

# $^1\text{H}$ and $^{13}\text{C}$ NMR Chemical shift assignments of a cyclopentane-fused *cis*-azetidinone (*cis*-azabicyclo[3.2.0]heptan-7-one). A theoretical and experimental investigation

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**Dedicated to Professor Kalevi Pihlaja on the occasion of his 60<sup>th</sup> birthday**

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## Abstract

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR chemical shifts of cyclopentane-fused *cis*-azetidinone (*cis*-azabicyclo[3.2.0]heptan-7-one) were determined with the help of full spectral analysis. The geometry and electronic structure of the molecule were investigated at both the RHF and the B3LYP level with different basis sets. The NMR data were calculated by means of the GIAO, CSGT and IGAIM methods. All quantum-chemical calculations, including those of NMR data, were performed by *ab initio* level RHF and DFT methods. The geometry optimization resulted in an envelope-type conformation, while the four-membered heterocycle proved to be planar. Excellent agreement between the theoretical and experimental results was found for the RHF-level  $^1\text{H}$  chemical shifts and for the B3LYP-type  $^{13}\text{C}$  chemical shifts. The experimental spectra revealed equivalent methylene protons at position 5, indicating that the cyclopentane ring has a high degree of conformational freedom at this carbon.

**Keywords:** Proton and carbon chemical shifts, cyclopentane-fused *cis*-azetidinone, spectral analysis

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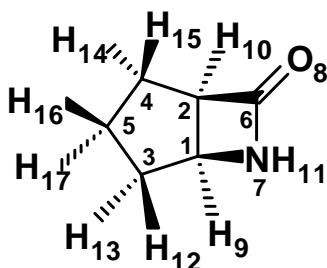
## Introduction

The calculation of NMR parameters is a recent, but extremely rapidly progressing area of quantum chemistry. During the past decade numerous *ab initio* methods have been developed,

implemented and tested, and several theoretical overviews<sup>1,2,3</sup> and routinely applicable implementations of methods are currently available.<sup>4</sup>

## Results and Discussion

The numbering of the atoms is illustrated in Figure 1. The numbering of the atoms does not correspond to the IUPAC nomenclature.



**Figure 1.** Numbering of the atoms.

The geometrical parameters computed are listed in Table 1. A comparison of the C1 - H16 and C1 - H17, or C2 - H16 and C2 - H17 bond lengths demonstrates that the most favoured conformation is of envelope type, with conformational freedom only at C5. These results are in accordance with the experimental data obtained by X-ray crystallography.<sup>5</sup>

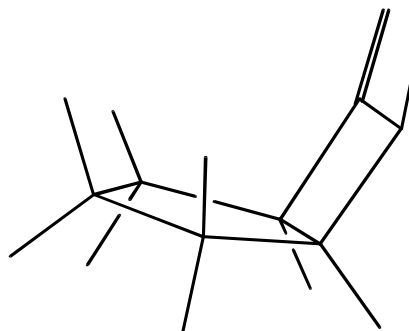
For comparison of the calculated and the experimental NMR data, the shielding tensors of the molecule in question were calculated with the standard Gaussian 94 program. The electronic structure of the molecule was treated by both RHF and B3LYP methods<sup>1</sup>, with four different basis sets [6-31G; 6-31G(d,p); 6-31 + G(d,p) and 6-311 + G(2d,2p)].

For both the RHF and the B3LYP method, with all basis sets, a geometry optimization was first performed for the molecule and for TMS. This means that we calculated eight geometries of the two molecules. To compare the *ab initio* methods, the NMR parameters were calculated by using the individual geometric parameters, despite these geometries being close to each other. The NMR shielding tensors were computed with three different methods: the GIAO (gauge-independent atomic orbital),<sup>6</sup> CSGT (continuous set of gauge transformations)<sup>7</sup> and IGAIM (individual gauges for atoms in molecules)<sup>8</sup> methods. Table 2 gives <sup>13</sup>C and <sup>1</sup>H chemical shifts. RHF/GIAO denotes the following procedure: the geometry minimized the corresponding RHF energy and the wave function was calculated at the RHF level, presuming calculation of the optimum geometry. The NMR data were calculated by the GIAO method. The notations B3LYP/GIAO, RHF/IGAIM, B3LYP/IGAIM, etc. are similar. The results are presented in Tables 1 and 2.

**Table 1.** Calculated and X-Ray crystallographic<sup>5</sup> data on bond lengths (pm) and bond angles

Bond lengths				Bond angles			
C1 – C2	156.8447	C4 - H15	108.2479	C2-C1-C3	106.5245	C6-N7-H11	131.1326
	155.8 <sup>5</sup>				106.5 <sup>5</sup>		
C1 – C3	152.7997	C5 - H16	108.4187	C1-C2-C4	106.538	C1-C3-H12	112.3597
	151.0 <sup>5</sup>				106.5 <sup>5</sup>		
C2 – C4	153.4251	C5 - H17	108.2671	C2-C4-C5	104.6694	C1-C3-H13	108.979
	151.7 <sup>5</sup>				104.7 <sup>5</sup>		
C3 – C5	154.1876	C6 - O8	121.2270	C1-C2-C6	85.8504	H12-C3-H13	107.5999
	152.0 <sup>5</sup>		122.1 <sup>5</sup>		85.9 <sup>5</sup>		
C4 – C5	154.3232	C6 - N7	136.4190	C4-C2-C6	114.7488	C2-C4-H14	109.4535
	151.8 <sup>5</sup>		133.3 <sup>5</sup>				
C2 – C6	153.2191	C1 - N7	147.7383	C2-C6-N7	91.8881	C5-C4-H14	110.1841
	152.3 <sup>5</sup>		147.7 <sup>5</sup>		91.9 <sup>5</sup>		
C1 – C7	147.7383	N7 - H11	99.1398	C2-C6-O8	135.4495	C2-C4-H15	111.9967
					135.4		
C6 – C7	136.4190	C1 - H16	286.1400	N7-C6-O8	132.6443	C5-C4-H15	112.8649
					132.6 <sup>5</sup>		
C1 – H9	107.9028	C1 - H17	337.7420	C2-C1-H9	117.713	H14-C4-H15	107.6512
C2 – H10	107.8964	C2 - H16	286.9662	C3-C1-H9	114.6181	C4-C5-H16	110.2287
C3 – H12	108.3261	C2 - H17	338.0017	C1-C2-H10	117.7412	C4-C5-H17	112.3055
C3 – H13	108.6152			C4-C2-H10	114.6478	H16-C5-H17	107.2265
C4 – H14	108.5055			C6-C2-H10	114.0263		

The energetically optimized *ab initio* structure of the compound in question is plotted in Figure 2.

**Figure 1.** *Ab initio* calculated geometry of cyclopentane-fused azetidinone.

Since these calculations are very computational time-consuming, the calculations on other cycloalkane-fused azetidinones will be performed on the basis of these results. The goal of this study is to find an appropriate theoretical method for the calculation of NMR parameters of small and medium-sized heterocycles.

## Experimental Section

**General procedures.** The purity of the compound was checked by thin-layer chromatography, by melting point determination and via its NMR spectra. The synthetic route is described elsewhere.<sup>9</sup>

The <sup>1</sup>H, <sup>13</sup>C and <sup>13</sup>C JMOD NMR spectra, and the z-PFG <sup>1</sup>H, <sup>13</sup>C HMQC 2D spectra were recorded on a Bruker Avance DRX 500 NMR spectrometer equipped with an inverse detection 5 mm broad band probehead operating at 500.13 MHz for <sup>1</sup>H and at 125.77 MHz for <sup>13</sup>C in 0.05-0.1 M CDCl<sub>3</sub> solutions at 300 K. The <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts were referenced to TMS: δ <sup>1</sup>H and <sup>13</sup>C (CH<sub>3</sub>)<sub>4</sub>Si = 0.00 ppm. The <sup>1</sup>H spectrum was iterated with the program PERCH<sup>16</sup> to calculate the experimental chemical shifts and indirect coupling constants. The <sup>13</sup>C NMR chemical shift assignments are based on <sup>13</sup>C DEPT-135 and z-PFG <sup>1</sup>H, <sup>13</sup>C HMQC experiments.

The *ab initio* geometry was fully optimized on an IBM PC (450 MHz Intel Celeron processor, 286 MB SDRAM) with Gaussian 94 software, using default basis sets: 6-31G, 6-31G(d,p), 6-31 + G(d,p), 6-311 + G(2d2p). The chemical shifts were calculated with Gaussian 94 software, using B3LYP/GIAO, B3LYP/IGAIM, B3LYP/CSGT, RHF/GIAO, RHF/IGAIM and RHF / CSGT methods.

**Table 2.** Calculated (RHF and B3LYP) and experimental <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts (ppm from TMS, δ<sub>TMS</sub> = 0.00) for 6-azabicyclo[3.2.0]heptan-7-one

Atom	Method	Basis set				Experi- mental
		6-31G	6-31G(d,p)	6-31 + G(d,p)	6-311 + G(2d,2p)	
C1	RHF/GIAO	53.0605	48.4429	48.5087	49.8566	<b>54.7</b>
	RHF/IGAIM	46.7490	48.5964	50.4247	51.0776	
	RHF/CSGT	46.7494	48.5965	50.4246	51.0780	
C1	B3LYP/GIAO	59.4630	55.9920	57.2521	59.4292	54.7
	B3LYP/IGAIM	54.2851	56.7379	59.0302	60.8086	
	B3LYP/CSGT	54.2855	56.7396	59.0302	60.8092	

Atom	Method	Basis set				Experi- mental
		6-31G	6-31G(d,p)	6-31 + G(d,p)	6-311 + G(2d,2p)	
C2	RHF /GIAO	57.3647	51.3501	51.8518	52.8747	<b>56.8</b>
	RHF /IGAIM	51.3824	50.8082	53.3657	53.3160	
	RHF /CSGT	51.3827	50.8077	53.3652	53.3162	
C2	B3LYP/GIAO	62.9666	58.9528	60.7473	63.2374	56.8
	B3LYP/IGAIM	56.0315	58.7540	62.4934	64.0135	
	B3LYP/CSGT	56.0317	58.7552	62.4929	64.0138	
C3	RHF /GIAO	29.8427	29.4386	30.0807	30.8006	<b>30.8</b>
	RHF /IGAIM	25.8596	27.8306	30.3740	31.5584	
	RHF /CSGT	25.8594	27.8301	30.3733	31.5581	
C3	B3LYP/GIAO	32.5933	32.4641	33.8236	34.7161	30.8
	B3LYP/IGAIM	28.7875	31.6795	34.2331	35.6604	
	B3LYP/CSGT	28.7869	31.6806	34.2325	35.6603	
C4	RHF /GIAO	24.3054	23.5386	23.8160	24.6333	<b>26.0</b>
	RHF /IGAIM	21.5267	22.3558	24.3832	25.3920	
	RHF /CSGT	21.5269	22.3561	24.3834	25.3923	
C4	B3LYP/GIAO	28.6115	28.0407	28.8912	29.4204	26.0
	B3LYP/IGAIM	25.3904	27.2911	29.3649	30.3873	
	B3LYP/CSGT	25.3909	27.2930	29.3652	30.3877	
C5	B3LYP/GIAO	23.0781	21.8448	21.9438	22.6228	<b>23.2</b>
	RHF /GIAO	19.6947	20.6722	22.4866	23.4380	
	RHF /CSGT	19.6949	20.6722	22.4865	23.4380	
C5	RHF /GIAO	27.2204	25.8109	26.4741	27.2143	23.2
	B3LYP/IGAIM	24.5558	25.7516	27.4661	28.2813	
	B3LYP/CSGT	24.5557	25.7529	27.4659	28.2815	
C6	RHF /GIAO	182.5865	164.0123	166.6686	173.8309	<b>171.3</b>
	RHF /IGAIM	194.1306	171.5816	172.8418	174.9440	
	RHF /CSGT	194.1306	171.5814	172.8416	174.9443	
C6	B3LYP/GIAO	164.8997	156.7690	161.8017	172.5302	171.3
	B3LYP/IGAIM	181.4935	164.2820	166.9622	173.6805	
	B3LYP/CSGT	181.4934	164.2834	166.9619	173.6807	
N7		---	---	---	---	---
O8		---	---	---	---	---

Atom	Method	Basis set				Experi- mental
		6-31G	6-31G(d,p)	6-31 + G(d,p)	6-311 + G(2d,2p)	
H9	RHF/GIAO	3.5860	3.5167	3.5542	3.5990	4.05
	RHF /IGAIM	1.1167	1.9340	2.1744	3.6023	
	RHF /CSGT	1.1167	1.9339	2.1741	3.6023	
H9	B3LYP/GIAO	3.7284	3.8107	3.8818	3.9905	<b>4.05</b>
	B3LYP/IGAIM	1.3737	2.2702	2.5489	3.9655	
	B3LYP/CSGT	1.3738	2.2707	2.5489	3.9656	
H10	RHF /GIAO	3.2252	2.9887	2.9979	3.0912	3.50
	RHF /IGAIM	1.0330	1.6052	1.7287	3.0677	
	RHF /CSGT	1.0332	1.6052	1.7285	3.0677	
H10	B3LYP/GIAO	3.3825	3.2667	3.2987	3.4332	<b>3.50</b>
	B3LYP/IGAIM	1.1026	1.8755	2.0125	3.3920	
	B3LYP/CSGT	1.1029	1.8761	2.0127	3.3921	
H11	RHF /GIAO	3.7987	3.7430	4.0281	3.9386	5.70
	RHF /IGAIM	0.2655	2.2560	2.5315	3.9251	
	RHF /CSGT	0.2656	2.2559	2.5315	3.9250	
H11	B3LYP/GIAO	4.4430	4.4738	4.7422	4.7139	<b>5.70</b>
	B3LYP/IGAIM	0.7035	2.9551	3.2035	4.6823	
	B3LYP/CSGT	0.7037	2.9555	3.2037	4.6824	
H12	RHF /GIAO	1.7359	1.6232	1.6231	1.5821	1.86
	RHF /IGAIM	0.3820	0.6608	0.7038	1.5537	
	RHF /CSGT	0.3819	0.6609	0.7037	1.5536	
H12	B3LYP/GIAO	1.7626	1.7306	1.7545	1.7547	<b>1.86</b>
	B3LYP/IGAIM	0.4665	0.8012	0.8488	1.7334	
	B3LYP/CSGT	0.4665	0.8018	0.8490	1.7334	
H13	RHF /GIAO	1.2474	1.0240	1.0942	1.1535	1.38
	RHF /IGAIM	-0.0461	0.0540	0.2099	1.1213	
	RHF /CSGT	-0.0461	0.0540	0.2098	1.1213	
H13	B3LYP/GIAO	1.3983	1.2641	1.3258	1.3842	<b>1.38</b>
	B3LYP/IGAIM	0.1352	0.2694	0.4022	1.3495	
	B3LYP/CSGT	0.1353	0.2699	0.4023	1.3496	
H14	RHF /GIAO	1.4261	1.1834	1.2173	1.2046	1.44
	RHF /IGAIM	0.1707	0.1979	0.3231	1.1687	
	RHF /CSGT	0.1711	0.1980	0.3231	1.1686	
H14	B3LYP/GIAO	1.4699	1.3440	1.3751	1.4199	<b>1.44</b>
	B3LYP/IGAIM	0.2308	0.3528	0.4727	1.3825	
	B3LYP/CSGT	0.2312	0.3534	0.4729	1.3826	

Atom	Method	Basis set				Experi- mental
		6-31G	6-31G(d,p)	6-31 + G(d,p)	6-311 + G(2d,2p)	
H15	RHF /GIAO	2.0078	1.9077	1.9130	1.9022	2.05
	RHF /IGAIM	0.6606	0.8660	0.9412	1.8010	
	RHF /CSGT	0.6608	0.8661	0.9413	1.8009	
H15	B3LYP/GIAO	2.0799	2.0441	2.0634	2.0939	<b>2.05</b>
	B3LYP/IGAIM	0.7084	1.0273	1.0809	2.0027	
	B3LYP/CSGT	0.7089	1.0279	1.0812	2.0028	
H16	RHF /GIAO	2.1071	1.7165	1.7072	1.6539	1.83
	RHF /IGAIM	1.9985	1.2536	1.2355	1.5866	
	RHF /CSGT	1.9982	1.2536	1.2355	1.5865	
H16	B3LYP/GIAO	2.2495	1.9503	1.9301	1.9358	<b>1.83</b>
	B3LYP/IGAIM	1.8977	1.4290	1.3834	1.8706	
	B3LYP/CSGT	1.8979	1.4295	1.3837	1.8707	
H17	RHF /GIAO	1.6673	1.5890	1.5945	1.5886	1.83
	RHF /IGAIM	0.5541	0.7293	0.7540	1.5041	
	RHF /CSGT	0.5542	0.7294	0.7540	1.5040	
H17	B3LYP/GIAO	1.7006	1.6716	1.6873	1.7626	<b>1.83</b>
	B3LYP/IGAIM	0.6421	0.9014	0.9085	1.6831	
	B3LYP/CSGT	1.8979	1.4295	1.3837	1.8707	

The data in Table 2 reveal that the RHF-based calculation results are in excellent agreement with the experimental  $^{13}\text{C}$  chemical shift data. The B3LYP-based calculation demonstrates similar agreement for the  $^1\text{H}$  chemical shifts. The results are based on fixed geometry and a rigid conformation. The high-amplitude conformational movement of C5 at the top of envelope causes the equivalency of the two methylene protons on this carbon (H16 and H17).

The vibrational correction of the computed data is in progress to take into account the conformational equilibrium so as to calculate NMR data on larger saturated cycloalkane-condensed azetidinones (C6, C7, C8 and C12).

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