2	**2.6**	3.2
$\mathbf{2}_{exp}$	3.1	**2.9**	3.0	**2.9**
$\mathbf{3}_{exp}$	2.7	2.2	**1.9**	2.5
$\mathbf{4}_{exp}$	2.5	2.1	2.1	**1.9**

Table 10. MAD of combined MM (SPINUS) calculated ^{3}J(H,H) coupling constants from experimental values of benzyloxy isomers **5–7**

	$\mathbf{5}_{calc}$	$\mathbf{6}_{calc}$	$\mathbf{7}_{calc}$
$\mathbf{5}_{exp}$	3.6	3.2	**2.6**
$\mathbf{6}_{exp}$	3.1	**2.8**	2.9
$\mathbf{7}_{exp}$	3.1	2.7	**2.0**

Table 11. MAD of combined MM (NMRPredict) calculated ^{3}J(H,H) coupling constants from experimental values of methoxy isomers **1–4**

	$\mathbf{1}_{calc}$	$\mathbf{2}_{calc}$	$\mathbf{3}_{calc}$	$\mathbf{4}_{calc}$
$\mathbf{1}_{exp}$	**2.2**	2.6	3.3	2.9
$\mathbf{2}_{exp}$	2.9	3.2	3.2	**2.8**
$\mathbf{3}_{exp}$	**2.2**	2.6	3.3	2.8
$\mathbf{4}_{exp}$	2.6	**2.3**	2.5	2.6

Table 12. MAD of combined MM (NMRPredict) calculated ^{3}J(H,H) coupling constants from experimental values of benzyloxy isomers **5–7**

	$\mathbf{5}_{calc}$	$\mathbf{6}_{calc}$	$\mathbf{7}_{calc}$
$\mathbf{5}_{exp}$	3.9	**2.7**	3.3
$\mathbf{6}_{exp}$	3.8	3.3	**3.2**
$\mathbf{7}_{exp}$	3.9	3.1	**3.1**

computing power of PC-s, it is very likely that the use of empirical Karplus-type equations for small and medium size molecules will become obsolete in near future.

Computational Procedure

A total conformational analysis of all the diastereomeric epoxides was performed by using Hyperchem 7.0[18] and employing the MM+ force field. The conformational search module as implemented in Hyperchem allows the acceptance of unique conformers while duplicate structures and higher energy conformers are discarded. The conformers obtained were subjected to further geometry optimization by using the Gaussian 03 set of programs.[10] The initial computational level was the Hartree-Fock (HF) method with the 3-21G* basis set followed by the optimization at the density functional level (DFT) using the hybrid B3LYP exchange-correlation functional and the 6-31G(d) basis set. Additionally, the frequency analysis was performed at the highest optimization level (i.e. B3LYP/6-31G(d)) to verify that the optimized conformers correspond to local minima on the potential energy surface (all positive Hessian eigenvalues). Each optimization step was followed by a geometrical comparison of conformers with the aim of extracting the unique structures only while discarding the duplicates. Finally, the NMR calculation including the ^{3}J(H,H) coupling constants was performed at the DFT B3LYP/6-311+G(d,p) level (on the DFT B3LYP/6-31G(d) optimized geometries; for **4a** and **4b** the B3LYP/6-311+G(d,p)-level optimized geometries were used) for the low-energy conformers of all the diastereomeric epoxides using the default GIAO method as implemented in Gaussian 03. CAL3JHH (for calculations, we used web application CAL3JHH developed by Aguirre-Valderrama and Dobado[13c]) was accessed in December 2009 for coupling constant calculations with Karplus-type equation of HLA. SPINUS[14] was accessed in December 2009 for coupling constant calculations. Coupling constant calculations with Monograph NMRPredict Desktop using algorithm BEST[15] were done at a spectrometer frequency of 400.13 MHz and chloroform as a solvent (accessed December 2009).

Experimental

All commercially available compounds were used without purification. Bicyclic 3-methoxy-2-oxabicyclo[3.3.0]oct-6-enes[7] and 3-benzyloxy-2-oxabicyclo[3.3.0]oct-6-enes[8a] were synthesized according to the literature procedures and used in epoxidation as crude products. Silica gel LK with particle size 40–100 μm was used for chromatographic purification of final products. Full assignment of ^{13}C- and ^{1}H-NMR chemical shifts is based on the 1D and 2D FT NMR spectra on a, Bruker Avance III 400, Bruker AMX 500 and Bruker 800 Avance III instruments. Solvent peaks in ^{13}C ($CDCl_3$ – 77.16 ppm) and ^{1}H ($CHCl_3$ – 7.26 ppm) NMR were used as chemical shift references. Typically, 5–20 mg of sample was dissolved in 1 ml of $CDCl_3$, the ^{1}H spectra were recorded with 16 scans, 1 s relaxation delay, 4 s acquisition time, spectral size 65K and spectral with 20 ppm at 400.13 Hz. To read coupling constants from 1D ^{1}H-NMR spectra following apodization, functions were applied to FID: exponential −1 Hz and Gaussian 0.5 GB (Hz) multiplication. In case of small deviations in coupling constants values concerning the same spin system, the average was taken

for comparison with calculations. ^{13}C spectra were recorded with 1024 scans, 2 s relaxation delay, 1.4 s acquisition time, spectral size 65K and spectral width 240 ppm at 100.61 Hz. The mass spectra were recorded on a Hitachi M80B spectrometer using electron ionization (EI) at 70 eV. IR spectra were recorded on a Perkin-Elmer Spectrum BX FT-IR infrared spectrophotometer. Optical rotation was measured with polarimeter Krüss, Optronic GmbH P3002 and Anton Paar MCP500.

Physical Constants of Compounds

From mixture of epoxides (1*S*, 3*R*, 5*S*, 6*R*, 7*S*)-3-benzyloxy-6,7-epoxy-2-oxabicyclo[3.3.0]octane **5** and (1*S*, 3*S*, 5*S*, 6*R*, 7*S*)-3-benzyloxy-6,7-epoxy-2-oxabicyclo[3.3.0]octane **6**: colorless oil

IR (film) 457 w, 596m, 699s, 737s, 837s, 946m, 1024s, 1083s, 1130 w, 1166 w, 1210m, 1339m, 1396m, 1454s, 1496m, 1575 w, 1812 w, 1879 w, 1956 w, 2935s, 3031s.; GC-MS (EI) *m/z*: 155 [M^+], 232,189, 156, 125, 108, 91, 85.

(1*S*, 3*R*, 5*S*, 6*S*, 7*R*)-3-benzyloxy-6,7-epoxy-2-oxabicyclo [3.3.0]octane **7**: white solid

$[\alpha]_D{}^{20} = -110$ ($c = 0.6$ in $CHCl_3$); IR (film) 512 w, 539 w, 699s, 740s, 849s, 881m, 976s, 1028s, 1232s, 1282m, 1299m, 1320m, 1338m, 1393m, 1454m, 1497m, 1574 w, 2930s, 3030s; GC–MS (EI) *m/z*: 155 [M^+], 232, 189, 167, 154, 141, 125, 108, 104, 91, 78; HRMS (EI) *m/z*: [$M^+ -$ Bn] found 141.0549 and calc. 141.0552.

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Supporting information

Supporting information may be found in the online version of this article.

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