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Utility of calculated ^{13}C NMR chemical shifts in differentiating conformational isomers: a study of metal-complexed and uncomplexed bispidines

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Received (in Corvallis, OR, USA) 22nd February 2002, Accepted 8th May 2002
First published as an Advance Article on the web 19th June 2002

Calculated ^{13}C NMR chemical shifts were key to assigning the structures of the conformational forms of complexed and uncomplexed bispidine derivatives

Quantum chemical calculations of molecular properties have proven to be powerful tools to supplement and facilitate the interpretation of experiments and for systematic studies where experiments are not feasible. Among the various properties that can be computed, NMR chemical shieldings and chemical shifts are very useful. Calculated chemical shifts have facilitated the assignment of experimental spectra in numerous studies.[1,2] In this study we demonstrate that calculated chemical shifts can be used to distinguish between two conformational isomers in the flexible bicyclic bispidine compounds **1**, **2** and **3**.

We began our efforts with *N,N′*-dimethyl-2-*exo*-methylbispidine **1** (Fig. 1).[3] NMR measurements were taken in toluene-d_8 at 303 K using a Bruker AMX-500 spectrometer. The coupling constants of H3 in **1** (δ = 2.32 ppm) are 6.5 Hz (CCH_3) and 2.5 Hz (CCH) and in **1·ZnEt$_2$** (δ = 3.18 ppm) the corresponding values are 6.7 Hz and 1.7 Hz. Upon comparison with the calculated coupling constants[4] (**1-out**: 6.2, 3.0 Hz; **1-in**: 6.2, 1.4 Hz), we conclude that **1** undergoes a conformational change from **1-out** in its uncomplexed form to **1-in** upon the addition of $ZnEt_2$. Comparison of the ^{13}C NMR spectra (Table 1) of these two forms showed that a significant change occurs in the chemical shift value of C10. The δ value of C10 is shielded by ~ 10 ppm upon addition of $ZnEt_2$. This may be attributed to the axial orientation of the methyl group (C10) in one form *vs.* the equatorial orientation in the other form.[5] The δ values of the remaining carbon atoms change by 1 to 4 ppm.

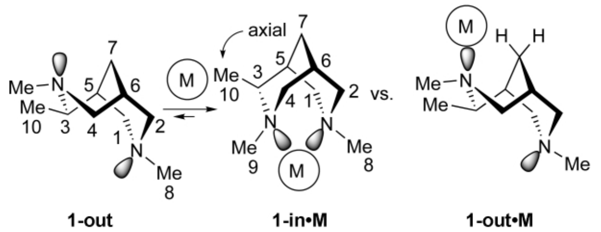


Fig. 1 **In** and **out** conformers of **1**.

Table 1 Calculated[a] and experimental[b] ^{13}C NMR shifts (ppm) for **1** and **1·M** (M = $ZnMe_2$ for calculation and $ZnEt_2$ for NMR measurement)

Entry	**1-out** Calcd.	**1** Expt.	**1-out·M** Calcd	**1-in** Calcd.	**1 + M** Expt.	**1-in·M** Calcd
C1	60.3	61.0	59.2	61.8	59.8	60.0
C2	60.6	60.1	60.0	60.9	56.9	58.7
C3	61.1	61.2	65.1	61.3	60.6	58.3
C4	59.0	57.2	58.6	54.4	52.5	52.3
C5	41.8	37.5	40.7	40.6	36.3	40.7
C6	33.4	29.1	32.6	35.6	30.2	35.0
C7	27.8	25.1	30.3	28.6	25.9	28.8
C8	45.0	46.5	44.4	44.8	46.6	44.4
C9	40.6	42.4	40.0	41.3	42.3	40.9
C10	**23.5**	**20.0**	20.3	10.2	**10.7**	**12.3**

[a] Chemical shift values were obtained relative to isotropic shielding of TMS as calculated at the same level. [b] Spectra were taken in toluene-d_8.

The ^{13}C chemical shifts (δ) of **1**–**3** were computed using the GIAO-B3LYP/6-31+G(d,p) method[6] (Table 1, 3, 4).[7] The diagnostic chemical shift change for C10 is reproduced by the calculations (23.5 ppm for **1-out**; 12.3 ppm for **1-in·ZnMe$_2$**). Comparison of these calculated values with those from the NMR spectra (20.0 ppm for **1**; 10.7 ppm for **1·ZnEt$_2$**) confirms that uncomplexed **1** occupies the **out** conformation. Upon addition of metal, **1** switches to the **in** conformation. Comparison of calculated δ values for **1-out** and **1-out·ZnMe$_2$** shows that coordination alone does not account for the observed chemical shift differences. These studies indicate that the δ values of C10 can be used to differentiate the **in** and **out** conformers of **1**. Overall, the ^{13}C NMR chemical shifts calculated using the structures we propose on the basis the ^{1}H NMR coupling constants correlate well with the measured NMR chemical shifts.

These results are further supported by the relative energies of uncomplexed **1-out** and **1-in** (Table 2). As noted in earlier studies of sparteine and related compounds,[8] molecular mechanics calculations overestimate the stability of the **in** conformers and are unreliable for these compounds. HF, DFT, and MP2 calculations do corroborate that **1-out** is more stable.

We had synthesized **2** and **3**, substituted analogues of **1**, and wished to determine if these compounds undergo conformational changes upon addition of metal species. In an earlier report[9] the conformation of uncomplexed **2** was assigned as **2-out** based on the chemical shift equivalence of the H9 hydrogens. In our studies, we found that the backbone coupling constant pattern (*cf.* **1** above) in the high resolution NMR spectrum of uncomplexed **2** is more consistent with the structure of **2-in** (Fig. 2). The coupling constants of H3 (δ = 2.85 ppm) for **2** are 6.4 Hz (CCH_3) and 1.7 Hz (CCH). The corresponding calculated values are: **2-in** 6.2, 1.4 Hz and **2-out** 6.2, 2.9 Hz. At this juncture, theoretical chemical shift calculations were used to confirm these assignments, since the validity of such calculations had been demonstrated for **1**. The calculated and experimental ^{13}C shift values of **2** are given in Table 3.

The measured chemical shift value for C10 of **2** (14.9 ppm) in its uncomplexed form is close to the calculated value for **2-in** (11.5 ppm). This provides additional evidence that **2** adopts the

Table 2 Calculated relative energies (kcal mol^{-1}) for **1**–**3**

	1-out	**1-in**	**2-out**	**2-in**	**3-out**	**3-in**
Amber[a]	3.5	0.0	3.4	0.0	2.2	0.0
HF/6-31G(d)[b]	0.00	0.60	1.39	0.00	0.97	0.00
B3LYP/6-31G(d)[b]	0.00	0.80	0.97	0.00	0.85	0.00
MP2/6-31G(d)[b]	0.00	1.81	1.27	0.00	0.09	0.00

[a] Similar results obtained with MM2, MM2($CHCl_3$), MMFF, and MMFF($CHCl_3$). [b] Full geometry optimization.

DOI: 10.1039/b201950g

in conformation. This assignment is further supported by the lack of change in the ^{13}C spectrum upon addition of $LiClO_4$. Since **2** already occupies the N-in form, the addition of metal did not perturb the conformational form, in contrast to **1**.

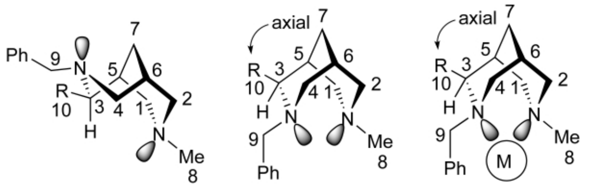
We propose that uncomplexed **2** favors **2-in** due to a destabilizing gauche interaction between the *N*-Bn and the equatorial C3 Me of **2-out** which supersedes the 1,3-diaxial interaction imposed by the axial C3 Me in **2-in**. In contrast, **1-out** is more stable than **1-in**, because the **1-out** *N*-Me gauche interaction is smaller than the **1-in** axial C3 Me interaction. HF, DFT, and MP2 energies (Table 2) support this hypothesis.[10] Reasoning that a larger C3 substituent would destabilize the **in** C3 axial orientation, offsetting the **out** *N*-Bn gauche interaction, the C3 ethyl-substituted analog **3** was synthesized with the aim of stabilizing the **out** form of the uncomplexed compound. MP2 calculations for **3** indicated that the **out** form of **3** should be more stable compared to that of **2**.[10]

As opposed to **1** and **2**, the ^{1}H NMR spectra of compound **3** did not permit differentiation of the **in** and **out** conformers. The diagnostic ^{1}H NMR coupling constants, analogous to those used to assign the related **1-out** and **1-in·M**, were obscured by other signals. Due to the change of the C3 substituent from Me (**2**) to Et (**3**), the values of the ^{13}C NMR shifts could not be directly compared to assign **3**. As such, calculations (Table 4) were employed to assign the structures of **3**. As noted for **1** and **2**, the chemical shift of the C10 carbon atom was found to be diagnostic. Comparison of the observed chemical shift of C10 for **3** (23.6 ppm) with the calculated **3-out** (31.1 ppm) and **3-in** (18.8 ppm) suggests that neither conformer is dominant in the uncomplexed form. In contrast, the observed C10 chemical shift of **3·ZnEt₂**, (17.2 ppm) is close to the calculated value of **3-in·ZnMe₂** (19.7 ppm). These results imply that compound **3** is a mixture of **3-in** and **3-out** (~ 1 : 1)[11] in toluene-d_8 and that this mixture shifts completely to **3-in** upon the addition of Et_2Zn.

Table 3 Calculated[a] and experimental[b] ^{13}C NMR shifts (ppm) for **2**

Entry	**2-out** Calcd.	**2-in** Calcd.	**2** Expt.	**2+LiClO₄** Expt.
C1	60.1	62.2	61.4	61.0
C2	60.7	60.2	60.9	60.0
C3	60.3	63.0	58.4	58.2
C4	54.2	49.7	52.7	51.8
C5	42.5	41.4	37.0	37.3
C6	33.1	35.3	30.0	30.4
C7	28.3	28.6	25.2	26.2
C8	45.0	44.5	46.5	46.1
C9	58.6	60.7	59.3	60.1
C10	**23.7**	**11.5**	**14.9**	**12.8**

[a] Chemical shift values were obtained relative to isotropic shielding of TMS as calculated at the same level. [b] Spectra were taken in acetone-d_6.



R = Me **2-out**
R = Et **3-out**

2-in
3-in

2-in•M
3-in•M

Fig. 2 In and **out** conformers of **2** and **3**.

Table 4 Calculated[a] and experimental[b] ^{13}C NMR shifts (ppm) for **3** and **3·M** (M is $ZnMe_2$ for calculation and $ZnEt_2$ for NMR measurement)

Entry	**3-out** Calcd.	**3-in** Calcd.	**3** Expt.	**3-out·M** Calcd	**3-in·M** Calcd	**3 + M** Expt.
C1	60.4	62.0	61.6	61.2	60.0	60.6
C2	60.3	60.1	61.0	60.9	58.0	60.4
C3	64.0	69.6	64.4	70.6	67.1	63.7
C4	54.3	50.4	53.1	55.5	51.2	52.3
C5	39.6	34.0	33.4	39.5	32.5	31.5
C6	33.3	35.1	29.2	31.4	34.6	30.2
C7	29.1	28.6	25.7	27.6	28.9	26.4
C8	44.9	44.7	46.5	44.8	44.7	46.5
C9	58.3	60.9	59.1	61.6	61.8	59.8
C10	**31.1**	**18.8**	**23.6**	**31.0**	**19.7**	**17.2**
C11	7.5	12.0	9.6	12.6	12.5	11.7

[a] Chemical shift values were obtained relative to isotropic shielding of TMS as calculated at the same level. [b] Spectra were taken in toluene-d_8.

In conclusion, we have shown that NMR chemical shifts calculated using quantum mechanical methods are useful in assigning the structures of different conformational forms that arise in response to metal coordination. These calculations were key to demonstrating that bispidine **3** exists as a mixture of **3-in** and **3-out** forms in the absence of coordinating cation and as the **3-in** form in the presence of a such a cation. Bispidine **3** serves as the starting point for the construction of chemically controllable switches that allow introduction of various features by means of different nitrogen substitution patterns.

Financial support was provided by the National Institutes of Health (GM59945) and by the Petroleum Research Fund administered by the American Chemical Society. Computational support was provided by the NCSA. We thank Dr Ivan Keresztes for assistance with the NMR experiments.

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11 At low temperature (−120 °C), the two separate forms were not observed, indicating a low barrier of interconversion. Since broadening of some ^{13}C NMR peaks begins at −100 °C and most peaks are broadened at −120 °C, we estimate the interconversion barrier is approximately 5.0–6.5 kcal mol^{-1}.

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