Journal of Molecular Structure 981 (2010) 159–162

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstruc

Experimental and theoretical studies of the absolute configuration of (2S,1′R) and (2R,1′R)-2-acetoxymethyl-3-phenyl-N-(1′-phenylethyl)-propionamide

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ARTICLE INFO

Article history:
Received 28 March 2007
Received in revised form 22 July 2010
Accepted 27 July 2010
Available online 3 August 2010

Keywords:
Nuclear magnetic resonance spectroscopy
Absolute configuration
Diastereoisomer amide
Quantum chemistry calculation
Infrared spectroscopy

ABSTRACT

Two diastereoisomers (2S,1′R) and (2R,1′R)-2-acetoxymethyl-3-phenyl-N-(1′-phenylethyl)-propionamide(**2**), have been studied to investigate their discrimination on the absolute configuration using nuclear magnetic resonance (NMR), infrared (IR) spectroscopy were performed. The experimental results were supported by performing density functional theory (DFT) calculations for the NMR, IR spectra using the Becke 3-parameter, Lee, Yang and Parr (B3LYP) functional and the 6-311+G** basis set.

1. Introduction

2-Branched carboxylic acids and their derivatives are frequently found in enzyme inhibitors as optically active compounds with the chiral center at the α-position [1–4]. Optically D-(+)-1-phenylethylamine, is condensed with a carboxylic acid, giving the diastereoisomer which can be transformed into optically 2-branched amide (Scheme 1).

Both diastereoisomers (2S,1′R)-2-acetoxymethyl-3-phenyl-N-(1′-phenylethyl)-propionamide (**2**) [**2**(2S,1′R)] and (2R,1′R)-2-acetoxymethyl-3-phenyl-N-(1′-phenylethyl)-propionamide (**2**) [**2**(2R,-1′R)] (Scheme 2) were investigated by using NMR and IR spectra. In addition, GIAO calculations of **2**(2S,1′R) and **2**(2R,1′R) have been performed by using the B3LYP method. These calculations were valuable for providing insight into NMR and IR spectra. In this article, basic experimental and theoretical information about the structure of a **2**(2S,1′R) and **2**(2R,1′R) was presented. To the best of our knowledge, no evidence of studies for **2**(2S,1′R) and **2**(2R,1′R) has been reported to date in the open chemical literature.

2. Experimental and calculations

2.1. Physical methods

All NMR spectra were recorded on a Bruker AVANCE 300 superconductor spectrometer operating at 300.13 MHz for proton NMR and 75.04 MHz for carbon NMR, respectively. Sample was dissolved in chloroform-d (0.5 ml) with 0.1% tetramethylsilane (TMS) as an internal reference and transferred into a 5 mm NMR tube. Standard pulse programs provided by Bruker WinNMR 3.5 software packages were used to acquire; melting point was determined in open capillary tube and is uncorrected. Elemental analysis was performed on a Perkin–Elmer 204Q; the mass spectrometer using a LCQ Advantage (Thermo Finnigan) was operated in electron impact mode with ionization energy of 70 eV. The ion source temperature was maintained at 280 °C; the Fourier transform infrared spectrum was measured (in KBr disc) on an IRPrestige-21 (Shimadzu) in the 4000–400 cm^{-1} region with 4 cm^{-1} resolution.

2.2. Synthesis

The racemic 2-(acetoxymethyl)-2-phenylpropionic acid (**1**) was prepared starting from commercially available diethylmalonate according to literature methods [5–7]. To an ice-chilled stirred solution of **1** (0.4639 g, 2.09 mmol) in dichloromethane (5 ml) was added isobutylchloroformate (300 μl, 2.09 mmol) and 4-methylmorpholine (240 μl, 2.09 mmol) in dichloromethane. The resulting mixture was stirred for 30 min at 0 °C, D-(+)-1-phenylethylamine (240 μl, 2.09 mmol) was added to the mixture, stirred for 1 h at room temperature. After removal of the solvent, the residue was extracted with ethyl acetate (50 ml × 3) and the organic layer was washed with 10% citric acid (50 ml × 3), 5% sodium bicarbonate (50 ml × 3), and dried over anhydrous magnesium sulphate. Evaporation of the organic solvent afforded the product as a white solid.

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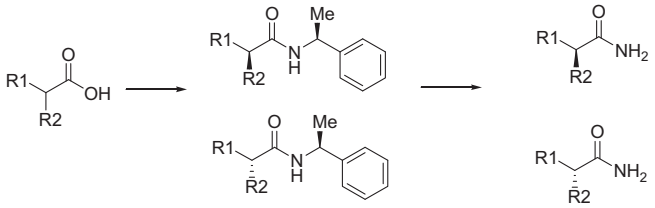
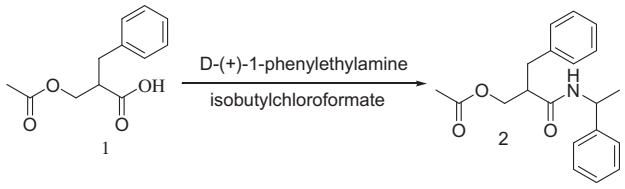
doi:10.1016/j.molstruc.2010.07.049



Scheme 1. 2-Branched carboxylic acids and their derivatives.



Scheme 2. The synthetic route of **2**(2S,1′R) and **2**(2R,1′R).

The crude product was separated by column chromatography over silica gel eluting with ethyl acetate/n-hexane = 3:1–1:1.

2(2S,1′R): 195 mg, R_f value, 0.27; $[\alpha]_D = -63.0°$ (c, 0.44, $CHCl_3$); m.p.: 112–114 °C; MS: $[M+H]^+ = 326.4$, $[M+Na]^+ = 348.6$; elemental analysis: Calcd. (found) C: 73.82 (73.81), H: 7.12 (7.13), N: 4.30 (4.29); **2**(2R,1′R): 105 mg, R_f value, 0.22; $[\alpha]_D = -33.2°$ (c, 0.44, $CHCl_3$); m.p.: 115–117 °C; MS: $[M+H]^+ = 326.4$, $[M+Na]^+ = 348.6$; elemental analysis: Calcd. (found) C: 73.82(73.80), H: 7.12(7.13), N: 4.30(4.30).

2.3. Computational methods

Geometries of the model systems were optimized using the hybrid density functional method B3LYP [8] with the 6-311G(d,p) basis set. Frequencies were calculated for the model systems in order to identify them as minima. The calculated vibrational frequencies were scaled by the recommended factor of 0.9688 [9] and calculated spectra were convoluted by applying a 10 cm^{-1} Lorentzian function with GaussSum program [10]. NMR shielding tensors were computed with the GIAO method [11]. The calculated values for the ^1H and ^{13}C isotropic chemical shifts were referenced to the corresponding values for TMS, which was calculated at the same level of theory. The effect of solvent on the theoretical NMR parameters was included using the integral equation formalism model IEF–PCM [12]. All calculations were performed with the Gaussian 03 package [13,14].

3. Results and discussions

The synthesis procedure is shown in Scheme 2. Two diastereomers **2**(2S,1′R) and **2**(2R,1′R) were characterized by elemental analysis, mass spectrometry, IR and NMR spectroscopy.

In the column chromatography, **2**(2S,1′R) isomer eluted faster than **2**(2R,1′R). This tendency has been already noticed in the previous work for simple chain carboxylic acids [15,16]. No crystal suitable for X-ray analysis was obtained for both diastereoisomers **2**(2S,1′R) and **2**(2R,1′R). Therefore, to further try to investigate their structure, both diastereoisomers **2**(2S,1′R) and **2**(2R,1′R) were studied by using NMR. First of all, proton NMR spectra of the pure diastereoisomers were performed to possibly point out any small difference between **2**(2S,1′R) and **2**(2R,1′R). In fact, it is very well known in literature that chiral reagents can enhance shielding/deshielding effects and help resolve diastereoisomers and/or enantiomers [15–18]. In parallel, two-dimensional NMR experiments such as NOESY were run on diastereoisomers and confirm one-dimensional NMR assignments. The proton NMR chemical shifts of the CH(H25) and CH_3(H33–H35) of the fast-eluting **2**(2S,1′R) (Fig. 1) were always more upfield than those of the slow-eluting 2(2R,1′R), which suggest that the CH(H25) and CH_3(H33–H35) of the fast-eluting compounds were magnetically shielded by the benzene ring (C6–C11), thus confirming the fast-eluting compound is **2**(2S,1′R) and the slow-eluting is **2**(2R,1′R). In the case of **2**(2R,1′R), preferential anisotropic shielding of the CH_3(H35–H36) by the phenyl (H43–H47) is resulted. In the case of **2**(2S,1′R), preferential anisotropic shielding of the phenyl (C19–C24) is observed. Observed magnitudes of chemical shift differences are consistent with others earlier observation, such as diastereomeric pairs of 2-hydroxymethyl-2-methyl-3-phenyl-N-(1′-phenylethyl)-propionamide**,** 2-hydroxymethyl- 3-phenyl-N-(1′-phenylethyl)-propionamide, 2-phenyl-N-(1′-phenylethyl)-propionamide [15,16,19–25].

A useful conformational mode that accounts for the observed signs of the chemical shift differences between the **2**(2S,1′R) and **2**(2R,1′R) is shown in Scheme 3. The proton chemical shift of H26 was clearly identified through correlations in the 2D-NOE with the H25, it was also correlations in the COSY with the H27 chemical shift for **2**(2S,1′R) and **2**(2R,1′R). Conformation [A] will become much more stable than [B], resulting from rotation around the C1–C2 bond, owing to the steric interaction of the bulky C6–C11 moiety with the phenyl (C19–C24). This consideration suggests that

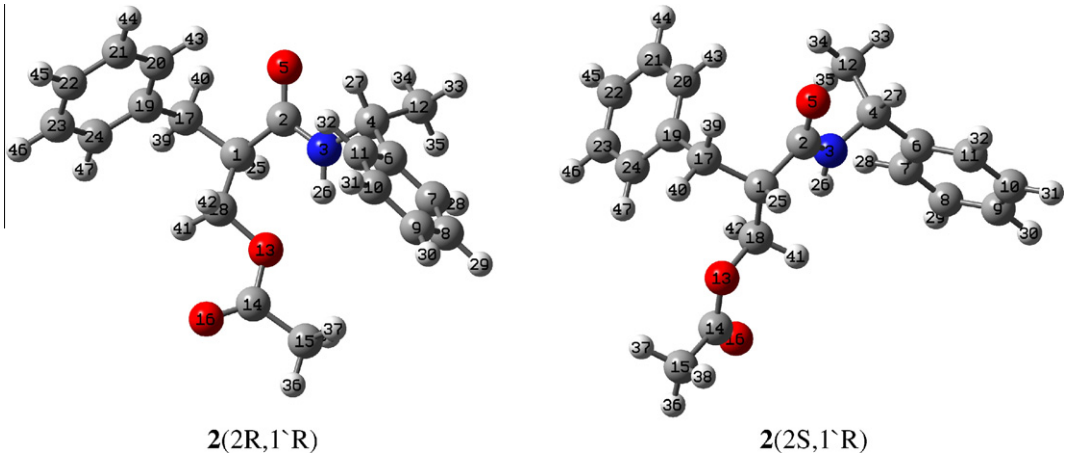
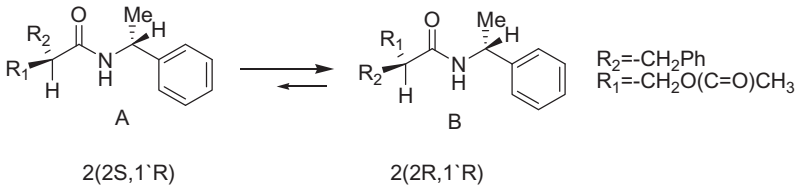


Fig. 1. Atom numberings and optimized structure of **2**(2S,1′R) and **2**(2R,1′R) from B3LYP/6-311+G** calculations.



Scheme 3. Conformational mode between the **2**(2S,1′R) and **2**(2R,1′R).

Table 1
Observed and calculated selected frequencies (cm^{-1}).

Mode no.	**2**(2S,1′R)		**2**(2R,1′R)	
	v (Exp.)	*v* (Calc.)	*v* (Exp.)	*v* (Calc.)
1		299		298
2		385		379
4	441.70	441	460.99	461
6	538.14	538	549.71	550
7	694.37	695	694.37	694
8	727.16	727	725.23	725
9	754.17	754	754.17	755
10	898.83	899	894.97	896
11	1006.84	1007	1010.70	1011
12	1020.34	1020	1018.41	1019
14	1031.92	1031	1033.84	1034
15	1035.77	1035	1082.06	1082
17	1080.14	1079	1099.42	1100
18	1101.35	1101	1195.86	1196
19	1190.08	1189	1203.58	1203
20	1211.30	1211	1222.87	1223
21	1226.73	1227	1354.03	1354
22	1354.03	1354	1375.24	1376
23	1379.10	1379	1425.39	1426
24	1427.32	1426	1435.04	1435
25	1442.75	1442	1446.61	1446
26	1473.61	1474	1477.47	1478
27	1489.00	1489	1498.69	1499
28	1660.71	1661	1658.78	1660
29	1737.86	1739	1749.44	1749
30	2941.44	2941	2939.51	2940
31	3007.02	3008	3003.17	3004
32	3020.52	3020	3018.60	3019
33	3072.60	3073	3072.60	3073
34	3080.32	3081	3084.18	3084
35	3089.96	3091	3089.96	3091
36	3518.16	3519	3479.58	3480

Table 2
The experimental and theoretical ^{1}H NMR chemical shifts for **2**(2S,1′R) and **2**(2R,1′R).

Mode no.	**2**(2S,1′R)		**2**(2R,1′R)	
	Exp.	IEF–PCM (calc.)	Exp.	IEF–PCM (calc.)
25	2.67	2.97	2.79	2.86
26	4.25	4.42	6.94	6.30
27	5.06	5.08	5.07	5.34
28	7.21	7.46	7.20	7.70
29	7.30	7.74	7.20	7.70
30	7.29	7.67	7.10	7.63
31	7.28	7.64	7.19	7.68
32	7.28	7.60	7.11	7.53
33	1.21	0.97	1.42	1.20
34	1.21	1.67	2.04	1.90
35	1.21	1.18	1.42	1.49
36	1.93	1.74	1.42	1.48
37	1.93	2.29	2.04	1.49
38	1.93	2.23	2.04	1.94
39	2.79	3.60	2.71	2.47
40	2.92	3.08	4.25	4.07
41		3.73		4.35
42	4.25	3.68	2.91	2.99
43	7.30	7.66	7.22	8.18
44	7.27	7.56	7.12	7.62
45	7.25	7.54	6.97	7.57
46	7.29	7.67	6.96	7.53
47	7.19	7.32	6.95	7.45

Table 3
The experimental and theoretical ^{13}C NMR chemical shifts for **2**(2S,1′R) and **2**(2R,1′R).

Mode no.	**2**(2S,1′R)		**2**(2R,1′R)	
	Exp.	IEF–PCM calc.	Exp.	IEF–PCM calc.
25	48.38	51	48.34	50
26	170.72	176	170.96	177
27	48.99	56	49.06	54
28	142.47	151	142.93	150
29	126.06	131	126.05	131
30	128.89	136	127.32	135
31	127.17	135	127.32	135
32	128.49	135	128.57	135
33	128.63	136	128.94	138
34	21.44	23	20.29	19
35	170.96	180	170.71	178
36	20.84	23	21.16	22
37	35.21	38	35.35	38
38	65.27	64	65.19	71
39	138.37	147	138.53	148
40	128.89	138	128.94	138
41	128.49	135	127.32	134
42	126.55	132	126.67	132
43	127.17	134	127.32	134
44	128.63	136	128.61	136
45	48.38	51	48.34	50
46	170.72	176	170.96	177
47	48.99	56	49.06	54

the NMR and IR method is possible for the absolute configuration determination of 2-branched carboxylic acid.

To confirm the configuration of **2**(2S,1′R) and **2**(2R,1′R), the GIAO based carbon and proton NMR chemical shifts calculations were carried out on the two configurations of **2.** The geometries of the two configurations of **2** were fully optimized by the B3LYP/6-311++G** method [26]. The vibrational frequency analysis performed at the same level gave no imaginary frequencies, ensuring that they are true energy minimum structures [27–31]. In a study of the IR spectra of diastereomeric, it was different in 441.70, 538.14, 694.37, 727.16, 754.17, 898.83, 1006.84, 1020.34, 1031.92, 1035.77, 1080.14, 1101.35, 1190.08, 1211.30, 1226.73, 1354.03, 1379.10, 1427.32, 1442.75, 1473.61, 1489.0, 1660.71, 1737.86, 2941.44, 3007.02, 3020.52, 3072.60, 3080.32, 3089.96, 3518.16 cm^{-1}; 460.99, 549.71, 694.37, 725.23, 754.17, 894.97, 1010.70, 1018.41, 1033.84, 1082.06, 1099.42, 1195.86, 1203.58, 1222.87, 1354.03, 1375.24, 1425.39, 1435.04, 1446.61, 1477.47, 1498.69, 1658.78, 1749.44, 2939.51, 3003.17, 3018.60, 3072.60, 3084.18, 3089.96, 3479.58 cm^{-1}. The observed and calculated frequencies are summarized in Table 1. The calculated frequencies C=O for the **2**(2S,1′R) were 1660.71 and 1737.86 cm^{-1}, while the observed frequencies were 1661 and 1739 cm^{-1}; the calculated frequencies C=O for the **2**(2R,1′R) were 1658.78 and 1749.44 cm^{-1}, while the observed frequencies were 1660 and

1749 cm^{-1}. These calculated frequencies for the **2**(2S,1′R) and **2**(2R,1′R) conformers were in fair agreement with those of the observed bands, respectively.

Meanwhile, the same procedure was applied on TMS to calculate the relative chemical shifts of these two isomers. All the calculations were performed using the Gaussian 03 program. The plots were made using experimental proton NMR and carbon NMR data versus theoretical values, and then analyzed with linear regression. The correlation coefficient (R^2) for the carbon NMR chemical shifts with the isomer **2(2**S,1′R**)** is 0.9979, for **2(2**R,1′R**)** is 0.9993. The R^2 for the proton NMR chemical shifts with the isomer **2(2**S,1′R**)** is 0.9908, for **2(2**R,1′R**)** is 0.9940 [32].

The computational results are summarized in Tables 2 and 3. It can be seen that the chemical shifts deduced by the B3LYP/6-311++G** method for isomer **2(2**S,1′R**)** and **2(2**R,1′R**)** are closer to the experimental carbon and proton NMR data. Comparison of the experimental and theoretical data made it clear that **2** has a greater probability of adopting the structure of **2(2**S,1′R**)** and **2(2**R,1′R**)**.

4. Conclusions

In conclusion, the NMR and IR strategy for determination of the absolute configuration of a stereogenic center in the α-position of a carboxylic acid is reliable. The quantum chemistry calculation results of NMR and IR spectra suggest a relative stereo structure of **2**(**2**S,1′R) and **2**(**2**R,1′R) with a great probability.

Acknowledgement

The Project Sponsored by the Scientific Research Foundation financially supported the work for the Doctoral Program of Yanbian University, China. Dr Sihong Wang is grateful to Prof. Lixin Wu (Jilin University), Dr. Shrongshi Lin (Peking University), Prof. Qifan Yin (Huaiyin Normal University) for their assistance in the proofing of this manuscript, careful review, measuring IR and MS spectra.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2010.07.049.

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