

# SCOPES AND LIMITATIONS OF DFT METHODS FOR ACCURATE SPECTROSCOPIC PREDICTION OF SYSTEMS WITH INTRAMOLECULAR HYDROGEN BONDS



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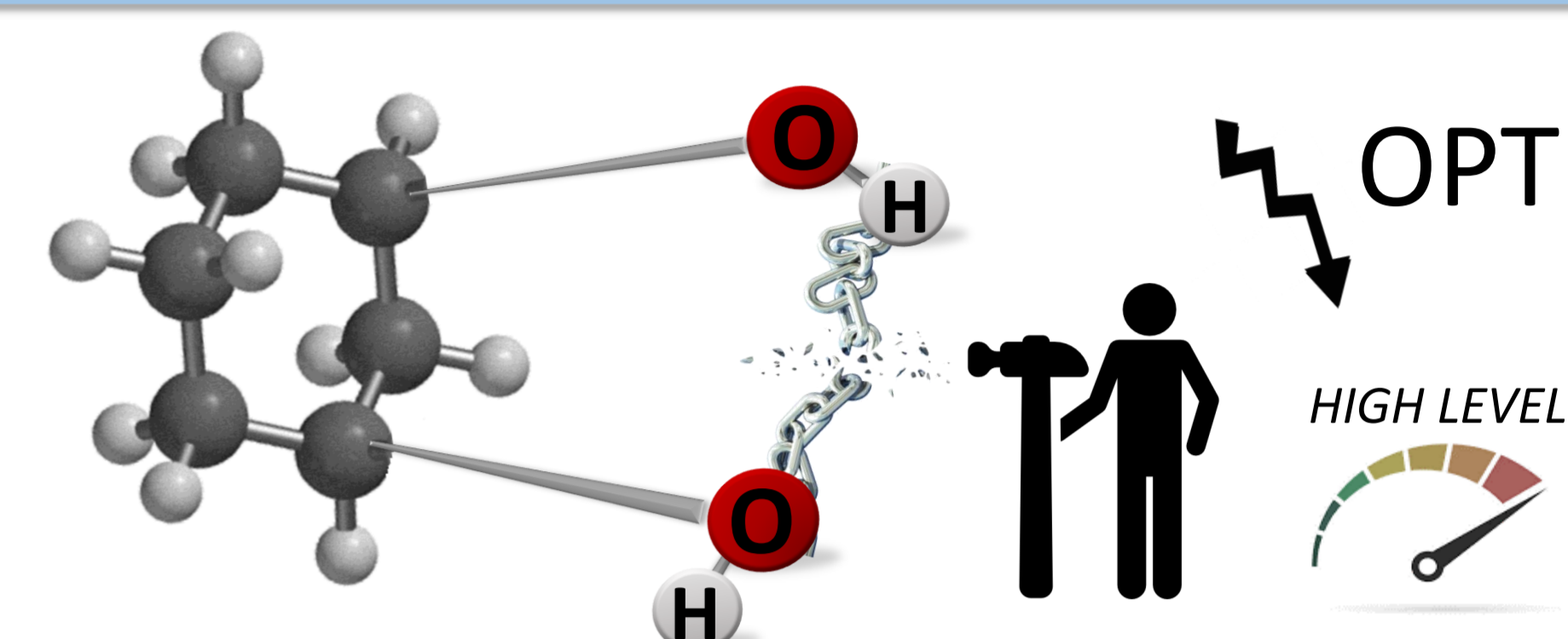
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## Introduction

In recent years, the use of computational chemistry to address structural assignment and validation problems has increased significantly. Among the most prominent tools is DP4+, which has been successfully applied in the structural and stereochemical elucidation of diverse and complex systems.<sup>1</sup> However, its performance is modest when assigning flexible molecules with intramolecular hydrogen bonds (IHB). In-depth analyses have revealed that this limitation stems from an inherent issue in DFT calculations for accurately describing the conformational landscape.<sup>2</sup> For such systems, our group developed an innovative strategy inspired by the wisdom of the masses, breaking away from the traditional single-ensemble approach, and named it MESSI (*Multi-Ensemble Strategy for Structural Identification*).<sup>3</sup> Although MESSI enables the stereochemical assignment of compounds with IHB, achieving suitable conformational descriptions for other purposes remains a challenge.

## Objective

To explore strategies for improving the conformational description of systems with IHB. The study proposes examining 16 diastereoisomers of *O*-methyl hexapyranosides, which predominantly adopt <sup>1</sup>C<sub>4</sub> and <sup>4</sup>C<sub>1</sub> chair conformations. Numerous computationally accessible levels of theory have been tested but fail to resolve the problem. Consequently, it was proposed to perform geometry optimization and energy calculations (SCF and Gibbs) at more demanding levels. The adjustment of Boltzmann distributions would be carried out through NMR calculations ( $\delta$  and  $J$ ) and DP4+.



## Resultados y discusión

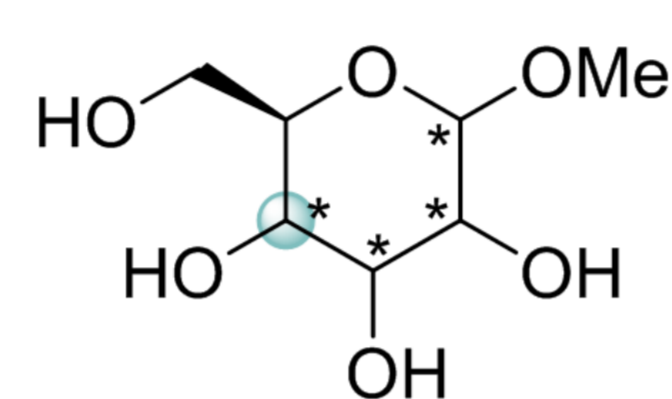
### Case study

- The structural assignment of *O*-methyl hexapyranosides is incorrect in 46.67% of cases when using DP4+ at the standard level.

PCM/MPW1PW91/6-31+G\*\*//B3LYP/6-31+G\*\*

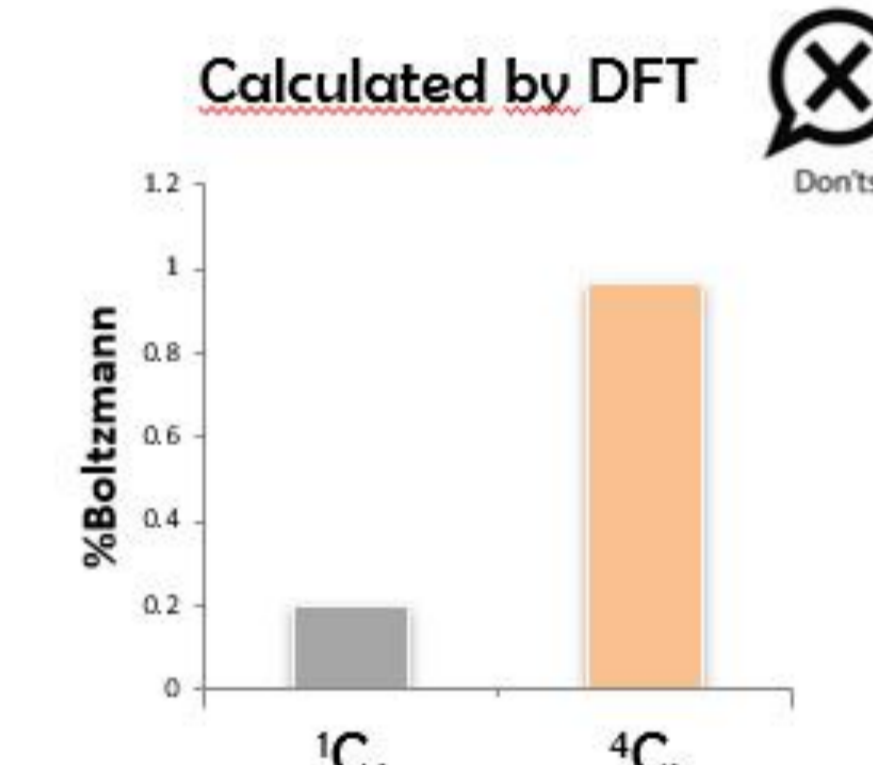
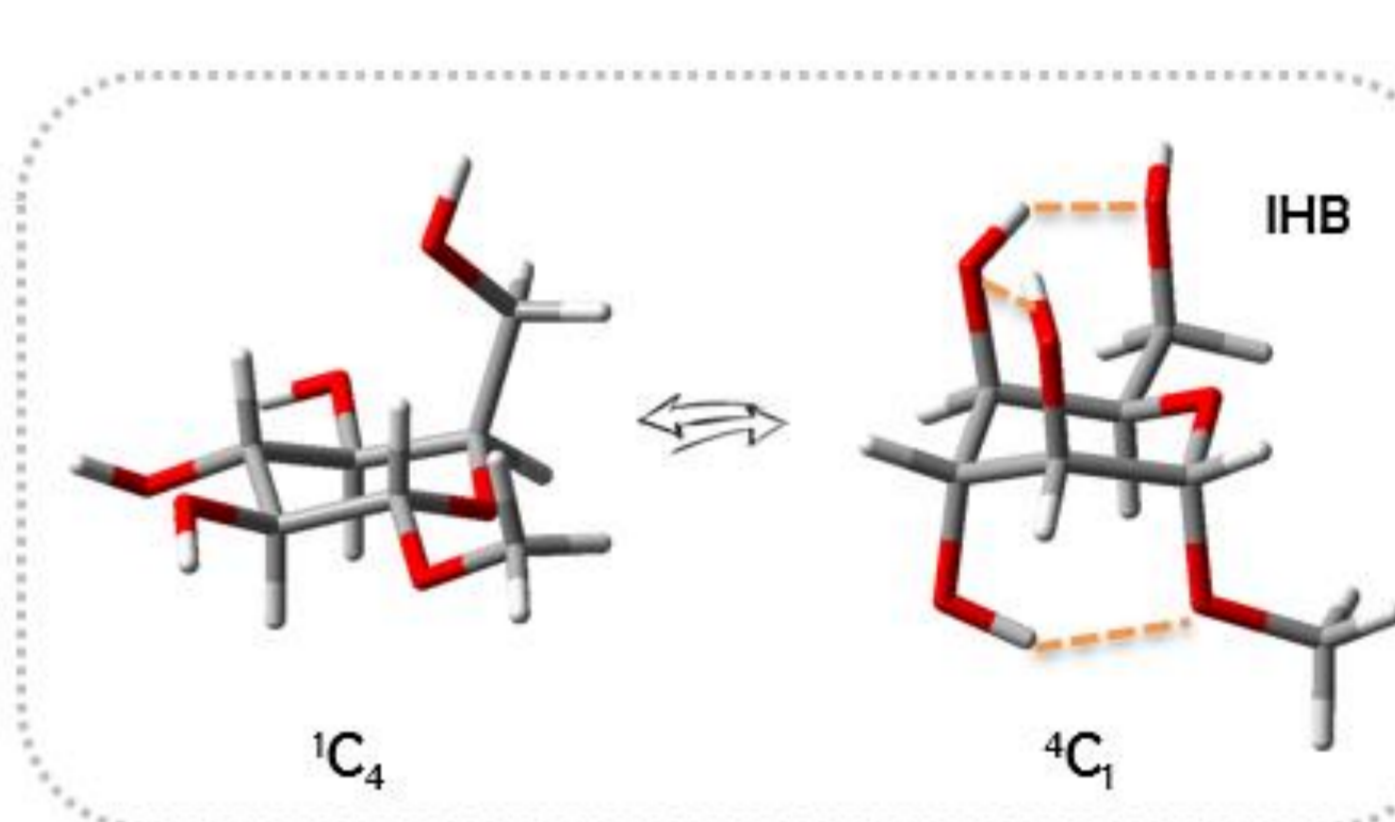
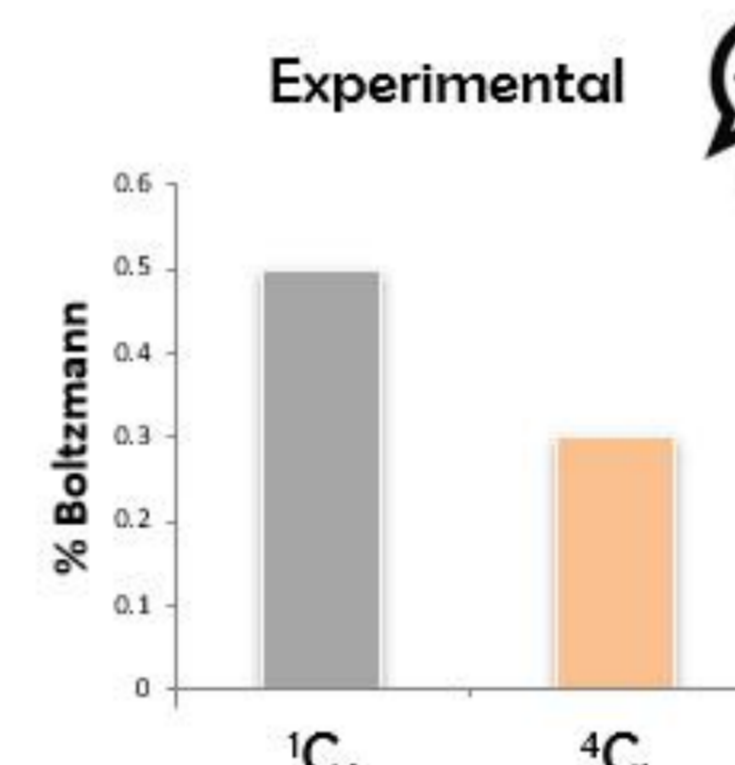
- Previous studies suggested that the erroneous results are due to an overestimation by DFT of spurious conformations capable of forming intramolecular hydrogen bonds (IHB).

DP4+ Probability

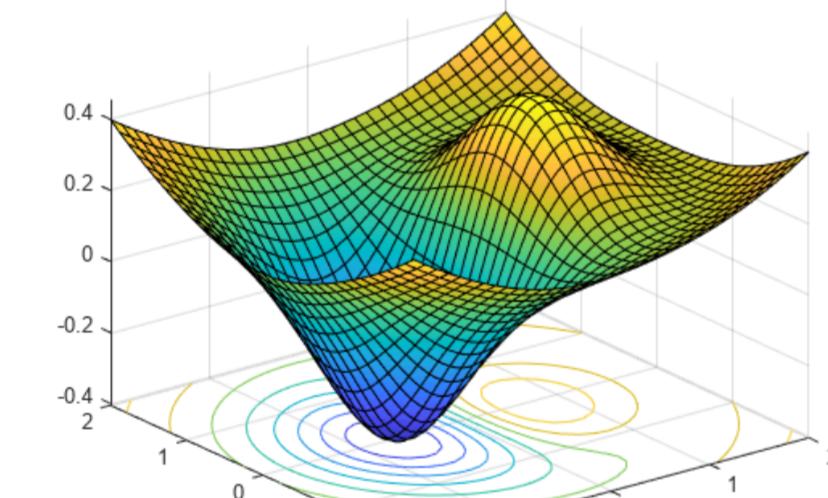
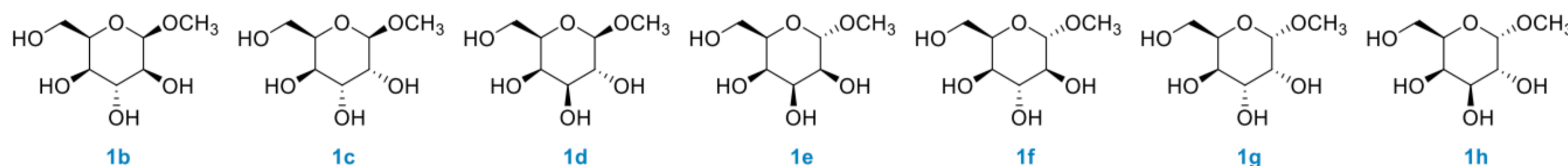


1b (RSRR) = <0.1%	1i (RRSS) = 99.9%
1c (RRRR) = 0.8%	1j (RSSS) = 99.4%
1d (RRSR) = 1.3%	1k (RRSS) = 99.9%
1e (SSSR) = <0.1%	1l (RRRS) = 99.9%
1f (SSRR) = <0.1%	1m (SRSS) = 98.4%
1g (SRRR) = <0.1%	1n (SSSS) = 93.7%
1h (SRSR) = <0.1%	1o (SSRS) = 99.9%
	1p (SRRS) = 99.9%

Experimental and calculated conformational distribution of isomer 1f.



### Geometry reoptimization



B3LYP/6-311+G\*\*  
wB97XD/6-311+G\*\*

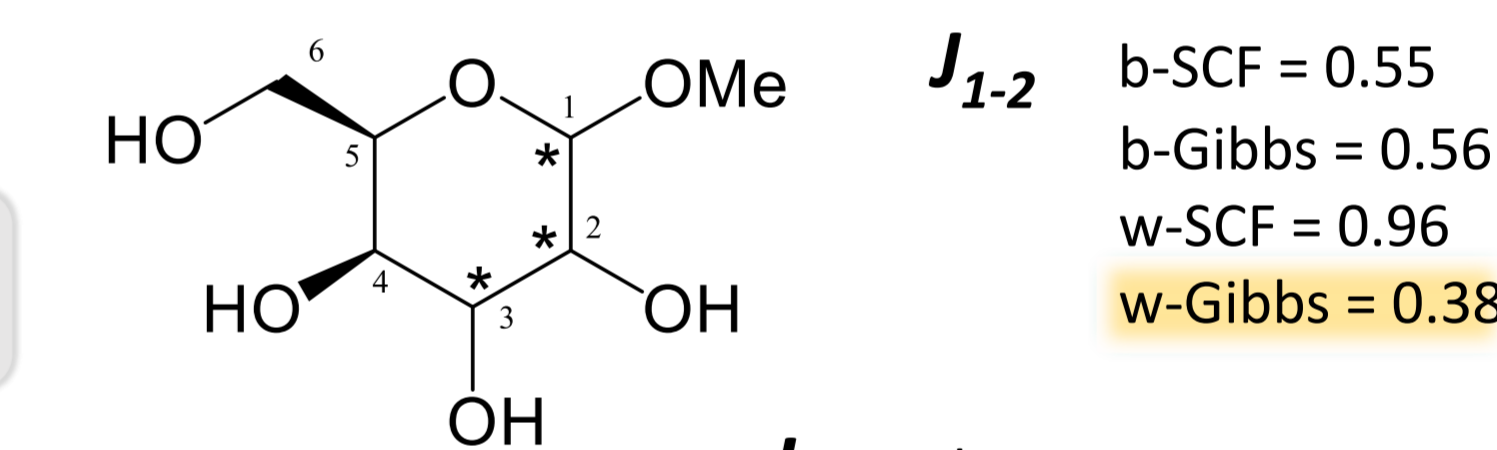
Calculation of fitting parameters  
 $^3J_{HH}$   
 $\delta H, \delta C$   
DP4+

### Results

MAEs  $J_{calc}$

b = B3LYP/6-311+g\*\*  
w = wB97XD/6-311+g\*\*

$J_{4-5}$  b-SCF = 0.52  
b-Gibbs = 0.30  
w-SCF = 0.83  
w-Gibbs = 0.37



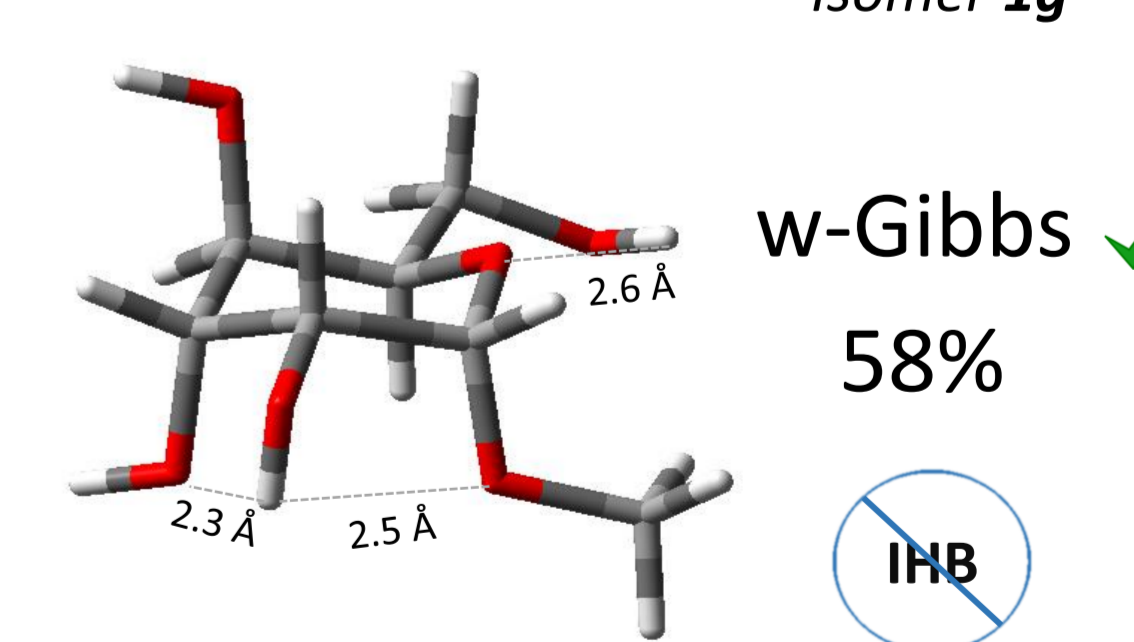
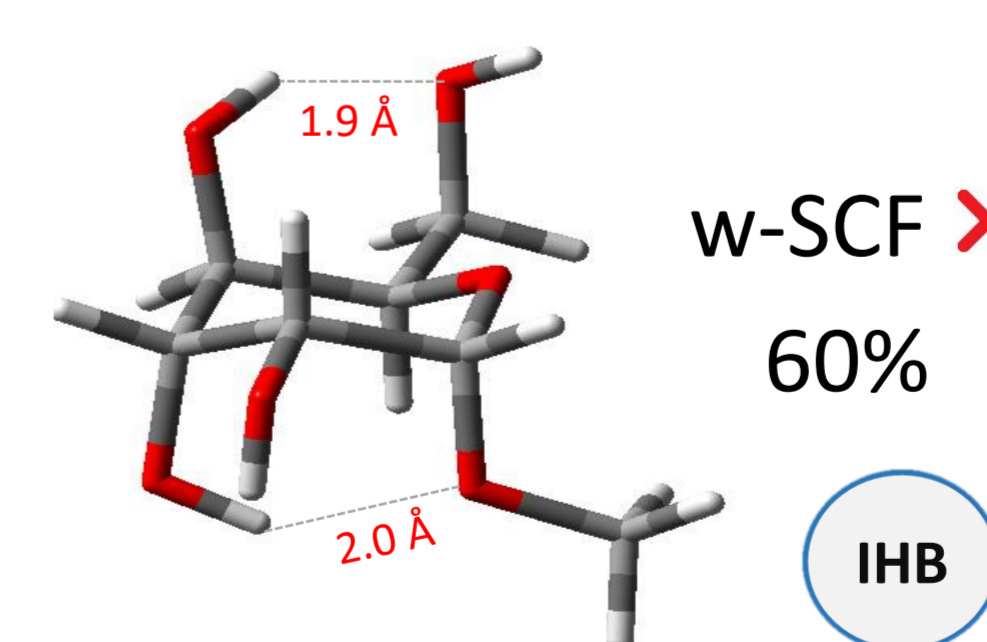
$J_{3-4}$  b-SCF = 0.54  
b-Gibbs = 0.70  
w-SCF = 1.14  
w-Gibbs = 0.41

$J_{1-2}$  b-SCF = 0.55  
b-Gibbs = 0.56  
w-SCF = 0.96  
w-Gibbs = 0.38  
 $J_{2-3}$  b-SCF = 0.66  
b-Gibbs = 0.63  
w-SCF = 1.05  
w-Gibbs = 0.52

DP4+

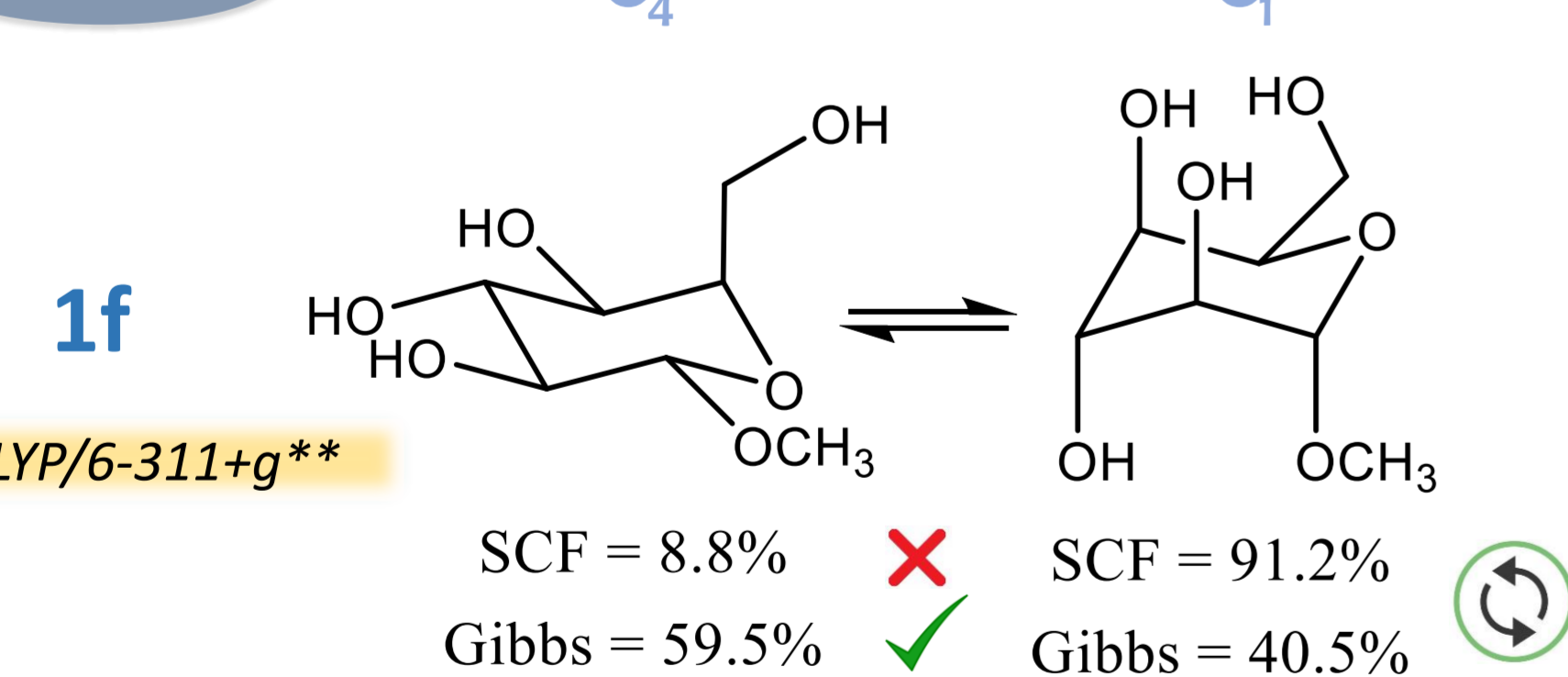
Level opt	B3LYP/6-311+g**		wB97XD/6-311+g**	
	SCF	GIBBS	SCF	GIBBS
DP4+ probability	1b = <0.1%	1b = 98.8%	1b = <0.1%	1b = 7.7%
	1c = <0.1%	1c = 100%	1c = <0.1%	1c = 99.3%
	1d = <0.1%	1d = 100%	1d = 99.6%	1d = 100%
	1e = <0.1%	1e = 99.5%	1e = <0.1%	1e = 84.4%
	1f = <0.1%	1f = 100%	1f = <0.1%	1f = 100%
	1g = <0.1%	1g = 100%	1g = <0.1%	1g = 100%
	1h = <0.1%	1h = 33.9%	1h = <0.1%	1h = 82.0%

Major conformations <sup>4</sup>C<sub>1</sub>

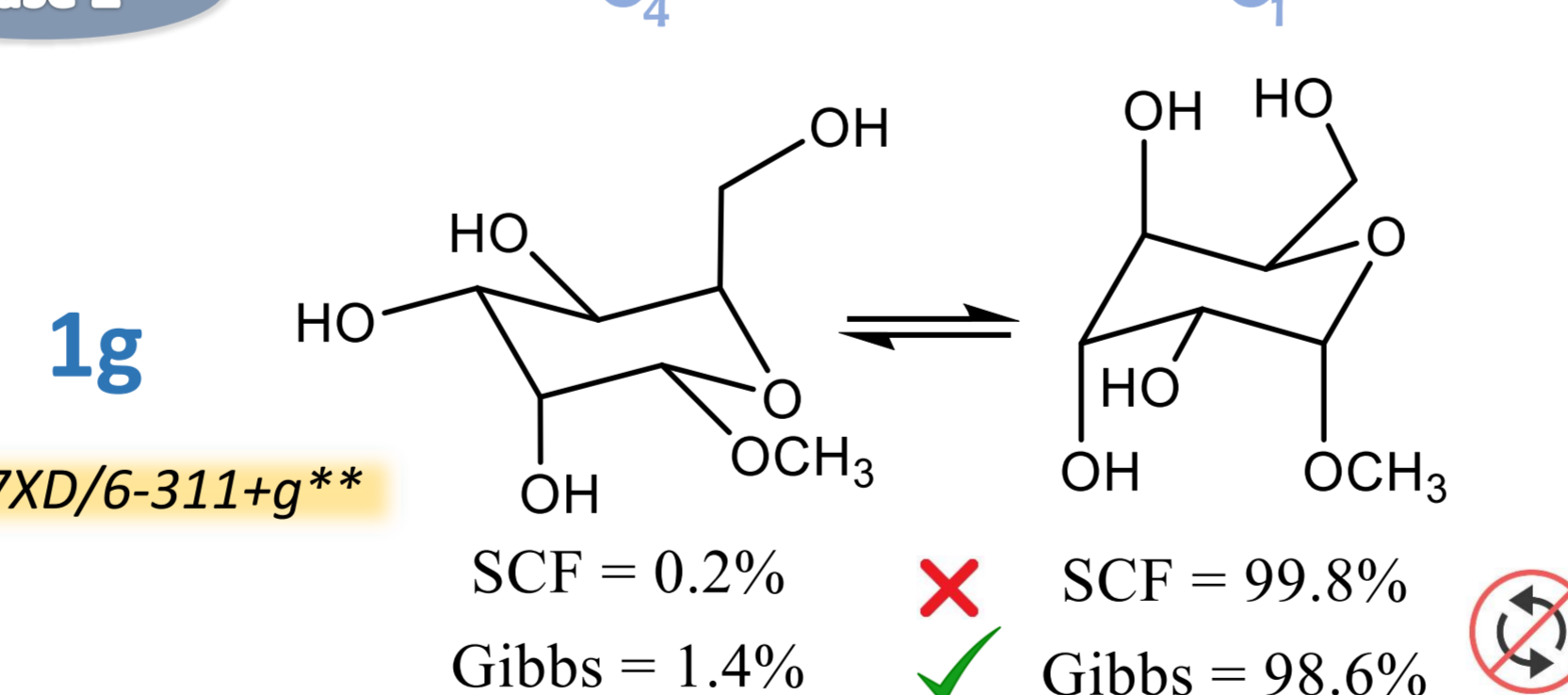


### Boltzmann Analysis

Case 1



Case 2



- SCF overestimates the population of <sup>4</sup>C<sub>1</sub>, whose structure allows the formation of an IHB network.
- Gibbs provides a more realistic description of the contributions and successfully corrects the assignment in DP4+.

- CF and Gibbs return similar conformational descriptions, where the major structure is <sup>4</sup>C<sub>1</sub>.
- SCF provides a probability in DP4+ < 0.1% for the correct structure, while Gibbs corrects the assignment.

## Conclusions

- The main source of variability in the calculated chemical shifts for the same conformation lies in the rotation of the -OH group on carbon 6, which is subject to the possibility of forming a hydrogen bond.
- Some isomers exhibit poor conformational descriptions related to the equilibrium between <sup>1</sup>C<sub>4</sub> and <sup>4</sup>C<sub>1</sub>, while others, despite adequately describing the ring conformation, form stronger IHB networks.
- The use of Gibbs energies for Boltzmann weighting significantly improved the conformational descriptions, which may be attributed to the entropic contribution.

## References

- M. O. Marcarino, M.M. Zanardi, S. Cicetti, A. M. Sarotti, *Acc.Chem. Res.* **2020**, 53 (9), 1922-1932.
- M. M. Zanardi, M. O. Marcarino, A. M. Sarotti, *Org. Lett.* **2020**, 22, 52-56.
- Marcarino, M. O., Passaglia, L., Zanardi, M. M., Sarotti, A. M. *Chem. Eur. J.*, **2023**, e202300420.

## Acknowledgments



Website