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Journal of Molecular Structure: THEOCHEM 716 (2005) 143–148

THEO CHEM

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GIAO calculations of chemical shifts in enantiometrically pure 1-trifluoromethyl tetrahydroisoquinoline alkaloids

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Received 31 July 2004; revised 20 November 2004; accepted 2 December 2004
Available online 7 January 2005

Abstract

Isotropic ^{1}H and ^{13}C nuclear magnetic shielding constants of enantiometrically pure 1-trifluoromethyl tetrahydroisoquinoline alkaloids have been calculated by employing the gauge-including-atomic-orbital (GIAO) method at the B3LYP density functional level of theory. Geometry of each compound has been optimized employing 6-31G(d,p) and 6-311G basis sets. The theoretical trends are compared with experimental data taken from the literature. The least squares regression analyses of the results indicate *R*-square values greater than 0.82 in the range for total data set.

Keywords: ^{1}H; ^{13}C; NMR; HF; DFT; GIAO calculation

1. Introduction

Compounds containing 1-trifluoro-methyl analogues have attracted great attention because of their biological activity [1]. Fluorine-free natural tetrahydroisoquinolines in which C-1 is quaternary stereogenic centre have been reported to feature very interesting biological properties [2]. A report by Corey et al. described the stereo selective synthesis of the spyro-tetrahydroisoquinoline unit of the anti tumour marine-derived molecule ecteinascidin 743 [3,4].

NMR spectroscopy has been proven to be an exceptional tool to elucidate structure and molecular conformation. Ab intio and DFT calculation of NMR shielding at very accurate levels of approximation are available at literature [5–20]. There are the most used methods to calculate chemical shifts: IGLO (individual gauge localized orbital), LORG (localized or Loacaorbital origin) and GIAO (gauge independent or invariant or including atomic orbital). The GIAO/DFT approach [21] is known to give satisfactory chemical shifts for different nuclei [21–23] with larger molecules. These quantum chemical calculations, however, often have to be limited to isolated (gas-phase) molecules and to some preferred (optimized) structures while experimental NMR spectra are commonly statical averages affected by dynamic processes such as conformational equilibria as well as intra and/or intermolecular interactions.

The present paper applies the HF and DFT methods to analyze the experimental ^{1}H and ^{13}C data of enantiometrically pure 1-trifluoromethyl tetrahydroisoquinoline alkaloids published by P. Barovo et al. [1]. The aim of this work is to calculate the theoretical chemical shifts of 1-trifluomethyl tetrahydroisoquinoline molecular structure based on proper assignment of observed ^{1}H, and ^{13}C resonances by using proper computational method and basis set. The calculated chemical shifts are then compared with the experimental values.

2. Computational methods

The compounds for which calculations were carried out are given in Tables 1–3. The numbering systems are shown in Figs. 1–3. All the structures were fully optimized with the GAUSSIAN G03 program at the DFT B3LYP/6-31G(d,p)// B3LYP/6-311G theoretical level [24]. After the optimization, ^{1}H, and ^{13}C chemical shifts were calculated with GIAO method [25–28], using corresponding TMS shielding

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doi:10.1016/j.theochem.2004.12.004

Table 1
Comparision between experimental and calculated chemical shifts (ppm) of (R)-6,7-dimethoxy-2-methyl-1-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline-1-carbaldehyde

Nuclei	Experimental	B3LYP 6-31G(d,p)	Error	B3LYP 6-311G	Error
H22	6.64	6.33	0.31	6.10	0.54
H23	6.70	6.70	0	6.25	0.45
H24	3.88	3.48	0.4	3.62	0.26
H25	3.88	3.51	0.37	3.74	0.14
H26	3.88	4.00	−0.12	4.24	−0.36
H27	3.81	3.53	0.28	3.73	0.08
H28	3.81	3.55	0.26	3.73	0.08
H29	3.81	4.00	−0.19	4.27	−0.46
H30	2.74	2.21	0.53	2.33	0.41
H31	2.82	3.03	−0.21	3.34	−0.52
H32	3.11	3.12	−0.01	3.24	−0.13
H33	2.94	2.57	0.37	2.78	0.16
H34	2.71	2.51	0.2	2.59	0.12
H35	2.71	2.72	−0.01	2.88	−0.17
H36	2.71	2.21	0.5	2.47	0.24
H37	9.06	10.69	−1.63	11.58	−2.52
C1	112.0	106.84	5.16	116.00	−4
C2	149.9	143.96	5.94	159.57	−9.67
C3	147.2	142.56	4.64	157.25	−10.05
C4	111.8	106.35	5.45	116.89	−5.09
C5	115.6	120.24	−4.64	130.58	−14.98
C6	125.7	125.67	0.03	138.70	−13
C9	56.0	52.47	3.53	57.57	−1.57
C10	55.8	52.61	3.19	57.90	−2.1
C11	28.6	32.68	−4.08	34.67	−6.07
C12	46.2	50.70	−4.5	53.41	−7.21
C13	71.9	74.25	−2.35	78.79	−6.89
C15	41.5	41.81	−0.31	43.01	−1.51
C16	130.2	131.36	−1.16	155.61	−25.41
C20	193.9	191.57	2.33	216.41	−22.51

Table 2
Comparision between experimental and calculated chemical shifts (ppm) of (R)-(6,7-dimethoxy-2-methyl-1-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)methanol

Nuclei	Experimental	B3LYP 6-31G(d,p)	Error	B3LYP 6-311G	Error
H22	6.60	6.40	0.2	6.14	0.46
H23	6.94	7.00	−0.06	6.93	0.01
H24	3.86	3.72	0.14	4.04	−0.18
H25	3.86	3.21	0.65	3.45	0.41
H26	3.86	4.42	−0.56	5.13	−1.27
H27	3.86	3.61	0.25	3.79	0.07
H28	3.86	3.55	0.31	3.72	0.14
H29	3.86	4.01	−0.15	4.23	−0.37
H30	3.05	3.01	0.04	3.01	0.04
H31	2.91	2.19	0.72	2.42	0.49
H32	2.64	2.63	0.01	2.76	−0.12
H33	2.74	3.71	−0.97	3.83	−1.09
H34	2.71	2.92	−0.21	3.59	−0.88
H35	2.71	2.54	0.17	2.73	−0.02
H36	2.71	1.92	0.79	2.08	0.63
H37	4.17	4.55	−0.38	4.80	−0.63
H38	4.02	3.67	0.35	3.81	0.21
H39	2.39	2.11	0.28	2.73	−0.34
C1	110.5	107.49	3.01	117.08	−6.58
C2	149.0	148.23	0.77	162.64	−13.64
C3	147.3	143.09	4.21	157.45	−10.15
C4	111.3	117.99	−6.69	129.32	−18.02
C5	127.3	119.11	8.19	130.79	−3.49
C6	130.6	127.63	2.97	139.71	−9.11
C9	56.0	56.84	−0.84	64.35	−8.35
C10	55.7	52.39	3.31	57.45	−1.75
C11	28.7	24.54	4.16	25.80	2.9
C12	47.7	48.13	−0.43	51.82	−4.12
C13	61.0	69.06	−8.06	74.28	−13.28
C15	39.2	36.88	2.32	39.23	−0.03
C16	121.5	132.18	−10.68	157.35	−35.85
C20	66.3	63.85	2.45	68.01	−1.71

calculated at the same theoretical level as the reference. All the computations were done using an IBM PC Pentium-IV computer having 1024 MB ram. Linear correlation analyses were carried out using SIGMAPLOT program. The quality of each correlation was judged with *R* value, the Pearson correlation coefficient [29].

Table 3
Comparision between experimental and calculated chemical shifts (ppm) of (S)-6, 7-dimethoxy-1,2-dimethyl-1-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline

Nuclei	Experimental	B3LYP 6-31G(d,p)	Error	B3LYP 6-311G	Error
H21	6.58	6.24	0.34	6.05	0.53
H22	6.90	6.85	0.05	7.24	−0.34
H23	3.86	3.54	0.32	5.19	−1.33
H24	3.86	3.58	0.28	3.38	0.48
H25	3.86	3.98	−0.12	4.03	−0.17
H26	3.86	3.54	0.32	3.75	0.11
H27	3.86	3.54	0.32	3.81	0.05
H28	3.86	3.98	−0.12	4.21	−0.35
H29	2.90	2.19	0.71	2.30	0.6
H30	3.16	3.08	0.08	2.53	0.63
H31	2.70	2.76	−0.06	2.90	−0.2
H32	2.70	2.47	0.23	2.71	−0.01
H33	2.62	3.15	−0.53	3.38	−0.76
H34	2.62	2.33	0.29	2.67	−0.05
H35	2.62	2.10	0.52	2.32	0.3
H36	1.65	1.55	0.1	1.78	−0.13
H37	1.65	1.28	0.37	1.24	0.41
H38	1.65	1.57	0.08	2.00	−0.35
C1	111.0	105.88	5.12	115.73	−4.73
C2	148.5	143.47	5.03	162.03	−13.53
C3	147.0	142.33	4.67	156.71	−9.71
C4	111.4	107.01	4.39	131.30	−19.9
C5	128.0	123.20	4.8	134.79	−6.79
C6	129.4	125.87	3.53	143.26	−13.86
C9	56.1	52.40	3.7	64.17	−8.07
C10	56.1	52.60	3.5	57.50	−1.4
C11	28.0	33.24	−5.24	35.86	−7.86
C12	48.5	50.25	−1.75	53.13	−4.63
C13	62.3	66.56	−4.26	70.55	−8.25
C15	39.7	40.34	−0.64	40.96	−1.26
C16	125.5	132.81	−7.31	156.97	−31.47
C20	20.0	18.89	1.11	20.72	−0.72