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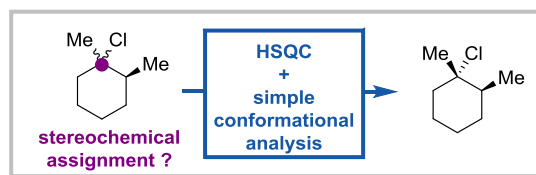
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Utilization of ^{13}C NMR Carbon Shifts for the Attribution of Diastereomers in Methyl-Substituted Cyclohexanes

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Supporting Information Placeholder



ABSTRACT: In this report, we address the challenge of assigning diastereomers for methyl cyclohexanes, particularly those with quaternary centers, which remains non-trivial despite modern NMR techniques. By utilizing a HSQC NMR experiment to identify methyl-carbons coupled with a simple conformational analysis, we identified an effective and quite general method for assigning stereochemistry, even in cases where diastereomeric mixtures are inseparable.

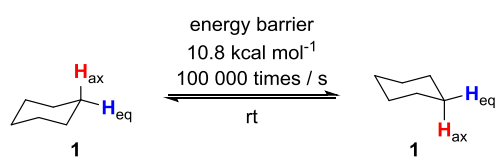
The identification of diastereomers in cyclohexane derivatives is commonly accomplished using modern NMR techniques.¹ Most frequently NOE (nuclear Overhauser effect) experiments or the interpretation of coupling constants allows for unequivocal attributions. Nevertheless, for cyclohexane rings with conformationally labile situations or mixtures of non-separable diastereomers with significant peak overlapping the attribution of diastereomers can be challenging. We have encountered this problem ourselves in a recent study² and we also identified several recent reports with unassigned stereochemistry (see figure S1 in the Supporting Information (SI) for details). Herein we demonstrate the utility of methyl ^{13}C -NMR chemical shifts and propose a simple rule for the identification of diastereomers in substituted methyl cyclohexanes. We also carried out DFT-calculations and demonstrated the usefulness thereof for the assignment of diastereomeric mixtures when the ^{13}C -NMR chemical shifts of the methyl groups are too close to be interpreted.

The rapid ring inversion in cyclohexane (**1**), facilitated by rotation about carbon-carbon bonds, is well-established, with an activation energy of 10.8 kcal/mol for cyclohexane chair-chair interconversion (Figure 1A).³ At room temperature, this results in cyclohexane undergoing ring flipping 100,000 times per second, a process too fast for NMR measurement.⁴ A consequence of ring inversion is the transformation of an axial substituent into an equatorial substituent. At $-80\text{ }^\circ\text{C}$ the ring inversion becomes slow enough to distinguish axial and equatorial hydrogens by ^1H -NMR (1.19 and 1.68 ppm respectively).⁵ In methylcyclohexane, the conformer **2E** with the methyl in an equatorial position is more stable than the axial conformation **2A** by 1.7 kcal/mol (Figure 1B).⁶ The resulting free energy difference (ΔG) between the equatorial and axial form is also known as *A* value introduced by Winstein and Holness (*A* selection of *A*-values for the substituents reported herein are given in Figure 1C).⁷ The calculation of the equilibrium constant *K* at a given temperature can be easily done via the equation $\Delta G^\circ = -2.303RT \log K$ for a given substituent. For methylcyclohexane ($\Delta G = 1.7\text{ kcal/mol}$) the equilibrium constant *K* = 19 which implies a 95:5 mixture of **2E** to **2A**. The axial conformation (e.g. **2A**; Figure 1D) introduces van

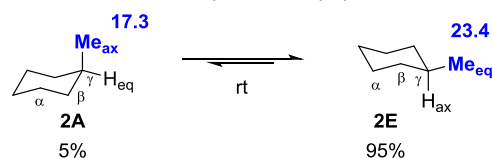
der Waals strain, leading to polarization of electrons and increased electron density on carbon atoms at the 3 and 5 position as well as the carbon of the methyl group (all highlighted in red). This causes an upfield (low-frequency) shift, known as the γ shift,^{8,9} in the ^{13}C -NMR spectrum of these three carbons. Alternative origins of the γ -effect were discussed in the literature.^{10,11} This upfield shift was observed in a pioneering study by Bradley and co-workers for methylcyclohexane at $-110\text{ }^\circ\text{C}$.⁶ While the low temperature renders the minor form detectable within the NMR time frame, it also leads to very small populations of the minor form (**2A**). At $-110\text{ }^\circ\text{C}$ the equatorial form (**2E**) predominates (99% of the mixture) with slow interconversion to the axial form (1% axial form, *K* = 100). Despite the strong ^{13}C -NMR signals from the equatorial form (major compound, 99%), the chemical shifts of C3, C5 and the axial CH_3 carbon were all observed with a significant upfield shift. High temperature trapping methods were developed which allow to stop interconversion of the cycle while maintaining a high population of the minor conformer. This technique allowed to determine the exact chemical shifts for **2A** and **2E** (Figure 1B).¹² At room temperature the ^{13}C -NMR of compound **2** shows a single peak at 22.9 ppm for the methyl carbon which is approximately the weighted average chemical shift of the axial and equatorial shift.¹³ It should be noted, that when there is a single dominant conformation and a canonical chair conformation the Karplus equation allows facile attribution of diastereomers with distinguishable axial or equatorial hydrogens.¹⁴ However, when it comes to diastereomers featuring quaternary stereocenters, NOE experiments or, as detailed in this paper, analysis of methyl ^{13}C NMR shifts are essential for accurate experimental identification. In addition, precise molecular mechanics and DFT calculations enable accurate predictions of ^{13}C -NMR shifts by identification of the relevant conformers and Boltzmann-weighted calculation of the corresponding chemical shifts over all conformations.¹⁵

Figure 1. Conformational analysis and the γ -effect.

A. Fast "flipping" for cyclohexane



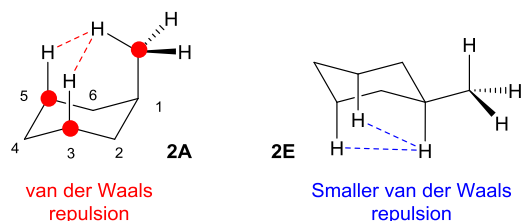
B. Conformational analysis of methylcyclohexane^a



C. Experimental A-values of selected substituents

Substituent	A-value	Substituent	A-value
Me	1.74	F	0.25–0.42
<i>i</i> -Pr	2.21	Cl	0.53–0.64
<i>t</i> -Bu	4.90	Br	0.48–0.67
Ph	2.80	I	0.47–0.61
OH	0.6, 0.9 ^b	CN	0.20

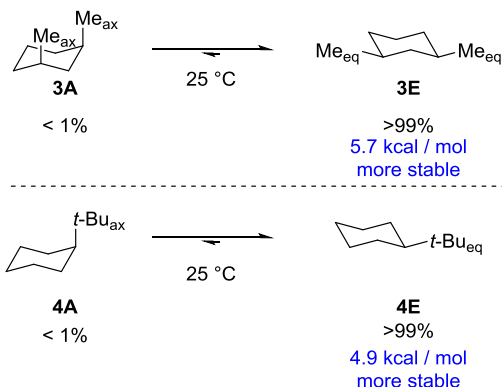
D. Simplified explanation for the γ -effect



^a Chemical shifts are given in ppm and were measured at $-150\text{ }^{\circ}\text{C}$ in a mixture of deuterated solvents, see ref. 10 for details. ^b In non hydrogen bonding solvents ~ 0.6 kcal / mol; in hydrogen bonding solvents ~ 0.9 kcal / mol.¹⁶

Regarding ring interconversion, a mere 3 kcal/mol energy difference between the two conformers is ample to quantitatively favor the equilibrium toward the more stable conformer at $25\text{ }^{\circ}\text{C}$ ($K = 160$; 99.4:0.6 mixture). Consequently, *cis*-1,3-dimethylcyclohexane (**3**) or *tert*-butylcyclohexane (**4**) exclusively exist as single isomers (**3E** or **4E**) at $25\text{ }^{\circ}\text{C}$ (Scheme 1).¹⁷ Even though conformational analysis can be easily done for mono and di-substituted cyclohexanes considering *A*-values,⁶ experimental values or DFT-calculations should be considered for more substituted cyclohexanes.^{18–21} Substituents with a strong-dipole moment can however give counterintuitive conformational preferences. For instance, *trans*-1,4-dichlorocyclohexane is more stable in the diaxial conformation than in the diequatorial conformation despite an *A*-value of 0.53–0.64.^{22,23} Sterically encumbered substituents, can also cause deviation from the expected chair conformation, e.g. *cis*-1,4-di-*tert*-butylcyclohexane prefers the twist boat conformer in order to avoid steric repulsion.¹⁷

Scheme 1. Conformationally "locked" cyclohexanes



Upon studying the early literature, we identified the publication by Crews as the first systematic study concerning the constant upfield shift of axial-methyl groups in cyclohexanes.^{24,25} Although Crews primarily focused on calculating new additivity constants, this work presents the first compilation of ¹³C-NMR data for axial and equatorially oriented methyl-substituted cyclohexanes. To further substantiate Crews' observations, we compiled data for diastereomers of 32 compounds (Figure 2). Typically, the γ -shift of the axial methyl group, in comparison to the equatorial methyl group, falls within the 5–10 ppm range (Figure 2). Some exceptions were observed; for instance, *p*-menthane (**7**) exhibited only a Δ ppm of 2.9 ppm. This is attributed to the similar *A*-values of the isopropyl group (2.21) and the methyl group (1.70). Consequently, structure **7A** exists at 298 K as a mixture of the axial form (68%; methyl in axial position) and the equatorial form (32%, not shown). This results in a higher shift value of the axial methyl group due to the 32% equatorial contribution, leading to a net reduction in the γ -shift. It should be noted that compound **24A** was also analyzed as a mixture of conformers. Additionally, we noted that geminal vinyl or phenyl substitution led to relatively high Δ ppm values of 10.0 and 12.0 ppm, respectively. Geminal-halo substitution (**14** \rightarrow **17**; entries 10–13) gave constant increase of the Δ ppm from 4.6 to 7.8 ppm. It appears reasonable to argue that larger geminal substituent reinforces steric repulsion and thus gives rise to greater γ -shifts. Other exceptions with very small (3.3 ppm) or high values (11.7 ppm) were observed for cyclohexanols **25** and **27**, respectively. In particular neighboring axial hydroxyl groups seem to significantly diminish the γ -shift of the methyl group (e.g compound **25**). This is further demonstrated by decalins **33** and **34** which show a small upfield shift (1.4 ppm for **33**) or even a downfield shift (-1.8 ppm for **34**). Hence, shifts < 5 ppm should be interpreted with caution as the γ -shift might have been reduced or even inverted by other substituents, in particular hydroxyl-groups. Importantly, the rule does not apply to cyclohexanes which do not contain axial C-H bonds at the α -position (numbering according to Figure 1E), as demonstrated by 1,3-dioxane **35** (entry 31). Structures **30** (entry 26) and **36** (entry 32) were unequivocally assigned through single crystal X-ray analysis.

Figure 2. ¹³C NMR shifts for axial and equatorial methyl groups.^a

Entry	axial conformer	equatorial conformer	Δ ppm	Entry	axial conformer	equatorial conformer	Δ ppm
1	 5A Me 17.5	 5E Me 22.8	5.3	17	 21A Me 26.1	 21E Me 31.9	5.8
2	 6A Me 17.6	 6E Me 23.4	5.8	18	 22A Me 25.4	 22E Me 31.4	6.0
3	 7A Me 20.0 68:32 mixture	 7E Me 22.9	2.9	19	 23A Me 25.8	 23E Me 31.4	5.6
4	 8A Me 17.4	 8E Me 23.3	5.9	20	 24A Me 18.2 87:13 mixture	 24E Me 22.3	4.1
5	 9A Me 11.8	 9E Me 20.9	9.1	21	 25A Me 24.2	 25E Me 27.5	3.3
6	 10A Me 19.5	 10E Me 28.3	8.8	22	 26A Me 18.8	 26E Me 27.2	8.4
7	 11A Me 21.3	 11E Me 31.3	10.0	23	 27A Me 13.2	 27E Me 24.9	11.7
8	 12A Me 24.0	 12E Me 36.0	12.0	24	 28A Me 20.1	 28E Me 29.4	9.3
9	 13A Me 23.7	 13E Me 31.8	8.1	25	 29A Me 19.9	 29E Me 27.7	7.8
10	 14A Me 23.3	 14E Me 27.9	4.6	26	 30A Me 25.5 X-ray	 30E Me 31.4 X-ray	5.9
11	 15A Me 27.5	 15E Me 34.2	6.7	27	 31A Me 21.3	 31E Me 28.4	7.1
12	 16A Me 29.0	 16E Me 35.8	6.8	28	 32A Me 20.4	 32E Me 27.5	7.1
13	 17A Me 31.5	 17E Me 39.3	7.8	29	 33A Me 14.1	 33E Me 15.5	1.4
14	 18A Me 26.0	 18E Me 35.3	9.3	30	 34A Me 16.7	 34E Me 14.9	-1.8
15	 19A Me 20.8	 19E Me 28.9	8.1	31	 35A Me 15.9	 35E Me 12.4	-3.5
16	 20A Me 26.1	 20E Me 31.8	5.7	32	 36 Me 28.6 X-ray	 36 Me 21.6 R = iPr	7.0

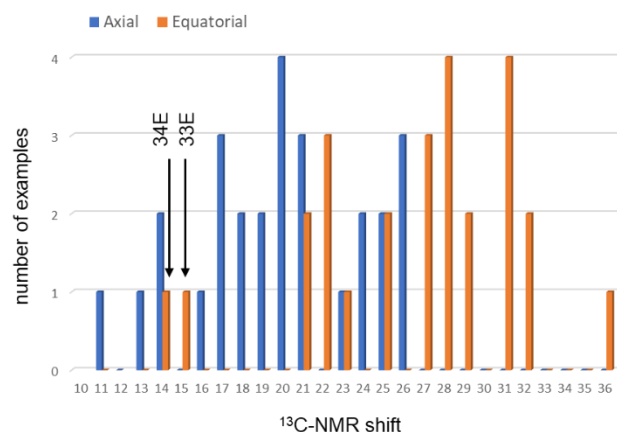
^a Chemical shifts for methyl groups (blue) are given in ppm, exact conditions are given in references. For all cases the most stable conformer is shown. Except for compound **7A** and **24A** all values refer to the single conformer shown and not mixtures thereof, this was achieved in several cases by low-temperature measurements, refer to the references for more details. References for compounds: **5**,²⁶ **6**,²⁷ **7**,²⁸ **8**,^{27,29} **9**,²⁴ **10**,²¹ **11**,²⁵ **12**,²⁷ **13**,³⁰ **14-17**,²⁶ **18**,²⁵ **19-21**,³¹ **22**,²⁶ **23**,³² **24**,²⁸ **25-26**,²⁴ **27-28**,³³ **29**,³⁴ **30**,³⁵ **31**,³⁶ **32**,³⁷ **33-34**,³⁶ **35**,²¹ and **36**.³⁸

In a recent study, Fleming examined the ¹³C-NMR chemical shifts of cyclohexanecarbonitriles, revealing distinct shifts for

axial and equatorial nitrile groups.³⁹ However, when analyzing methyl shifts of all compounds shown in Figure 2 except

chloro-, bromo-, and iodo-cyclohexanes, which exhibit strong upfield shifts, the distinction is less clear compared to cyclohexanenitriles (Figure 3). Overlapping occurs notably in the range of 21-26 ppm. Nevertheless, a shift within 10-19 ppm likely indicates an axial methyl group, while a shift between 27-36 ppm suggests an equatorial methyl group. Exceptionally low ^{13}C -NMR shifts of 14 and 15 ppm are observed in **33E** and **34E**, substituted decalins rather than substituted cyclohexanes.

Figure 3. Frequency vs. chemical shifts of axial and equatorial methyl ^{13}C NMR shifts.



To test whether the experimental data collected in this study can be reproduced by DFT calculations, we calculated the Boltzmann-averaged ^{13}C chemical shifts of the methyl groups of selected methylcyclohexanes shown in Figure 2 using DFT (Figure 4). For this purpose, we performed a conformational search based on meta-dynamic simulations with tight-binding DFT using the CREST code.^{40,41} The conformer ensemble was then prescreened by single-point calculations with B97-D3/def2-SV(P) and $r^2\text{SCAN-3c}$.⁴²⁻⁴⁵ All conformers below a threshold of 3.5 kcal/mol were then optimized at the $r^2\text{SCAN-3c}$ level. The optimized structures that were within a 2.5 kcal/mol window were Boltzmann weighted and subjected to NMR shift calculations at the PBE0/def2-TZVP level.⁴⁶⁻⁴⁷ For all computations except the initial B97-D3/def2-SV(P) single-point calculations and the NMR shift calculations, thermostat contributions were calculated within the rigid rotor harmonic oscillator (RRHO) approximation at the GFN2-xTB level, while the solvent was implicitly considered using the SMD or the ALPB model for chloroform.⁴⁸⁻⁵¹ Conformer sorting, optimization and NMR calculations were performed using the CENSO code linked to the ORCA and XTb codes.⁵²⁻⁵⁶ The results of these calculations are summarized in Figure 4.

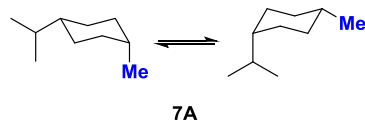
Figure 4. Experimentally observed ^{13}C NMR shifts in ppm (blue) compared to Boltzmann-averaged, calculated chemical shifts (red).^a

Entry	axial conformer	equatorial conformer	Δ ppm
1	 5A 1 conformer	 5E 1 conformer	5.3 5.7
2	 7A 3 conformers	 7E 2 conformers	2.9 3.5
3	 11A 5 conformers	 11E 3 conformers	10.0 9.9
4	 14A 1 conformer	 14E 1 conformer	4.6 5.0
5	 15A 1 conformer	 15E 1 conformer	6.7 6.8
6	 24A 13 conformers	 24E 6 conformers	4.1 2.0
7	 34A 2 conformers	 34E 3 conformers	-1.8 -1.6

^a Calculated shifts are related to tetramethylsilane (TMS). The number of conformers refers only to those conformers that were included in the final NMR shift calculation.

For the *tert*-butyl-substituted methylcyclohexanes **5A**, **5E**, **14A**, **14E**, **15A** and **15B**, the calculated chemical shifts of the methyl groups and the γ -shifts agree well with the experimentally determined values. As expected, no conformer sampling is required for these examples. However, for the vinyl-substituted compounds **11A** and **11E**, the conformers must already be considered in order to reproduce the experimentally found larger difference in the chemical shifts of the methyl groups of the diastereomers. For the isopropyl-substituted methylcyclohexane **7A**, the conformer sampling is even more important, since the calculations predict in full agreement with the experiment that the conformer with an axially oriented isopropyl group is also populated (Figure 5). Consistent with the conclusions of this study, the chemical shift of the equatorially positioned methyl group of this conformer of **7A** differs by 6.1 ppm from the chemical shift of the axial methyl group of the other two conformers of **7A**. The fact that the chemical shift of the conformer with the equatorially aligned methyl group contributes to the Boltzmann-averaged shift of **7A** explains why the difference between the shifts of the methyl groups of **7A** and **7E** is calculated to be only 3.5 ppm, which agrees well with the observed difference in chemical shifts of 2.9 ppm.

Figure 5. Equilibrium between two conformers of **7A** and calculation of averaged value.



	2	1
Number of conformers	2	1
Boltzmann-weight [%]	60.6	39.4
δ ^{13}C Me [ppm]	18.8	24.9
	averaged: 21.2	

For the calculation of the Boltzmann-averaged shift of **24A** (Figure 4, entry 6), 12 conformers have to be considered, of which in six the methyl group is equatorially oriented. The calculations slightly overestimate the contribution of these conformers, which leads to a calculated Boltzmann-averaged shift of **24A** that is shifted to the lower field compared to the experimental shift. Consequently, the calculated difference in the ^{13}C shifts of the methyl groups of **24A** and **24E** is smaller than that determined experimentally. Encouragingly, the calculations reproduce the inverted γ -shift of the equatorial and axial methyl groups of **34A** and **34E**, demonstrating the reliability of the computational approach used for this study.

Despite the accuracy of the DFT calculations with regard to the γ -shift, a comparison with the experimental ^{13}C shifts of the two diastereomers is necessary for the stereochemical assignment, since slight deviations in the calculated NMR shifts impede the unambiguous assignment of the diastereomers. For example, the calculated value of 21.2 for compound **7A** closely resembles the experimental value of **7E**. Similarly, for conformer **24A**, the situation is even more striking, as the calculated value for **24A** is nearly identical to **24E**. The same observation was made for the calculated value of **34E** which matches closely the experimental value of **34A**.

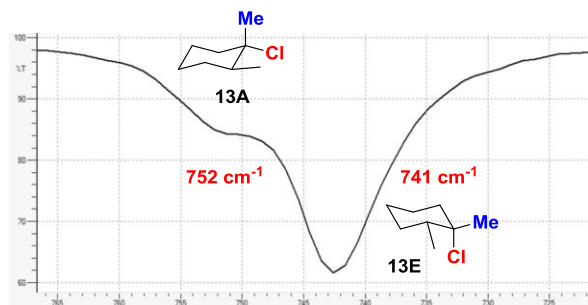
In the following we will present two case studies to further illustrate the practicality and validity of the ^{13}C -methyl shift. Our first example is that of dimethylcyclohexane **13**. This compound was first described by Allinger and co-workers in 1967 who synthesized **13** via hydrochlorination of the corresponding 1,2-dimethyl cyclohexene.⁵⁷ The attribution of the stereochemistry was done by comparison of the infrared stretching frequencies of the C–Cl bond based on the fact that equatorial cyclohexane bonds are stronger compared to axial cyclohexane bonds (Figure 6A). In general, the C–H stretching frequency of an equatorial C–H bond in a cyclohexane ring is approximately 2% higher compared to the corresponding axial C–H bond.⁵⁸ Calculations concerning the C–Cl bond distance of an equatorial C–Cl bond in comparison to an axial C–Cl bond confirm this general rule with the equatorial C–Cl bond having a bond length of 1.799 Å and the axial C–Cl bond having a bond length of 1.808 Å.⁵⁹

We prepared independently this compound in our laboratory and obtained a 77:23 mixture of **13E**:**13A** (see supporting information; SI). Comparison of IR-absorption spectra with the values provided by Allinger⁵⁷ and the ^1H and ^{13}C -NMR data with data reported by Kropp³⁰ suggested that the major diastereomer was **13E**. The HSQC (Heteronuclear single quantum coherence) spectroscopy experiment of the

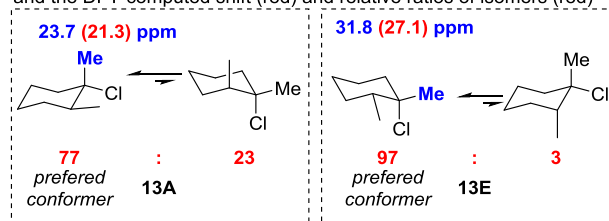
diastereomeric mixture easily identified the two methyl carbons which appear with a chemical shift of 23.7 and 31.8 ppm (see SI). A simple conformational analysis based on *A*-values shown in figure 6B substantiated by DFT-computations identified unambiguously the preferred conformers of diastereomers **13A** and **13E**. Attribution of the lower carbon shift value to compound **13A** according to the γ -shift correctly predicted that **13E** was the major compound in the mixture. Thus, the attribution by Allinger by IR-spectrometry could be confirmed by the characteristic γ -shift of the axial methyl group. Note, that coincidentally, the balance between conformers aligns exactly with the proportion of the two diastereomers (77:23).

Figure 6. Case study on attribution of **13A** and **13E**.^a

A. Recorded IR-absorbance spectrum of a mixture of **13A** and **13E**

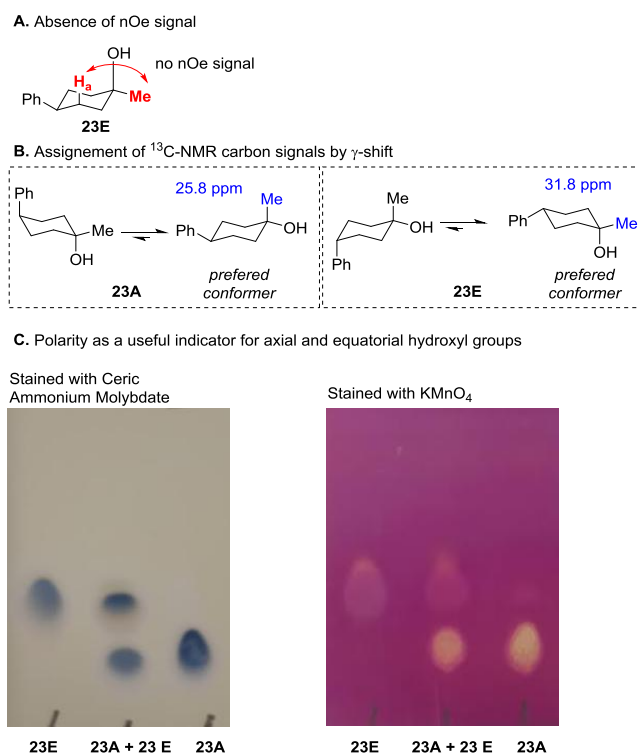


B. Assignment of experimental ^{13}C -NMR carbon signals (blue) by γ -shift and the DFT-computed shift (red) and relative ratios of isomers (red)



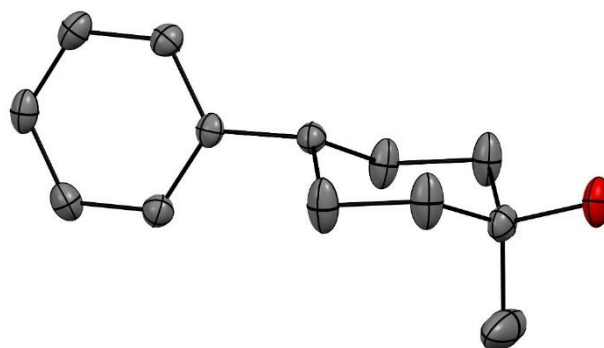
The second case study concerns compound **23**. The two diastereomers **23A** and **23E** have been reported.^{32,60–63} However, diastereomeric attributions contradict each other (see SI for details). Only the group of Studer actually reported experimental attribution of **23E** by a 1D NOESY experiment (Figure 7A).³²

Figure 7. Case study on (Attribution of **13A** and **13E**).



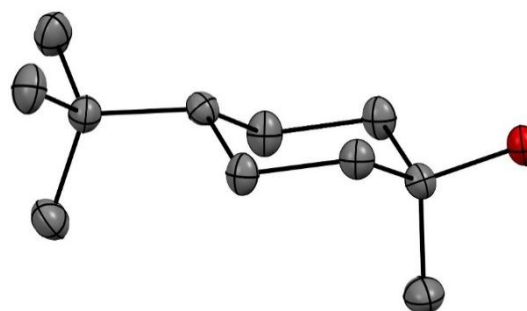
Following the described procedure for compound **13** we identified the two preferred conformers for compound **23** and attributed after HMBC experiment and consideration of the γ -shift the corresponding ^{13}C -signals as shown in Figure 7B. The attribution agreed with the data reported by Studer. Thin layer chromatography (pentane / ether = 1:1) of **23A** and **23E** indicated that **23A** is more polar than **23E**, very likely due to the more exposed equatorial hydroxyl group (Figure 7C). The higher polarity of equatorial hydroxyl groups in comparison with axial hydroxyl groups appears to be quite general, as evidenced by a collection of literature reported R_f values for several cyclohexanols (see SI). Although staining with ceric ammonium molybdate solution⁶⁴ revealed no significant difference between **23A** and **23E**, staining with KMnO_4 demonstrated higher reactivity of **23A** compared to **23E** upon careful heating (Figure 7C). This is again in accordance with the equatorial hydroxyl group being more accessible and thus more reactive. Additionally, we successfully obtained X-ray quality crystals of **23A** (CCDC 2335757), confirming the depicted stereochemistry (Figure 8).

Figure 8. Confirmation of stereochemistry of **23A** by X-ray crystallography.



A third case study regarding the stereochemical attribution of compound **22** is described in the SI. In this instance, X-ray analysis of **22A** (CCDC 2335758) corroborated the ascribed stereochemistry derived from the ^{13}C -NMR analysis (Figure 9).

Figure 9. Confirmation of stereochemistry of **22A** by X-ray crystallography.



In conclusion, this study provides a simple basis for assigning whether a given cyclohexane methyl group is axial or equatorial. When there are 1,3-diaxial interactions between the methyl group and a substituent (in this work mainly hydrogen), the ^{13}C chemical shift of the methyl group is displaced upfield. When both diastereomers of a given methylcyclohexane are available, and the difference in the methyl chemical shift exceeds 5 ppm, the upfield isomer can be generally assigned as containing the axial methyl group with high confidence. This rule is supported by extensive spectroscopic and computational analysis of X conformers. When hydroxyl groups are present, or 1,3-diaxial interactions are not present, this gamma effect can be reduced or even reversed, and meticulous conformational analysis is necessary. Even in such cases, Boltzmann-weighted DFT calculations faithfully reproduce the observed methyl chemical shifts..

ASSOCIATED CONTENT

Data Availability statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

Experimental procedures and characterization data (^1H NMR, ^{13}C NMR and X-ray structures). The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

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