

difference in potential energy between a reactant and a TS structure (see Chapter 15). Even in those cases where the force field makes possible the computation of heats of formation and the experimental data are available as enthalpies, it must be remembered that the effect of zero-point vibrational energy is accounted for in an entirely average way when atom-type reference heats of formation are parameterized, so some caution in comparison is warranted.

Finally, any experimental measurement carries with it some error, and obviously a comparison between theory and experiment should never be expected to do better than the experimental error. *The various points discussed in this last section are all equally applicable to comparisons between experiment and QM theories as well, and the careful practitioner would do well always to bear them in mind.*

## 2.6 Case Study: (2*R*\*,4*S*\*)-1-Hydroxy-2,4-dimethylhex-5-ene

Synopsis of Stahl *et al.* (1991), 'Conformational Analysis with Carbon-Carbon Coupling Constants. A Density Functional and Molecular Mechanics Study'.

Many natural products contain one or more sets of carbon backbones decorated with multiple stereogenic centers. A small such fragment that might be found in propiogenic natural products is illustrated in Figure 2.10. From a practical standpoint, the assignment of absolute configuration to each stereogenic center (*R* or *S*), or even of the relative configurations between centers, can be difficult in the absence of single-crystal X-ray data. When many possibilities exist, it is an unpleasant task to synthesize each one.

An alternative means to assign the stereochemistry is to use nuclear magnetic resonance (NMR). Coupling constant data from the NMR experiment can be particularly useful in assigning stereochemistry. However, if the fragments are highly flexible, the interpretation of the NMR data can be complicated when the interconversion of conformers is rapid on the NMR timescale. In that case, rather than observing separate, overlapping spectra for every conformer, only a population-averaged spectrum is obtained.

Deconvolution of such spectra can be accomplished in a computational fashion by (i) determining the energies of all conformers contributing to the equilibrium population, (ii) predicting the spectral constants associated with each conformer, and (iii) averaging over all spectral data weighted by the fractional contribution of each conformer to the equilibrium (the fractional contribution is determined by a Boltzmann average over the energies, see Eq. (10.49)). The authors adopted this approach for (2*R*\*,4*S*\*)-1-hydroxy-2,4-dimethylhex-5-ene, where the conformer energies were determined using the MM3 force field and the NMR coupling constants were predicted at the density functional level of theory. As density functional theory is the subject of Chapter 8 and the prediction of NMR data is not discussed until Section 9.4, we will focus here simply on the performance of MM3 for predicting conformer energies and weighting spectral data.

In order to find the relevant conformers, the authors employed a Monte Carlo/minimization strategy that is described in more detail in the next chapter – in practice, (2*R*\*,4*S*\*)-1-hydroxy-2,4-dimethylhex-5-ene is sufficiently small that one *could* survey every possible torsional isomer by brute force, but it would be very tedious. Table 2.2 shows, for the nine lowest energy conformers, their predicted energies, their contribution to the 300 K equilibrium population, their individual  $^3J_{CC}$  coupling constants between atoms C(2)C(5), C(2)C(8), C(1)C(4), and C(4)C(7), and the mean absolute error in these coupling

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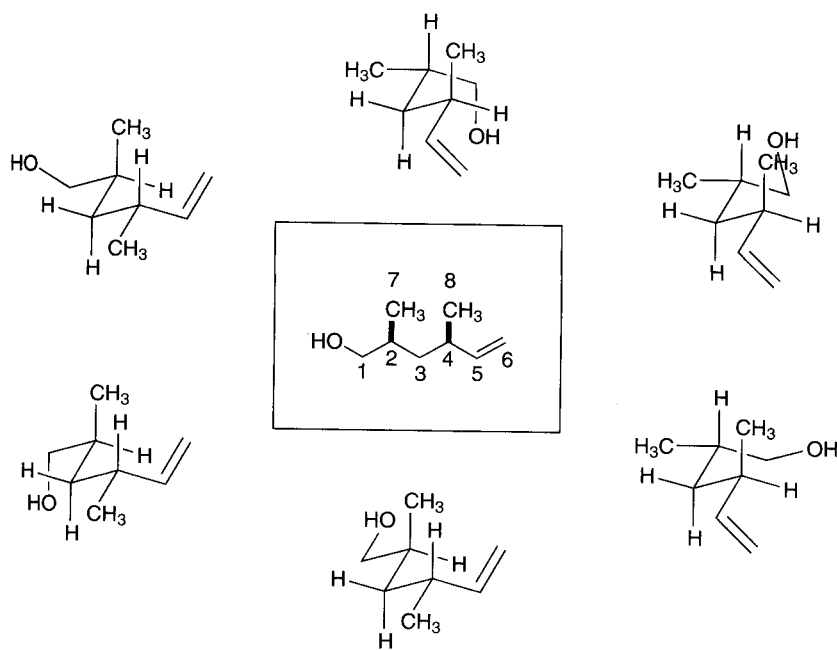
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constants compared to experiment (see Figure 2.10 for atom-numbering convention). In addition, the spectral data predicted from a population-weighted equilibrium average over the nine conformers making up 82% of the equilibrium population are shown.

The population-averaged data are those in best agreement with experiment. Conformer G shows similar agreement (the increased error is within the rounding limit for the table), but is predicted to be sufficiently high in energy that it is unlikely that MM3 could be sufficiently in error for it to be the only conformer at equilibrium. As a separate assessment of this point, the authors carry out *ab initio* calculations at a correlated level of electronic structure theory (MP2/TZ2P//HF/TZ2P; this notation and the relevant theories are discussed in Chapters 6 and 7, but exact details are not important here), and observe what they characterize as very good agreement between the force-field energies and the *ab initio* energies (the data are not provided).

In principle, then, when the relative configurations are not known for a flexible chain in some natural product backbone, the technique outlined above could be used to predict the expected NMR spectra for all possibilities, and presuming one prediction matched to experiment significantly more closely than any other, the assignment would be regarded



**Figure 2.10** Some plausible conformations of (2*R*\*,4*S*\*)-1-hydroxy-2,4-dimethylhex-5-ene. How many different torsional isomers might one need to examine, and how would you go about generating them? [Note that the notation 2*R*\*,4*S*\* implies that the *relative* stereochemical configuration at the 2 and 4 centers is *R,S* – by convention, when the absolute configuration is not known the first center is always assigned to be *R*\*. However, the absolute conformations that are drawn here are *S,R* so as to preserve correspondence with the published illustrations of Stahl and coworkers. Since NMR in an achiral solvent does not distinguish between enantiomers, one can work with either absolute configuration in this instance.]

**Table 2.2** Relative MM3 energies (kcal mol<sup>-1</sup>), fractional equilibrium populations *F* (%), predicted NMR coupling constants (Hz), and mean unsigned error in predicted coupling constants for different conformers and the equilibrium average of (2*R*\*,4*S*\*)-1-hydroxy-2,4-dimethylhex 5-ene at 300 K.

Conformer	rel <i>E</i>	<i>F</i>	<sup>3</sup> <i>J</i>				MUE
			C(2)C(5)	C(2)C(8)	C(1)C(4)	C(4)C(7)	
A	0.0	24	1.1	4.2	3.9	1.3	0.6
B	0.1	21	1.1	4.0	5.8	1.2	1.0
C	0.2	19	1.0	4.2	4.1	1.2	0.7
D	0.9	5	3.8	1.5	1.7	4.5	2.2
E	1.1	4	4.1	0.8	1.1	4.4	2.5
F	1.3	3	4.1	0.9	0.4	5.3	2.9
G	1.4	2	1.2	3.7	3.8	1.5	0.3
H	1.4	2	1.4	4.2	5.7	1.4	0.9
I	1.5	2	0.1	5.1	0.0	5.3	2.5
average		82	1.4	3.7	4.1	1.8	0.3
experiment			1.4	3.3	3.8	2.2	

as reasonably secure. At the least, it would suggest how to prioritize synthetic efforts that would be necessary to provide the ultimate proof.

In that regard, this paper might have been improved by including a prediction (and ideally an experimental measurement) for the NMR coupling data of (2*R*\*,4*R*\*)-1-hydroxy-2,4-dimethylhex-5-ene, i.e., the stereoisomer having the *R*\*,*R*\* relative configuration between the stereogenic centers instead of the *R*\*,*S*\* configuration. If each predicted spectrum matched its corresponding experimental spectrum significantly more closely than it matched the non-corresponding experimental spectrum, the utility of the methodology would be still more convincingly demonstrated. Even in the absence of this demonstration, however, the work of Stahl and his coworkers nicely illustrates how accurate force fields can be for 'typical' C,H,O-compounds, and also how different levels of theory can be combined to address different parts of a computational problem in the most efficient manner. In this case, inexpensive molecular mechanics is used to provide an accurate map of the wells on the conformational potential energy surface and the vastly more expensive DFT method is employed only thereafter to predict the NMR spectral data.

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