

Modeling NMR Parameters by DFT Methods as an Aid to the Conformational Analysis of cis-Fused 7a(8a)-Methyl Octa(hexa)hydrocyclopenta[d][1,3]oxazines and [3,1]benzoxazines

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Abstract: The energies of the preferred conformations of four 7a-methyl octa(or hexa)hydrocyclopenta[d][1,3]oxazines, five 8a-methyl octa(or hexa)hydro[3,1]benzoxazines, and 8a-methyl hexahydro[1,3]-benzoxazinone, all cis-fused, were investigated by DFT methods. Following geometry optimization at the B3LYP/6-31G(d,p) level, both the proton chemical shifts and the vicinal coupling constants between H-4a and the H-4 and H-5 protons were calculated at the B3LYP/cc-pVTZ level and compared to the previously experimentally measured values. The agreement between the calculated and the experimental chemical shifts was found to be good. Similarly, the agreement between the calculated and the experimental vicinal coupling constants was also found to be good, thus providing a methodology for determining the conformational equilibria of such systems that is comparable in many respects to experimental approaches such as variable-temperature NMR or to the use of model coupling constant values, when available, from analogous compounds.

Introduction

The calculation of NMR parameters by ab initio or DFT methods is obviously desirable for several reasons, ranging from a basic understanding of the involved phenomena, to more practical issues such as the total prediction of NMR spectra. Of the several physical quantities involved in the determination of the NMR spectrum, for a common spin-1/2 nucleus such as ¹H the chemical shift and spin-spin couplings dominate. Although the calculation of chemical shifts is an established tool of computational chemistry, that of spin-spin couplings has lagged behind somewhat owing to its intrinsically more complex nature. However, thanks to the advancements made in this field, viz., the recent development of theory, which has been suitably chronicled with timely reviews,¹⁻³ coupled with the ready availability of increased computing power and code, this situation has rapidly changed. The stage has now been reached where meaningful, and reliable, calculations can provide synthesized spectra amenable to structural analysis⁴ and the feasible application of calculated spin-spin couplings to structural analysis is becoming more evident.

Particular applications of this methodology might involve, e.g., the prediction of the NMR spectra of a "best guess"

candidate structure or a limited number of candidate structures resulting from a synthetic procedure⁴ or natural product isolation,⁵ or alternatively, the determination of the position of a conformational equilibrium. Indeed, the application of coupling constant calculations has been readily recognized for the determination of conformational preference and applied in limited cases for various homo- (including nuclei other than proton) or heteronuclear couplings. The calculation of coupling constants (especially for $J_{C,C}$ but also for $J_{C,H}$ and, very recently, for $J_{H,H}$) has been applied to conformational issues in carbohydrate chemistry⁶⁻¹² and other simple organic molecules,¹³⁻¹⁵ and recently it has also been successfully applied to the conformational analysis of simple peptide models.^{16,17}

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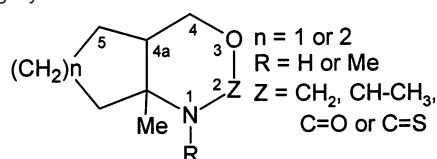
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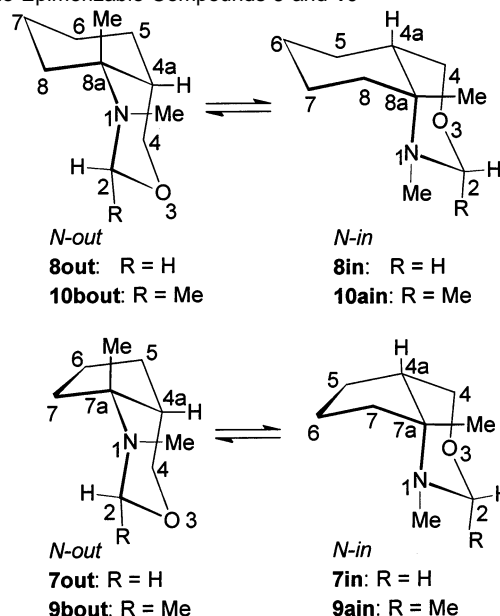
Chart 1. Compounds 1–10 Studied in This Work Together with the Numbering System in Use



In a previous experimental study,¹⁸ the adopted solution-state stereostructures as determined by NMR of a set of compounds (see Chart 1) comprising four 7a-methyl octa(or hexa)-hydrocyclopenta[*d*][1,3]oxazines (**1**, **4**, **7**, and **9**), five 8a-methyl octa(or hexa)hydro[3,1]benzoxazines (**2**, **3**, **5**, **8**, and **10**), and 8a-methyl hexahydro[1,3]benzoxazinone (**6**), all cis-fused, were described. The systematic study of the structure and stereochemistry of such ring-saturated heterocyclic compounds has been undertaken for many years concomitant with improvements to their synthetic methodologies¹⁹ and, in addition to being inherently interesting, many heterocyclic compounds also display marked physiological activity which provides further impetus for their study. Similar compounds possessing, or lacking, the 7a/8a-methyl have been studied earlier^{20–27} whereby it was ascertained that the cis-fused ring system in 3,1-oxazine (1,3-oxazine) derivatives can attain either a biased *N-in* or *N-out* (*O-in* or *O-out*) conformation (see Scheme 1), or exist as an interconverting equilibrium mixture of the two conformers depending on their relative stabilities as determined by the ring size, the ring substituents, and the ring structure. The compounds of this set displayed a mix of different dynamics under the current NMR conditions,¹⁸ ranging from totally biased systems, to simple interconverting pairs that are able to be spectroscopically frozen, to complex systems beyond dissemination.

The quintessential point of the previous paper was the assessment of the conformational equilibrium by variable-temperature NMR. However, the basic premise that it is simply a matter of going down in temperature is fraught with technical difficulties and experimental drawbacks, e.g., precipitation of the solute, freezing of the solvent, unattainable temperatures, B_0 field homogeneity problems, lack of observation of the minor conformer after decoalescence due to dissipating population, solvent property changes, line broadening due to increasing solvent viscosity, increased propensity for equipment failure, etc.; in short, there exists a veritable minefield of experimental limitations. Even accurate (± 1 °C) measurement of the temperature necessary for the calculation of thermodynamic properties presents a burdensome task and the entire variable temper-

Scheme 1. *N-in* and *N-out* Conformational Equilibria of **7** and **8** and the Epimerizable Compounds **9** and **10**



ature exercise represents a heavy investment in operator and instrument time. This report not only further demonstrates that the accurate calculation of J can be performed, but that it can be successfully applied to conformational analysis, thus providing a complementary, or indeed, alternative methodology to the experimentally demanding, variable-temperature methods which may in many cases be unavailable or not forthcoming. The computational methodology optimized in a previous examination⁴ and prescribed therein has been applied in this present study. Additionally, comparison between the calculated and the experimental coupling constants, and also the chemical shifts, helped facilitate assignment confirmation or correction in several suspect cases in these compounds.

Computational Method

A conformational search on each of the compounds **1–10** was based on chemical intuition and also use of the program HyperChem.²⁸ Candidate structures were pre-optimized using either molecular mechanics MM⁺ or semiempirical PM3^{29,30} methods implemented in HyperChem. The convergence criterion in the pre-optimizations was set loose to find a wide selection of starting conformations for density functional theory (DFT) geometry optimizations. Both the *N-in* and *N-out* conformations were constructed and optimized for each case. In the starting structure, the heteroring was in a chair conformation with either an axially- or equatorially oriented ring nitrogen substituent. In the optimizations of the cyclopentane-fused cases **1** and **4**, the heteroring conformation tended to veer away from a chair conformation due to steric hindrance, especially when the N-substituent was axial. The optimized structures of **1**, **4**, and **7** provided frameworks for additional initial structures of the other cyclopentane-fused compounds after appropriate modification. This was done in order to find all energetically feasible conformations for the cyclopentane ring within each molecular constitution. The final DFT geometry optimizations were performed on all of the conformations resulting from the pre-optimizations and the results are collected in Table 1.

DFT geometry optimizations were made with the Gaussian 98 program³¹ using the hybrid B3LYP functional^{32–35} and the 6-31G(d,p)

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Table 1. Optimized Conformations and Relative Thermodynamic Stabilities of Compounds 1–10

structure ⁴⁹	$\Delta G_{m,calc}^{\circ}$ (kJ/mol)	<i>X-in/X-out</i>	cycloalkane conformation	flap atom ^b	heteroring conformation	NH/NMe orientation
1in7	0.0	<i>N-in</i>	envelope	C-7	flat twist-boat	equatorial
1in6	2.7	<i>N-in</i>	envelope	C-6	boat	equatorial
1out7	3.8	<i>N-out</i>	envelope	C-7	boat	equatorial
1out6	4.9	<i>N-out</i>	envelope	C-6	flat twist-boat	equatorial
2in	0.0	<i>N-in</i>	chair		sofa ^c	equatorial
2out	4.8	<i>N-out</i>	chair		flat twist-boat	equatorial
3in	0.0	<i>N-in</i>	chair		sofa ^c	equatorial
3out	4.6	<i>N-out</i>	chair		flat twist-boat	equatorial
4in7	0.0	<i>N-in</i>	envelope	C-7	flat twist-boat	equatorial
4in6	1.4	<i>N-in</i>	envelope	C-6	boat	equatorial
4out7	0.2	<i>N-out</i>	envelope	C-7	boat	equatorial
4out6	34.7	<i>N-out</i>	envelope	C-6	boat	equatorial
5in	0.0	<i>N-in</i>	chair		sofa ^c	equatorial
5out	5.5	<i>N-out</i>	chair		flat twist-boat	equatorial
6in	0.0	<i>O-in</i>	chair		flat twist-boat	equatorial
6out	8.7	<i>O-out</i>	chair		sofa ^c	equatorial
7in7a	0.0	<i>N-in</i>	envelope	C-7a	chair	equatorial
7ina7a	13.3	<i>N-in</i>	envelope	C-7a	chair	axial
7in6	9.6	<i>N-in</i>	envelope	C-6	twist-boat	equatorial
7out7a	8.2	<i>N-out</i>	envelope	C-7a	chair	equatorial
7out6	17.6	<i>N-out</i>	envelope	C-6	twist-boat	equatorial
8in	0.0	<i>N-in</i>	chair		chair	equatorial
8ina	17.2	<i>N-in</i>	chair		chair	axial
8out	7.8	<i>N-out</i>	chair		chair	equatorial
8outa	8.4	<i>N-out</i>	chair		chair	axial
9ain	0.0	<i>N-in</i>	envelope	C-7a	chair	equatorial
9aina	14.5	<i>N-in</i>	envelope	C-7a	chair	axial
9aout	25.2 ^d	<i>N-out</i>	envelope	C-7a	chair	equatorial
9aouta	33.0 ^d	<i>N-out</i>	envelope	C-7a	chair	axial
9bout	7.4	<i>N-out</i>	envelope	C-7a	chair	equatorial
9bouta	12.5	<i>N-out</i>	envelope	C-7a	chair	axial
9bin	15.4 ^d	<i>N-in</i>	envelope	C-7a	chair	equatorial
9bina	32.5 ^d	<i>N-in</i>	envelope	C-7a	chair	axial
10ain	0.0	<i>N-in</i>	chair		chair	equatorial
10aina	19.3	<i>N-in</i>	chair		chair	axial
10aout	23.4 ^d	<i>N-out</i>	chair		chair	equatorial
10aouta	30.6 ^d	<i>N-out</i>	chair		chair	axial
10bout	8.4	<i>N-out</i>	chair		chair	equatorial
10bouta	11.3	<i>N-out</i>	chair		chair	axial
10bin	15.3 ^d	<i>N-in</i>	chair		chair	equatorial
10bina	36.2 ^d	<i>N-in</i>	chair		chair	axial

^a See the computational method section for the definition of $\Delta G_{m,calc}^{\circ}$. ^b The flap atom in the cyclopenta[*d*][1,3]oxazine derivatives refers to the carbon atom in the cyclopentane ring which is not in the plane formed by the other carbon atoms of that same ring. ^c See for example, refs 54–57. ^d $\Delta E_{m,calc}^{\circ}$ values (kJ/mol).

basis set³⁶ followed by vibrational analysis (1 bar, 298.15 K, scaling factor 0.9804³⁷) which proved that all optimized structures are true minimum energy structures on the potential energy surface. This level of theory for geometry optimization was previously found to be adequate for the calculation of ¹H NMR parameters.⁴ The vibrational analyses calculations also provided $\Delta G_{m,calc}^{\circ}$ values for the different conformations (see Table 1) by subtraction of the sums of the electronic

and thermal free energies. Finally, the mole fractions (based on Boltzmann populations where $p_i = e^{-\Delta G(i)/kT} / \sum_j e^{-\Delta G(j)/kT}$) of the conformations within each equilibrium were used for estimating the population-weighted averages of the calculated coupling constants in a manner similar to that applied recently to ¹³C chemical shifts.^{5,38}

For the evaluation of the spin–spin coupling constants, the Fermi contact (FC) contribution was calculated with Gaussian 98 by finite perturbation theory (*Field* keyword) at the spin-unrestricted B3LYP/cc-pVTZ level.³⁹ Tight SCF convergence criteria were always used.^{4,40} A perturbation of 10^{−2} au was applied on H-4a to obtain all couplings to this proton. For three structures, the paramagnetic and diamagnetic spin–orbit terms (PSO and DSO, respectively) along with the FC term were calculated using the deMon-NMR program^{41–46} to assess their contribution to the spin–spin coupling. These calculations were run

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Table 2. Contributions (in Hz) to the Spin–Spin Coupling Constants for Structures **7in7a**, **8ina**, and **8outa** from the Fermi Contact (FC), Paramagnetic Spin–Orbit (PSO), and Diamagnetic Spin–Orbit (DSO) Terms Calculated Using the deMon-NMR Program at the P86/IGLO–III/B3LYP/6-31G(d,p) Level of Theory

structure	coupled protons	calculated terms from deMon-NMR			J_{calc}	
		FC	PSO	DSO	deMon-NMR ^a	Gaussian ^b
7in7a	H-4a, H-4 α	1.12	0.04	–0.08	1.08	1.5
	H-4a, H-4 β	2.16	–0.65	0.65	2.16	2.8
	H-4a, H-5 α	8.82	1.95	–1.99	8.78	9.7
	H-4a, H-5 β	9.18	–0.94	0.91	9.15	10.0
8ina	H-4a, H-4 α	0.81	0.01	–0.04	0.78	1.2
	H-4a, H-4 β	2.95	–0.87	0.87	2.95	3.6
	H-4a, H-5 α	12.14	2.10	–2.13	12.11	13.3
	H-4a, H-5 β	4.12	–0.53	0.51	4.10	4.8
8outa	H-4a, H-4 α	11.13	2.06	–2.13	11.06	12.0
	H-4a, H-4 β	5.04	–0.75	0.72	5.01	5.8
	H-4a, H-5 α	1.64	–0.19	0.15	1.60	2.1
	H-4a, H-5 β	4.82	–0.85	0.81	4.78	5.7

^a Arithmetic sum of FC, PSO, and DSO terms; values not calibrated. ^b FC term only; calibrated values.

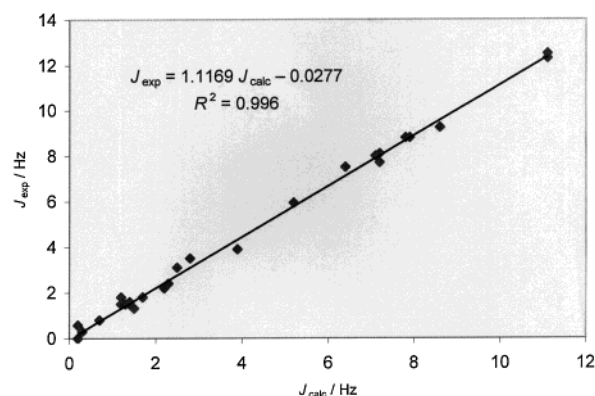


Figure 1. Regression analysis of experimental vs calculated coupling constants used for calibrating the calculated coupling constants.

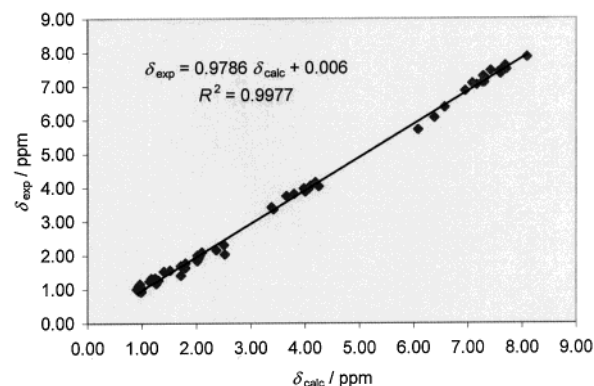


Figure 2. Regression analysis of experimental vs calculated ¹H chemical shifts used for calibrating the calculated ¹H chemical shifts.

with the Perdew–Wang exchange with Perdew correlation functional (P86)⁴⁷ and the IGLO–III basis set⁴⁸ on the B3LYP/6-31G(d,p) optimized geometry. These results are presented in Table 2. For the calculation of proton chemical shifts, nuclear shieldings were calculated using Gaussian 98 at the B3LYP/cc-pVTZ level and the shieldings so obtained were converted for selected protons into chemical shifts by referencing to TMS at 0 ppm ($\delta = \sigma_{\text{TMS}} - \sigma_n$).

Calibration of the coupling constants and the chemical shifts was effected by plotting experimental values against calculated values (see Figures 1 and 2, respectively) for the structurally well-defined **8in**, **9ain**, and **10ain**⁴⁹ and performing linear regression analyses. Also included in the calibration plots were the data for a series of compounds—furan, *o*-dichlorobenzene, *o*-bromochlorobenzene, 2,4- and 2,5-dichlorophenol, 3a,7a-methano-1H-indene, and naphthalene—taken from ref 4. The resulting equations were then used to adjust the calculated coupling constants and ¹H chemical shifts, presented in Tables 3 and 4, respectively.

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Results and Discussion

Pertinent Points of the Computational Methodology. It is worth recounting some of the essential points of the methodology as caveats remain in place. For example, the magnitudes of the PSO and DSO terms are not necessarily negligible and may even exceed that of the FC term, but their addition in the general case leads to a negligible effect because they are of similar magnitude but opposite in sign (at least for the case of homonuclear proton couplings^{4,50–53}), which justifies their general omission from the calculations. This was confirmed for three cases (**7in7a**, **8ina**, and **8outa**;⁴⁹ see Table 2); thus the conclusions reached from previous results,⁴ mostly pertaining to aromatic protons, are also applicable to the cases under study here involving aliphatic protons. The spin-dipole (SD) term was not calculated as it is generally known to be negligible and is computationally expensive.¹ It is also worth emphasizing that good geometry optimization is crucial for obtaining accurate coupling constant results.

Preferred Conformations and Coupling Constants for Compounds 2, 3, 5, and 6. In the previous study¹⁸ of compounds **2**, **3**, and **5**, distinct subspectra for two interconverting conformers were observed in CD₂Cl₂ solution at –95

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Table 3. Calculated and Calibrated Coupling Constants (in Hz) and Mole Fractions (X) of the Conformations for Compounds **1–10**

structure	J_{calc}				X	mole fraction of X_{out} based on:			integration of the signals at low temp. ^c
	H-4a, H-4 α	H-4a, H-4 β	H-4a, H-5 α	H-4a, H-5 β		J_{calc} and J_{obs} for: ^b		$J_{\text{obs}}^{\text{c,d}}$ at 25 °C	
						$J_{\text{H4a,H4}\alpha}$	$J_{\text{H4a,H5}\alpha}$		
1in7	2.2	2.4	4.6	11.7	0.59				
1in6	1.2	3.4	12.0	7.5	0.20				
1out7	12.0	6.2	6.2	8.6	0.13			n.d.	n.d.
1out6	12.6	7.8	0.6	8.6	0.08				
1, J_{pwa}	4.1	3.5	6.0	10.2					
1, $J_{\text{obs}}^{\text{c,e}}$	3.2	3.9	9.7	7.1					
2in	1.7	2.9	12.7	5.2	0.88				
2out	11.8	4.0	2.1	6.0	0.12	0.19	0.18	0.25	0.10
2, J_{pwa}	2.9	3.0	11.4	5.3					
2, $J_{\text{obs}}^{\text{c,e}}$	3.6	3.3	10.8	2.6					
3in	1.5	3.0	12.7	5.2	0.87				
3out	12.0	4.2	2.1	6.0	0.13	0.19	0.19	0.25	0.10
3, J_{pwa}	2.9	3.2	11.3	5.3					
3, $J_{\text{obs}}^{\text{c,e}}$	3.5	3.4	10.7	4.8					
4in7	2.5	2.1	6.1	11.7	0.40				
4in6	1.3	3.3	12.2	7.1	0.23				
4out7	12.0	6.5	7.5	8.5	0.37			n.d.	n.d.
4out6	12.4	7.9	8.6	9.9	0.00				
4, J_{pwa}	5.7	4.0	8.0	9.5	-				
4, $J_{\text{obs}}^{\text{c,e}}$	5.7	3.6	9.5	6.7	-				
5in	1.7	2.9	12.7	4.8	0.90				
5out	11.6	3.8	2.1	5.9	0.10	0.21	0.17	0.20	0.12
5, J_{pwa}	2.7	3.0	11.6	4.9					
5, $J_{\text{obs}}^{\text{c,e}}$	3.7	3.0	10.9	4.4					
6in	1.0	5.7	12.8	4.8	0.97				
6out	11.9	6.1	2.3	5.1	0.03	0.07	0.00	n.d.	n.d.
6, J_{pwa}	1.3	5.7	12.5	4.8					
6, $J_{\text{obs}}^{\text{c,e}}$	1.7	5.3	12.8	3.6					
7in7a	1.5	2.8	9.7	10.0	0.94				
7ina7a	1.2	3.6	12.2	9.1	0.00				
7in6	10.7	7.1	10.8	7.3	0.02				
7out7a	12.2	6.9	1.0	7.8	0.04			0.37	0.15
7out6	0.8	3.9	0.6	8.7	0.00				
7, J_{pwa}	2.1	3.1	9.4	9.9	-				
7, $J_{63:37}^f$	5.5	4.3	6.5	9.2	-				
7, $J_{\text{obs}}^{\text{c,e}}$	5.5	4.3	7.0	8.3	-				
8in	1.5	2.5	12.4	4.3	1.00 ^g				
8ina	1.2	3.6	13.3	4.8	0.00 ^g				
8in, J_{pwa}	1.5	2.5	12.4	4.3	-				
8in, $J_{\text{obs}}^{\text{c,e}}$	<0.5 ^h	2.4	12.5	n.r.	-				
8out	12.2	5.3	2.0	5.7	0.56 ^g			n.d.	0.57
8outa	12.0	5.8	2.1	5.7	0.44 ^g				
8out, J_{pwa}	12.1	5.5	2.0	5.7	-				
8out, $J_{\text{obs}}^{\text{c,e}}$	12.1	5.1	n.r.	n.r.	-				
9ain	1.5	2.8	9.8	9.9	1.00 ^g				
9aina	1.1	3.7	8.9	12.4	0.00 ^g				
9ain, J_{pwa}	1.5	2.8	9.8	9.9	-				
9ain, $J_{\text{obs}}^{\text{c,e}}$	1.5	3.1	n.r.	n.r.	-				
9bout	12.3	6.9	1.2	7.9	0.89 ^g			n.d.	n.d.
9bouta	11.8	7.2	0.5	7.1	0.11 ^g				
9bout, J_{pwa}	12.2	7.0	1.1	7.8	-				
9bout, $J_{\text{obs}}^{\text{c,e}}$	12.2	6.4	n.r.	n.r.	-				
10ain	1.5	2.5	12.4	4.3	1.00 ^g				
10aina	1.1	3.8	13.3	4.7	0.00 ^g				
10ain, J_{pwa}	1.5	2.5	12.4	4.3	-				
10ain, $J_{\text{obs}}^{\text{c,e}}$	1.6	2.4	12.3	3.9	-				
10bout	12.2	5.3	2.0	5.8	0.76 ^g			n.d.	n.d.
10bouta	12.0	6.0	2.1	5.7	0.24 ^g				
10bout, J_{pwa}	12.2	5.5	2.0	5.8	-				
10bout, $J_{\text{obs}}^{\text{c,e}}$	12.5	5.3	1.5	5.3	-				

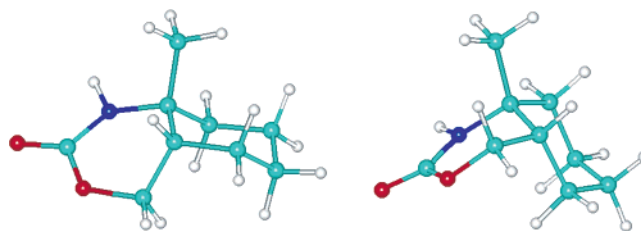
n.r., not resolved; n.d., not detected/determined; J_{obs} , the experimentally observed coupling; J_{pwa} , the population-weighted averaged coupling based on X derived from $\Delta G_{\text{m,calc}}^{\circ}$. The estimated error for the calibrated coupling constants is 0.5 Hz which is twice the standard error. ^a Boltzmann populations calculated using $\Delta G_{\text{m,calc}}^{\circ}$ values (see computational method section). ^b Mole fractions of the *N-out* conformations calculated with the aid of the experimentally measured¹⁸ coupling constants using calculated coupling constants as model values. Only the α -proton couplings were used because in these cases as the relative error of the couplings is less significant than with the β -protons. ^c From ref 18. ^d Mole fractions of the *N-out* conformations calculated with the aid of the experimentally measured¹⁸ coupling constants using the experimentally measured¹⁸ coupling constants of structurally well-defined systems as model values. $J_{\text{H4a,H4}\beta}$ or $J_{\text{H4a,H4}\alpha}$ was used for the calculation. ^e The coupling constants were measured from spectra recorded in CDCl_3 solution 25 °C except for **8in** and **8out** which were recorded in CD_2Cl_2 at solution at -50 °C. ^f Values estimated using the experimental¹⁸ *N-in*:*N-out* ratio of 63:37 and the calculated coupling constants of the lowest energy *N-in* and *N-out* conformations **7in7a** and **7out7a**. ^g Mole fractions for each of the pairs of axial/equatorial ring conformers (*N-in* or *N-out*), the mole fractions for the complete systems are 0.93:0.00:0.04:0.03, 0.94:0.00:0.05:0.01, and 0.96:0.00:0.03:0.01 for compounds **8**, **9**, and **10**, respectively. ^h A rough estimate only due to line broadening resulting from poor homogeneity.

Table 4. Selected Calculated and Experimental^a ¹H Chemical Shifts (in ppm) for Compounds 1–10

structure	H-4a	H-4α	H-4β	H-5α	H-5β	NH/NMe	X ^b
1in7	1.79	3.85	4.08	1.94	1.90	3.28	0.59
1in6	1.74	3.80	3.97	1.96	1.74	3.65	0.20
1out7	1.93	3.57	3.85	1.20	1.91	3.70	0.13
1out6	2.15	3.58	3.92	1.39	1.75	3.41	0.08
1 , δ _{pwa}	1.83	3.78	4.02	1.80	1.86	3.42	
1 , δ _{obs}	2.02	4.25	4.09	1.77	1.95	5.9	
2in	1.22	3.72	4.47	1.75	1.43	3.36	0.88
2out	1.72	4.28	3.71	1.57	1.73	3.70	0.12
2 , δ _{pwa}	1.28	3.79	4.38	1.73	1.47	3.40	
2 , δ _{obs}	1.65	4.06	4.47	1.59	1.62	6.3	
3in	1.29	3.78	4.40	1.57	1.44	5.70	0.87
3out	1.75	4.18	3.76	1.57	1.72	5.91	0.13
3 , δ _{pwa}	1.35	3.83	4.32	1.57	1.48	5.73	
3 , δ _{obs}	1.77	4.17	4.53	1.49	1.66	8.4	
4in7	1.82	3.82	4.10	1.97	1.87	2.61	0.40
4in6	1.78	3.72	3.95	1.96	1.71	2.88	0.23
4out7	2.05	3.50	3.83	1.24	1.93	2.66	0.37
4out6	2.05	3.50	3.84	1.24	1.93	2.66	0.00
4 , δ _{pwa}	1.90	3.68	3.97	1.70	1.86	2.69	
4 , δ _{obs}	2.11	3.96	4.17	1.69	1.96	2.87	
5in	1.27	3.63	4.49	1.77	1.44	2.89	0.90
5out	1.70	4.19	3.66	1.57	1.76	2.73	0.10
5 , δ _{pwa}	1.31	3.69	4.41	1.75	1.47	2.87	
5 , δ _{obs}	1.71	3.97	4.43	1.66	1.64	2.90	
6in	1.32	2.79	3.71	1.72	1.34	3.61	0.97
6out	1.87	3.62	2.89	1.50	1.77	3.66	0.03
6 , δ _{pwa}	1.34	2.81	3.69	1.71	1.35	3.61	
6 , δ _{obs}	1.65	2.99	3.63	1.57	1.52	6.3	
7in7a	1.37	3.62	3.62	1.68	2.31	2.07	0.94
7ina7a	1.37	3.71	3.78	2.17	1.82	2.65	0.00
7in6	1.76	3.54	3.61	1.15	1.70	2.08	0.02
7out7a	1.72	3.01	3.59	1.80	0.99	2.11	0.04
7out6	1.62	3.31	4.26	1.71	1.78	2.04	0.00
7 , δ _{pwa}	1.39	3.59	3.62	1.67	2.25	2.07	
7 , δ _{63:37} ^c	1.50	3.39	3.61	1.72	1.82	2.08	
7 , δ _{obs}	1.69	3.56	3.76	1.75	1.75	2.20	
8in	0.92	3.35	3.93	2.48	1.21	2.01	1.00
8ina	0.92	3.52	4.03	2.03	1.43	2.78	0.00
8in , δ _{pwa}	0.92	3.35	3.93	2.48	1.21	2.01	
8in , δ _{obs}	1.09	3.35	3.88	2.03	1.25	1.91	
8out	1.66	3.65	3.48	1.27	1.78	2.10	0.56
8outa	1.99	3.72	3.48	1.19	1.61	2.51	0.44
8out , δ _{pwa}	1.84	3.69	3.48	1.23	1.68	2.28	
8out , δ _{obs}	1.87	3.69	3.51	1.18	1.57	2.27	
9ain	1.38	3.59	3.72	2.33	1.69	2.07	1.00
9aina	1.33	3.73	3.86	2.10	1.79	2.45	0.00
9ain , δ _{pwa}	1.38	3.59	3.72	2.33	1.69	2.07	
9ain , δ _{obs}	1.53	3.75	3.81	2.15	1.69	2.09	
9bout	1.77	3.08	3.56	1.02	1.80	2.12	0.89
9bouta	1.80	3.17	3.68	1.10	1.72	2.31	0.11
9bout , δ _{pwa}	1.77	3.09	3.57	1.03	1.79	2.14	
9bout , δ _{obs}	1.94	3.21	3.74	1.13	1.79	2.22	
10ain	0.95	3.32	4.02	2.46	1.22	2.02	1.00
10aina	0.91	3.53	4.10	1.94	1.40	2.57	0.00
10ain , δ _{pwa}	0.95	3.32	4.02	2.46	1.22	2.02	
10ain , δ _{obs}	1.15	3.42	4.05	2.31	1.33	2.01	
10bout	1.69	3.73	3.46	1.29	1.78	2.08	0.76
10bouta	1.93	3.80	3.51	1.20	1.60	2.31	0.24
10bout , δ _{pwa}	1.87	3.78	3.50	1.22	1.64	2.14	
10bout , δ _{obs}	1.94	3.84	3.63	1.33	1.70	2.24	

δ_{obs}, the experimentally observed chemical shift; δ_{pwa}, the population-weighted averaged chemical shift based on the mole fraction, X. ^a Experimental data taken from ref 18. Chemical shifts were measured from spectra recorded in CDCl₃ solution at 25 °C except for **8in** and **8out** which were recorded in CD₂Cl₂ at solution at –50 °C. ^b Mole fraction derived from ΔG_{m,calc}^o (see the computational method section for the definition of ΔG_{m,calc}^o). ^c Values estimated using the experimental *N-in*:*N-out* ratio of 63:37 and the calculated chemical shifts of the lowest energy *N-in* and *N-out* conformations **7in7a** and **7out7a**.

°C; at ambient temperature, time-averaged spectra were observed and thus the measured coupling between H-4a and H-5ax is not the typically large diaxial value because of the contribution

**Figure 3.** Optimized conformations for **2**: **2out** (left) and **2in** (right). The corresponding conformations of **3** and **5** are very similar to these.

of the *N-out* conformation to the conformational equilibrium dominated by the preferred *N-in* conformation.¹⁸ The two conformers were readily identified at the lower temperature by the coupling constants of the H-4 and H-4a protons. Integration of these respective signals (and also the NH protons for compounds **2** and **3**) yielded their conformer ratios, 90:10 for both **2** and **3** and 88:12 for **5** at –95 °C). In all cases, the disposition of the N-substituent was assessed as equatorial.

Despite numerous attempts, only two conformers for each compound were obtained from the optimizations performed on compounds **2**, **3**, and **5** (Table 1). The structures of the *N-in* and *N-out* conformations of **2**, which are very similar to the conformations of **3** and **5**, are shown in Figure 3. Noteworthy is the fact that deviations of the heterocyclic ring away from a chair conformation are highly prevalent, distorting the dihedral angles between H-4a and the two H-4s and resulting in marked changes to the pertinent coupling constants. The heteroring is very flat in each case due to the lactamide moiety and the N-substituent was found to be equatorially oriented. It can be estimated from the relative energies of the conformers (Table 1) that the *N-in* sofa-like conformation^{54–57} is predominant in each case and that the contribution of the *N-out* conformation to the equilibrium varies between 10 and 13% (Table 3). The contribution of the *N-out* conformation estimated using the calculated coupling constants was 19% on average in each case (Table 3). The calculated percentages are in good agreement with the contributions estimated¹⁸ experimentally (10–12% at low temperatures; 20–25% at 25 °C), only the energy differences being slightly overestimated theoretically.

From the previous study,¹⁸ the *O-in* conformation was determined to be the predominant conformer for compound **6** which, furthermore, was the sole conformation in solution since there was scant evidence for the presence of any other conformation upon lowering the temperature. The NH proton was assessed as being equatorially oriented by previous NOE measurements. Computationally, only two conformers were found for **6** (Table 1 and Figure 4) which are similar to the conformers of **2** depicted in Figure 3. *O-in* is overwhelmingly predominant, as inferred by its lower relative energy and this is in accord with experimental observations (Table 3) whereby the contribution of the *O-out* conformation was estimated as either 0% or 7%, depending upon which particular experimental coupling was evaluated with the calculated couplings. Based on the calculations, the coupling constant assignments reported¹⁸

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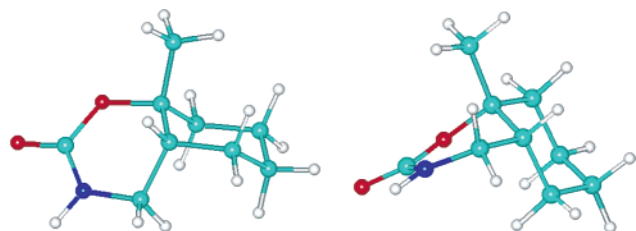


Figure 4. Optimized conformations for **6**: **6out** (left) and **6in** (right).

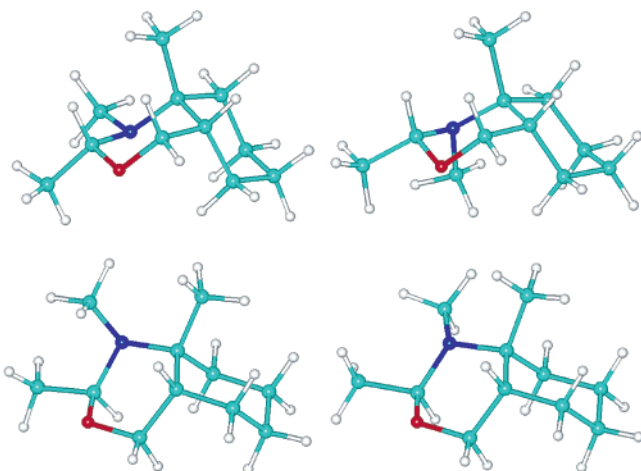


Figure 5. Most stable optimized conformations of the epimers of **10**: **10ain** (top left), **10aina** (top right), **10bouta** (bottom left), and **10bout** (bottom right). The corresponding conformations of **8** are very similar to these.

for H-4 α (denoted in that work as H-4eq) are incorrect—as a result of the crowded spectral region in which the pertinent signals reside—and thus the values of $J_{H4\alpha, NH}$ and $J_{H4\alpha, H4a}$ have been interchanged (now 4.2 and 1.7 Hz, respectively).

For **3**, a coupling constant of 1.4 Hz for $^4J_{H4a, NH}$ was measured¹⁸ experimentally (but not explicitly reported) on the NH signal. Calculations provided a value of 2.0 Hz for this coupling constant for the *N-in* conformation with an equatorial NH proton which agrees well with the experimental value and which can be anticipated given a favorable geometry for w-type coupling. For **2** and **6**, calculations of the corresponding coupling provided values of 2.0 and 1.2 Hz, respectively, but they were not, as is generally the case for the signals of NH protons, resolved experimentally for these particular samples due to the inherent breadth of the NH signal obscuring any coupling that was present.

Preferred Conformations and Coupling Constants for Compounds 8, 9, and 10. For compound **8**, it was possible to spectroscopically freeze out the equilibrium and the ratio of the two conformers (see Figure 5) was determined to be 3:4 (*N-in*:*N-out*) at -60 °C in $CDCl_3$ and 3:2 (*N-in*:*N-out*) in CD_2Cl_2 .¹⁸ The shifting of the equilibrium by this extent when changing from $CDCl_3$ to CD_2Cl_2 is quite exceptional and reflects an extensive degree of solvation. The *N*-methyl group was found to be predominantly equatorially oriented with respect to the heteroring for both the *N-in* and the *N-out* conformations of **8**.¹⁸ Compounds **9** and **10** are distinct from the other members of the set in that they exhibit slow epimerization with respect to the C-2 configuration in solution.¹⁸ Thus, in addition to conformational equilibrium there is also a chemical equilibrium in effect, but for the sake of simplicity and the fact that the chemical interconversion between the **9a** (**10a**) and **9b** (**10b**)

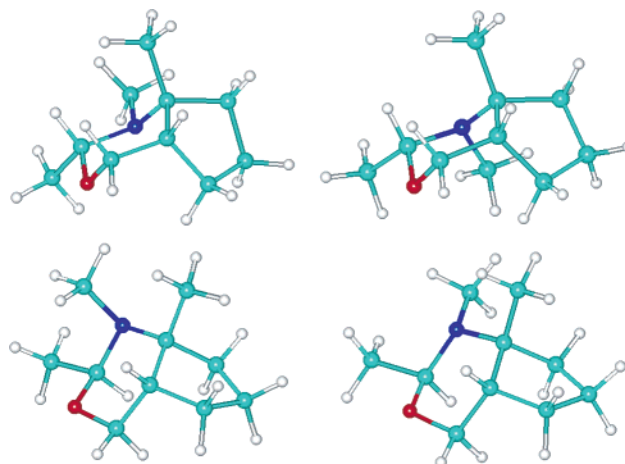


Figure 6. Most stable optimized conformations of the epimers of **9**: **9ain** (top left), **9aina** (top right), **9bouta** (bottom left), and **9bout** (bottom right).

epimers is comparatively slow (equilibration requires several hours at room temperature), the two epimers **a** and **b** were treated as separate systems. For the **9a** (**10a**) epimer, the *N-in* conformer dominated and for the **9b** (**10b**) epimer, the *N-out* conformer dominated, i.e., the C-2 methyl is equatorially oriented in both of the predominant *N-in* and *N-out* conformations adopted by the two epimers of **9** and **10** (see Figures 6 and 5 for **9** and **10**, respectively). At equilibrium, the observed ratio of the **9ain** and **9bouta** epimers in $CDCl_3$ solution was ca. 4:3, and for **10ain** and **10bouta**, ca. 1:1.⁴⁹ Presumably inversion at C-2 occurs by a ring opening mechanism, as postulated earlier by Szakonyi et al.²⁵ In fact, the *N-in*/*N-out* conformational equilibrium is completely biased for each of the two epimers of **9** and **10** and there was no evidence for the presence of a minor amount of the other ring-inversion conformer, **9/10aout** and **9/10bin**, in either epimer and the only additional dynamic process that occurs is N-inversion. The observed coupling constants therefore served¹⁸ previously as model values for evaluating the position of the conformational equilibrium in compounds **2**, **3**, **5**, and **7**. The *N*-methyl for the *N-in* conformations of **9ain** and **10ain** was also assessed¹⁸ as being equatorial with respect to the heteroring, whereas the *N*-methyl was assessed¹⁸ to be in an axial orientation with respect to the heteroring in the *N-out* conformation of the epimers.

Computationally, the *N-in* chair-chair (benzoxazines **8** and **10**) or chair-envelope (cyclopenta[*d*][1,3]oxazine **9**) conformation with an equatorial *N*-methyl (see Figures 5 and 6 and Table 1) was determined to be the most energetically stable structure for each of the compounds **8**, **9a**, and **10a**, and dominantly so. For **9a** and **10a**, the calculated energies indicated them to be highly biased systems with respect to ring inversion, i.e., the conformations **9aout** and **10aout**, were energetically insignificant. The axial orientation of the *N*-methyl in the *N-in* form is also highly disfavored rendering its contribution insignificant to the conformational equilibrium of **8** and the N-inversion process in the epimers of **9a** and **10a**. Similarly for **9b** and **10b**, the calculated energies indicated them also to be highly biased systems (*N-out* favored) with respect to ring inversion, i.e., the conformations **9bin** and **10bin**, were energetically insignificant. However, for the *N-out* conformer/epimers, the equatorial orientation of the *N*-methyl is energetically favored over the axial orientation in contrast to the postulation based on the

experimental observations for **9b** and **10b** (although in all three cases, **8**, **9b**, and **10b**, both *N*-invertomers are significant population-wise). Because of the close similarity in the calculated couplings for the two *N*-methyl orientations in the *N*-out conformations, one or other orientation cannot be ruled out on this basis and it is only the chemical shifts that enable this distinction (vide infra). The measured and the calculated coupling constants for **8**, **9**, and **10** were found to be in good agreement (Table 3), however, the calculated energy differences of **8in** and **8out**, **9ain** and **9bout**, and **10ain** and **10bout**, are inconsistent with the experimental observations.

Preferred Conformations and Coupling Constants for Compounds 1, 4, and 7. In the previous study,¹⁸ compounds **1** and **4** were experimentally determined to essentially adopt only one conformation in solution since there was scant evidence for the presence of any other conformation upon lowering the temperature. The *N*-in conformation was determined to be the predominant conformer for these compounds in solution. Although the signals in the spectra of **7** in either CDCl₃ or CD₂-Cl₂ solution broadened significantly upon lowering the temperature, only an average spectrum was observable at the lower limit of the temperature range. In a 1:3 mixture of CDCl₃ and (CD₃)₂CO, subspectra of two conformers started to decoalesce at temperatures below -100 °C, but acceptably sharp signals could not be obtained. The ratio of the two conformers at -110 °C was roughly estimated as 85:15. In the spectrum of the minor conformer, the presence of two large couplings (ca. 11.5 Hz) for one of the H-4 protons indicated it to be an *N*-out conformation and therefore the predominant conformer was an *N*-in conformer. The position of the conformational equilibrium for **7** at 25 °C was also estimated using model values for the vicinal coupling constants obtained from the *N*-in and *N*-out conformations of **9ain** and **9bout** (based on couplings $J_{H4a,H4\alpha}$ and $J_{H4a,H4\beta}$, vide supra), resulting in an approximate ratio for the *N*-in:*N*-out conformers of ca. 63:37, respectively, at 25 °C. The NH or *N*-methyl group was assessed¹⁸ as being equatorially oriented with respect to the heteroring in compounds **1**, **4**, and **7**.

The conformational searches yielded four nearly degenerate conformations initially for each of **1** and **4**, although thermal corrections (i.e., calculation of $\Delta G_{m,calc}^{\circ}$) did result in the exclusion of one of the conformations of **4** (see Table 1). An *N*-in conformer appeared to be the most stable in each case, although marginally so for **4** where an *N*-out conformer was close in energy. The resulting conformations lie reasonably close to each other on the potential energy surface and the optimized structures, being rather flexible (see Figure 7 for the conformations of **1**), easily interconvert into each other and suggest why it was not possible to freeze out the different conformers at low temperature. The oxazine ring in the *N*-in conformers of **1** and **4** was not found to be in a sofa conformation as could have been expected on the basis of the results of the corresponding cyclohexane-fused analogues, but instead it is in a flat twist-boat-type conformation (Table 1). A cyclopentane ring fused to an oxazine ring forms a structure that is more sterically strained in comparison to a cyclohexane-fused system, forcing the heteroring into a more twisted conformation to relieve some of this strain. In contrast to the low-temperature NMR measurements¹⁸ on **7** where only two forms, the *N*-in and *N*-out conformers, appeared to separate out, the conformational search

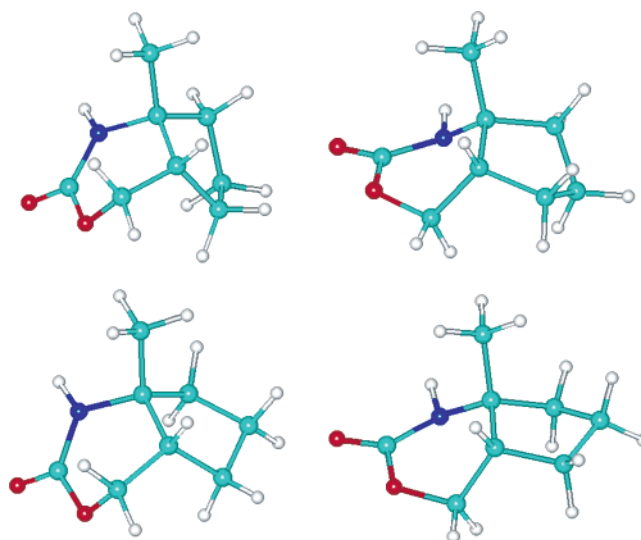


Figure 7. Optimized conformations for **1**: **1in7** (top left), **1in6** (bottom left), **1out6** (top right), and **1out7** (bottom right). The conformations of **4** are very similar to those of **1**, except that in the **4out6** C-6 lies below the plane of the other carbons in the cyclopentane ring whereas for **1out6** it lies above the plane.

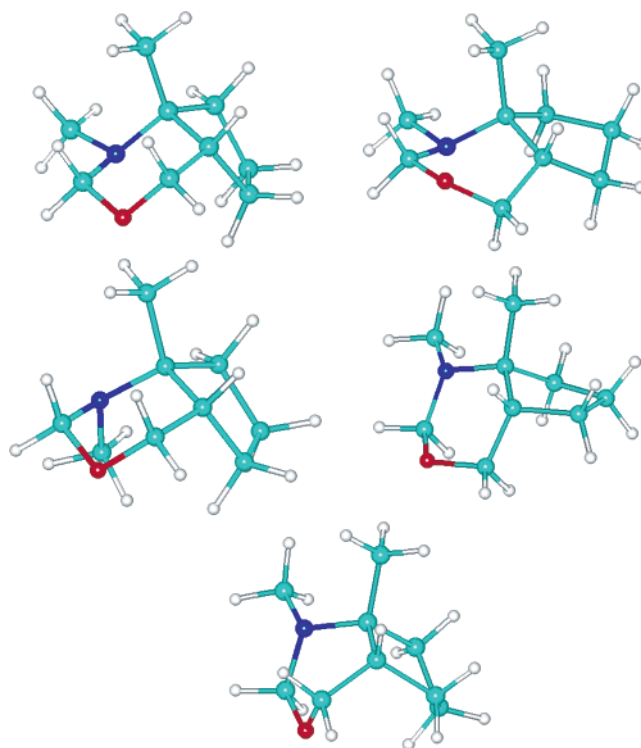


Figure 8. Optimized conformations for **7**: **7in7a** (top left), **7in6** (top right), **7ina7a** (middle left), **7out7a** (middle right), and **7out6** (bottom).

yielded a total of five structures (Figure 8). Of these, **7out6** and **7ina7a**,⁴⁹ are insignificant energetically as implied by the $\Delta G_{m,calc}^{\circ}$ values (Table 1) obtained from thermochemical calculations.

Population-weighted averages of the calculated coupling constants were evaluated for **1**, **4**, and **7** (Table 3) and comparison with the experimental values showed surprisingly good agreement for **1** and **4**, but not **7**. However, the accuracy of the experimentally determined couplings for those signals that reside in crowded spectral regions must be treated with due caution, especially the protons H-5 α and H-5 β .¹⁸ If the

experimentally determined ratio of the *N-in* and *N-out* conformations at 25 °C for **7** (63:37, respectively) is used for estimating the population-weighted averaged coupling constants, and the calculated values of the lowest energy forms of the corresponding conformations are used, **7in7a** and **7out7a**, the agreement between the population-weighted averaged couplings constants and the experimental values is very good (Table 3). This indicates that the accuracy of the computational $\Delta G_{m,calc}^{\circ}$ values is not always reliable in every case but that the accuracy of the calculated coupling constants is good. Solvent effects could, as a consequence of the small energy differences, significantly influence the population distribution of the contributing conformers but would add an unwieldy dimension to the calculations if they were included. In the case of the six-membered rings, the solvent effect was assumed to have a negligible effect on the coupling constants and this is borne out by the good agreement between the experimental and the calculated values.

Thus, the previous conclusions for **1** and **4** that they are heavily biased systems, drawn on the fact that it was not possible to freeze out the conformers, are overstatements. With several contributing forms—and rapid interconversion between them—it is not always possible to freeze out the forms as it is just too experimentally demanding. To separate such a mixture requires implausibly low temperatures or not-yet-available magnetic field strengths, and in any event, the resulting spectra would be extremely complex. Nonetheless, in both cases, the *N-in* conformers provide, as a combination, a substantial predominance of the generalized *N-in* conformation, and it cannot be construed that the experimental observations do not match with the theoretical predictions, as indeed the coupling constants suggest entirely the opposite, that the systems have in fact been well modeled.

Chemical Shift Calculations. From Table 4, it was readily adjudged that the calculated chemical shifts are not as good probes for approximating the ring-inversion conformational equilibrium as the coupling constants are. (Although clearly this is not due to a poor correlation as linear regression analysis provided an R^2 value of 0.9977 for the selected compounds used for the calibration.) With regard to the orientation of the N-substituent, not unexpectedly the calculation of the chemical shift of the NH protons given their labile nature was poor, and therefore, no stereochemical assessment of the NH protons can be made. The stereochemistry of the *N*-methyl group, however, was readily assessed based on the calculated chemical shifts. For structures **4**, **5**, **7**, **8in**, **9ain**, and **10ain**, the methyl group was previously assessed¹⁸ as equatorial, and the calculations are entirely consistent with this notion. Only for **8out**, where an equatorial disposition was previously assessed,¹⁸ did the calculations indicate that the two *N*-invertomers are of similar energy and that therefore both should be present in equitable amounts (Table 4). The limitations of the previous experimental work did not permit a quantitation of the *N*-invertomers, only the clear presence of one or the other and therefore the previous assessment was an overstatement. This is also the case for the *N-out* conformers **9bout**, and **10bout** where an axial orientation of the *N*-methyl was assessed yet there was also clear evidence, at least for **10b**, for the contribution¹⁸ of an equatorial *N*-methyl. Thus, a statement indicating the clear contribution of an axial *N*-methyl conformation to the time-averaged spectra would have

been more appropriate. For **10b**, the axial and equatorial dispositions are more equitable in energy in comparison to **9b** according to the calculations and indeed it was noted¹⁸ in the previous observations that the NOE between the *N*-methyl protons and H-4a indicative of an axial *N*-methyl-in **9b** was significantly weaker, an observation entirely consistent with the calculated mole fractions.

Finally, the comparison between the experimental and the calculated chemical shifts facilitated the confirmation of the correct assignment of the shifts and the reassignment of an incorrectly assigned pair of shifts for the *N-out* conformation of **8**, viz, the shifts of the H-5 α and H-5 β protons which were mis-assigned due to the crowded spectral region in which they reside. Similarly for the *N-in* conformation of compounds **4** and **9**, the assignment of the shifts for H-5 α and H-5 β have been interchanged. The correct assignment of the experimental chemical shifts and coupling constants are presented together with the calculated shifts and coupling constants in Tables 4 and 3, respectively.

Concluding Remarks

Quite clearly there are many factors which contribute to the final energy differences between the *N-in* and *N-out* conformers and hence the determination of the actual presence of more than one conformer is really a question of the limit of experimentation and the resources at hand, notably magnetic field strength. There is always, at some level, a contribution from energetically unfavored conformers and their quantification is bound by the constraints of the particular approach applied. The computational analysis on this set of compounds revealed them to be far more complex than was ever envisaged. The conformational changes, subtle or otherwise, mean that some of the couplings vary markedly for the “same” *N-in* or *N-out* heterocyclic ring conformation (e.g., **7**), yet it was possible in this study to obtain good agreement between experiment and theory. Slowing the rate of interconversion by lowering the temperature to enable the visualization of separate spectra for each conformer can become a self-defeating exercise as the contribution of the minor component is reduced in tandem with the reduction in temperature; calculating the contribution of each conformer to an observed averaged spectrum for a particular parameter (in this case $J_{H,H}$) is also heavily dependent on the availability and validity of correct model values. Model values are difficult to obtain for two main reasons: subtle and unexpected conformational changes can occur in either the model or the measured system; and attempting to lock the conformation by chemical derivitization introduces electronic and structural changes which then perturb the couplings, thus invalidating them to some degree. Previously,¹⁸ compounds **9** and **10** were used as model values, but these compounds adopt chair conformations for the heteroring which was rarely obtained as the heteroring conformation for compounds **1–7** (3 occurrences in 21 structures).

Thus, the contribution of computational analysis can be of immense value as shown here by how easily the conformation of a ring can change and furthermore, the results presented here imply that the now-accessible, chemically accurate calculation of J will become an important tool for conformational analysis. If the energies of the contributing structures can be accurately modeled, then the population-weighted averaged couplings can provide extremely accurate results and for pure conformational

changes in this study (compounds **1–6**), correctly calculated energy differences were indeed obtained and good agreement resulted for the coupling constants. Inexplicably though, when C-2 epimerization was involved, i.e., compounds **7–10** (note that epimerization can also occur for **7** and **8** but structural differences do not result), calculated mole fractions reflective of the experimentally observed values were not able to be obtained. This had little practical bearing for compounds **8–10** where the systems were either totally biased with respect to the *N-in/N-out* ring inversion (**9** and **10**) or the conformers could be spectroscopically frozen out (**8**). Although solvent effects were not taken explicitly into account in this study, aside from their direct effect on the conformational equilibrium, they can

also potentially perturb the magnitude of *J*. Nonetheless, the approach holds much promise and represents a step forward in the conformational analysis of such systems whereby one particular perturbation (couplings emanating from one particular spin) can define the conformational structure, and more so, to assess the position of such conformational equilibria.

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