

Synthesis and characterization of solid 2-methoxycinnamylidenepyruvic acid

C. T. de Carvalho¹, A. B. Siqueira¹, E. Y. Ionashiro², M. Pivatto¹, M. Ionashiro^{1*}.

¹Instituto de Química, UNESP, CP 355, CEP 14801-970, Araraquara, SP, Brazil.

²Instituto de Química, UFG, Campus II, CEP74001-979, Goiânia, GO, Brazil.

*massaai@iq.unesp.br

Abstract: The 2-methoxycinnamylidenepyruvic acid (2-MeO-HCP) was synthesized and characterized for nuclear magnetic resonance (¹H and ¹³C NMR), mass spectrometry (MS), Infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC). The application of DSC for purity determination is well documented in literature and is used in the analysis of pure organic compounds. The molecular geometry and vibrational frequencies of 2-MeO-HCP have been calculated.

Keywords: 2-methoxycinnamylidenepyruvic acid; synthesis; MS; NMR; IR.

Introduction

Various procedures concerning the preparation of α -keto acids have been reported in the literature.¹ The α -keto acids are of continuing interest as model substrates of enzymes, intermediates in chemical syntheses, in the development of enzyme inhibitors and drugs and in other ways.¹ The aldol condensation products between cinnamaldehyde and pyruvic acid as, 4-dimethylamino and cinnamylidenepyruvic acids has also been described in the literature^{2, 3}.

Extensive experimental and theoretical investigations have focused on elucidating the structure and normal vibrations of organic compounds⁴. Thus, calculations of optimal molecular geometry and vibrational of 2-MeO-HCP were made. The calculated harmonic frequencies are usually higher than the corresponding experimental quantities, due to a combination of electron correlation effects and basis set deficiencies. It is well known that Hartree-Fock (HF) method tends to overestimate vibrational frequencies.

However, density functional theory (DFT) calculations are reported to provide excellent vibrational frequencies of organic compounds if the calculated frequencies are scaled to compensate for the approximate treatment of electron correlation for basis set deficiencies and the anharmonicity.⁵

In this paper, the 2-MeO-HCP was investigated by means of infrared spectroscopy (IR), mass spectrometry (MS), nuclear magnetic resonance (NMR) spectroscopy and differential scanning calorimetry (DSC). The results allowed us to acquire information about these compounds in the solid state. The DSC purity determination method was established using melting point (122 °C) observations revealing a relation between a substance's melting point and its purity⁶.

The optimisation of the DSC purity determination method was done by Blaine *et al.*⁷ using a National Institute of Standards and Technology (NIST) purity standard – phenacetin doped with *p*-aminobenzoic acid – in 1984. As a result of their investigations, the experimental parameters

influencing purity results were assessed: specimen size, heating rate, level of impurity. An optimal specimen size (1.7 mg) and heating rate (0.5–2 °C min⁻¹) were deduced.

The 2-methoxycinnamaldehyde, (CH₃O-C₆H₄-(CH)₂-CHO, 96%) predominantly trans, was obtained from Aldrich and sodium pyruvate (H₃C-CO-COONa, 99%) was obtained from Sigma. 2-methoxycinnamylidenepyruvic acid (2-MeO-HCP) was synthesized following the same procedure as described in literature,⁸ with some modifications, as follows: an aqueous solution of sodium pyruvate (1.5 g per 10 mL) was added dropwise with continuous stirring to a methanolic solution of 2-methoxycinnamaldehyde (2.0 g per 50mL). Five millilitres of an aqueous sodium hydroxide solution 1.25 mol L⁻¹ was added slowly while the reacting system was stirred and cooled in an ice bath. The rate of addition of alkali was regulated so that the temperature remained between 5 and 9 °C. The system was stirred at ambient temperature (~28 °C) for about 5 h. To the pale yellow solution was added dropwise with continuous stirring with a glass rod, twenty millilitres of chilled concentrated (12 mol L⁻¹) hydrochloric acid. The system was left to stand for ca. 16 h in a freezer (-6 °C) and the yellow orange precipitate (impure 2-MeO-HCP) was filtered, washed with distilled water to remove most of the unreacted aldehyde and secondary products and dried on Whatman n° 44 filter paper. The aqueous suspension of the impure acid was dissolved with 5 mL of aqueous sodium hydroxide solution 2 mol L⁻¹ and filtered on Whatman n° 44 filter paper. The yellow solution was stirred with a glass rod and added slowly 20 mL of chilled concentrated (12 mol L⁻¹) hydrochloric acid and left to stand for ca. 16 h in freezer (-6 °C). The orange precipitate of 2-MeO-CP was filtered and washed with distilled water until elimination of chloride ions and dried on Whatman n° 44 filter paper and kept in a desiccator over anhydrous calcium chloride. (yield = 28,6%).

General methods

Infrared spectra for 2-MeO-HCP were run on a Nicolet Model Impact 400 FTIR instrument within the 4000–400 cm⁻¹ range. The solid samples were pressed into KBr pellets.

DSC curve were obtained with DSC Q10 from TA Instruments. The purge gas was an air flow of 50 mL min⁻¹. A heating rate 0.5 K min⁻¹ for the DSC was adopted, with samples weighing about 1,5 mg. Aluminium crucibles with perforated covers were used for the DSC.

The 1D – (¹H, ¹³C and DEPT) and 2D – (¹H – ¹H gCOSY, gHMBC and gHMBC) NMR experiments were recorded on a Varian INOVA 500 spectrometer (11.7 T) at 500 MHz (¹H) and 125 MHz (¹³C) at 30 °C and referenced using TMS as internal standard or residual solvent resonances of CDCl₃ at δ 7.20 and 77.0, respectively, for ¹H and ¹³C NMR.

High resolution mass spectra with ESI ionization was measured on Ultra-TOF instrument (Bruker Daltonics) operating in positive mode. MeOH/H₂O (4:1) was applied as solvent system.

Purity determination

The determination of purity is based on the assumption that an impurity will depress the melting point of a pure material whose melting is characterized by a melting point (T_0) and an enthalpy of fusion (ΔH_{fus}). The effect of an impurity on T_0 of the 2MeO-HCP was determined by DSC method basing on the Van't Hoff equation (1).

$$T_s = T_o - \frac{RT_o^2 x}{\Delta H_{fus} F} \quad (1)$$

Where T_s is the sample temperature at equilibrium (K), T_o is the melting point of the pure component (K), R is the gas constant, x is the concentration of impurity (mole fraction) and F is the fraction molten at T_s .

The obtained DSC curve exhibits the endothermic event corresponding to 2-MeO-HCP melting point ($\Delta H_{fus} = +23.36$ kJ mol⁻¹). The value of purity found was confirming low impurity content.

Structure elucidation

The molecular weight of 2-MeO-HCP, see Figure 1, was calculated from HRESIMS instrument operating in positive mode. The molecular formulae was established as C₁₃H₁₂O₄, with a hydrogen deficiency index of eight. The

observed cationized adduct ion peaks at m/z 233,0815 $[M + H]^+$ and m/z 255,0630 $[M + Na]^+$ were calculated for $C_{13}H_{13}O_4$, 233,0814 and $C_{13}H_{12}O_4Na$, 255,0633, respectively. The 1H NMR analysis of 2-MeO-HCP showed signals for a methoxy group at δ 3.90 (3H, s, H-7'), four aromatic hydrogen signals at δ 6.92 (1H, dd, $J = 8.0$; 1.0 Hz, H-3'), 7.35 (1H, ddd, $J = 8.0$; 8.0; 1.0 Hz, H-4'), 6.98 (1H, ddd, $J = 8.0$; 8.0; 1.0 Hz, H-5'), and 7.53 (1H, dd, $J = 8.0$; 1.0 Hz, H-6'), respectively, were indicative of a 1,2-disubstituted aromatic system, in addition to four other olefinic hydrogen signals at δ 7.05 (1H, d, $J = 15.5$ Hz), 7.96 (1H, ddd, $J = 15.5$; 11.2 Hz), 7.10 (1H, ddd, $J = 15.5$; 11.2 Hz), and 7.53 (1H, d, $J = 15.5$ Hz), which were assigned to H-3, H-4, H-5 and H-6, respectively, see Figure 1. Analysis of the 1H - 1H COSY NMR spectrum allowed to confirm the assignment of the signals, see Table 1. The ^{13}C NMR and DEPT spectra displayed 13 signals, including a methoxy group, eight methines, and four quaternary carbons (Table 1). The aromatic carbons signals were identified at δ 124.4 (C-1'), 158.2 (C-2'), 111.3 (C-3'), 131.7 (C-4'), 120.9 (C-5') and 128.3 (C-6'). The presence of a conjugated carbonyl and a vicinal carboxylic carbonyl group were indicated by the chemical shifts at 182.0 (C-2) and 160.6 (C-1), respectively, in the ^{13}C NMR spectrum of

this compound, in addition to four other olefinic carbons at δ 120.4 (C-3), 152.8 (C-4), 127.2 (C-5), and 142.3 (C-6) (Table 1). The aromatic ring was attached to the olefinic end-carbon (C-6), and this was evidenced by the observed gHMBC correlations between the signal at δ 7.53 (H-6) and that at δ 158.2 (C-2'), as well as between the signal at δ 7.53 (H-6') and C-6 (δ 142.3). Further more the 1,2-disubstituted aromatic ring was confirmed by the correlations between the signal at δ 3.90 (OCH₃-7') with C-2' (δ 158.2) (Table 1). The *E*-configuration of the conjugated double bonds C-3-C-4 and C-5-C-6 in the olefin moiety were determined by the large coupling constant (15.5 Hz) between H-3-H-4 and H-5-H-6. The structure of H-2-MeO-CP was therefore assigned as (3*E*,5*E*)-6-(2-methoxyphenyl)-2-oxohexa-3,5-dienoic acid.

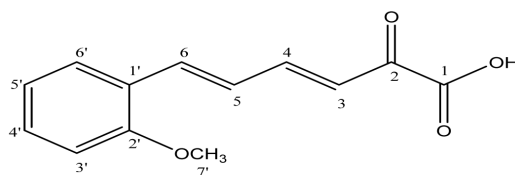


Figure 1. Plane structure of 2-MeO-HCP.

Table 1. MR Spectroscopic Data of H-2MeO-CP in CDCl₃^a.

C	δC^b	gHMBC δH (J in Hz)	gHMBC	gCOSY
1	160.6 s		H-3	
2	182.0 s		H-3; H-4	
3	120.4 d	7.05 d (15.5)	H-5	H-4
4	152.8 d	7.96 ddd (15.5; 11.2)	H-6	H-3; H-5
5	127.2 d	7.10 ddd (15.5; 11.2)	H-3	H-4; H-6
6	142.3 d	7.53 d (15.5)	H-4; H-6'	H-5
1'	124.4 s		H-5; H-3'; H-5'	
2'	158.2 s		H-6; H-3'; H-4'; H-6'; H-7'	
3'	111.3 d	6.92 dd (8.0; 1.0)	H-5'	H-4'
4'	131.7 d	7.35 ddd (8.0; 8.0; 1.0)	H-6'	H-3'; H-5'
5'	120.9 d	6.98 ddd (8.0; 8.0; 1.0)	H-3'	H-4'; H-6'
6'	128.3 d	7.53 dd (8.0; 1.0)	H-6; H-4'	H-5'
7'	55.6 q	3.90 s		

^a Recorded at 500 and 125 MHz for 1H and ^{13}C NMR, respectively. ^b Internal standard TMS, $\delta_{TMS} = 0.00$.

Computational Strategy

In the present investigation, the employed quantum chemical approach to determining the molecular structures was Becke three-parameter hybrid method⁹ using the Lee-Yang-Par (LYP) correlation functional¹⁰ and the basis sets used for calculations were the 6-311G.^{11,12} The performed molecular calculations in this work were done using the Gaussian 03 routine.¹³

Molecular structure of the compound could not be determined by the single crystal X-ray diffraction technique, a geometry optimization was computed using the optimized algorithm of Berny.¹⁴

Theoretical infrared spectrum was calculated using a harmonic field¹⁵ based on C_1 symmetry (electronic state 1A). Frequency values (not scaled), relative intensities, assignments and description of vibrational modes are presented. The calculations of vibrational frequencies were also implemented to determine an optimized geometry constitutes minimum or saddle points. The principal infrared-active fundamental modes assignments and descriptions were done by the GaussView 3.0 graphics routine.¹⁶

The optimized structure parameters of 2-MeO-HCP dimer calculated by ab initio DFT-B3LYP levels with the 6-311G basis set are listed in Table 2 in accordance with the atom numbering scheme given in Figure 2.

Optimized geometries and vibrational modes for studied molecular structures were compared with the experimental frequencies. The optimized geometric parameters (bond lengths and bond angles) obtained, see Table 2, did not can be compared with experimental parameters because the crystal structure of the title compound is not available until now. The Mulliken atomic charges, dipole moment and theoretically computed energies are gather in Table 3. Taking into account that the molecular geometry of the dimer alone in vapor phase may be different from that dimer in the solid phase, owing to extended hydrogen bonding and stacking interactions there is reasonable agreement between the calculated and experimental geometric parameters. As discussed by Johnson *et al.*¹⁷, DFT method predicts bond lengths which are systematically too long, particularly the CH bond lengths.

Table 2. Theoretical geometries parameters of 2-MeO- HCP compound.

Bond lengths(Å)		
d C1 – C2 ^a	1.41	< H53 – C8 – H54 109.3
d C2 – C3	1.42	< C12 – C11 – C10 125.0
d C3 – C4	1.40	< C11 – C10 – C9 122.2
d C5 – C6	1.39	< C10 – C9 – C2 127.5
d C1 – C6	1.39	< C9 – C2 – C1 123.1
d C2 – C9	1.46	< C9 – C2 – C3 119.3
d C9 – C10	1.35	< C2 – C3 – C4 120.5
d C10 – C11	1.43	< C3 – C4 – C5 120.1
d C11 – C12	1.35	< C4 – C5 – C6 120.5
d C12 – C13	1.46	< C5 – C6 – C1 119.4
d C13 – C15	1.55	< C6 – C1 – C2 122.0
d C3 – O7	1.36	< C3 – O7 – C8 119.3
d C8 – O7	1.42	< H36 – O17 – C15 127.2
d C15 – O16	1.31	< H35 – O16 – C15 110.2
d C15 – O17	1.23	< H14 – C13 – C12 125.7
d C13 – O14	1.22	< H14 – C13 – O15 119.5
d C12 – H51	1.08	< H51 – C12 – C11 121.6
d C11 – H37	1.09	< H51 – C12 – C13 117.7
d C10 – H42	1.09	< H37 – C11 – C12 117.3
d C9 – H43	1.09	< H37 – C11 – C10 117.6
d C1 – H58	1.08	< H42 – C10 – C11 116.9
d C6 – H57	1.08	< H42 – C10 – C9 120.9
d C5 – H56	1.09	< H43 – C9 – C10 117.4
d C4 – H55	1.08	< H43 – C9 – C2 115.2
d C8 – H52	1.10	< H58 – C1 – C2 119.1
d C8 – H53	1.10	< H58 – C1 – C6 119.0
d C8 – H54	1.09	< H57 – C6 – C1 120.1
d O16 – H35	0.99	< H57 – C6 – C5 120.4
d O17 – H36	1.73	< H56 – C5 – C6 120.3
Bond angles (°)		
< O16 – C15 – O17	125.1	< H56 – C5 – C4 119.3
< C15 – C13 – O14	119.5	< H55 – C4 – C5 119.4
< C15 – C13 – C12	114.8	< H55 – C4 – C3 120.6
< C13 – C12 – C11	120.7	< O7 – C3 – C4 123.5
< H53 – C8 – O7	111.4	< O7 – C3 – C2 116.1
< H53 – C8 – H52	109.6	< H52 – C8 – O7 111.4
		< H54 – C8 – O7 105.7

Key: H-2-MeO-CP = 2-methoxycinnamylidenepyruvic acid; d = bond lengths; < = bond angles;

^a Atom numbering accord Figure 2.

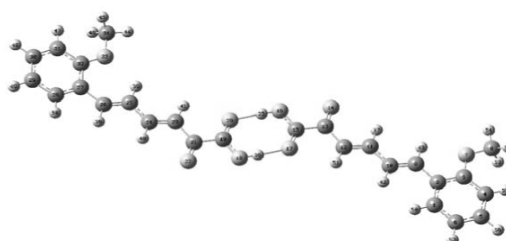


Figure 2. Theoretical 3D structure of solid-state of the 2-MeO-HCP dimer optimized using Becke three-parameter hybrid method, 6-311g basis set of Gaussian 03.

Table 3. Mulliken atomic charges and additional parameters calculated in B3LYP/6-311g level.

atom		atom		atom	
C1a	-0.20	C12	-0.30	H42	0.20
C2	-0.03	C13	0.17	H43	0.22
C3	0.23	C15	0.43	H51	0.22
C4	-0.27	O7	-0.35	H52	0.22
C5	-0.18	O14	-0.29	H53	0.22
C6	-0.19	O16	-0.47	H54	0.24
C8	-0.47	O17	-0.41	H55	0.22
C9	-0.19	H35	0.42	H56	0.20
C10	-0.17	H36	0.42	H57	0.20
C11	-0.11	H37	0.22	H58	0.20
E (a.u.)		-1607.36			
Dipole moment (Debye)		2.86			

^a Atom numbering accord Figure 2

The experimental and theoretical IR spectra of 2-MeO-HCP are given in Figure 3. The resulting vibrational frequencies for the optimized geometries and the proposed vibrational assignments are given in Table 4. Comparisons between theoretical and experimental IR spectra indicated that vibrations were more intense in experimental than theoretical spectrum.

For 2-MeO-HCP group the vibrational modes are C–H stretch, C=O stretch, O–H stretch, O–CH₃ stretch, CH₃O–C_{ar} stretch, C–C stretch, C_{co}–C_{coo} stretch, C–C–C bending, CH₃ bending, C–H bending, COO bending and ring bending.

O–H stretching band is characterized by very broad band appearing near about 2500–3600 cm⁻¹. This may be due combined effect of intermolecular hydrogen bonding. The O–H in plane bending vibration occurs in general at 1440–1395 cm⁻¹. The O–H out of plane bending vibration occurs in 960–875 cm⁻¹.¹⁸ In 2-MeO-HCP, O–H stretching were assigned at 3309 and 3358 cm⁻¹, and in plane and out of plane bending vibrations were assigned at 1385 and 957 cm⁻¹, respectively. Theoretically computed values (3300, 1400 and 970 cm⁻¹) were in agreement with experimental results.

The main feature of carboxylic group is a single band observed usually in the 1700–1800 cm⁻¹ region.¹⁸ This band is due to the C=O stretching vibration. Theoretically computed value of C=O (1750 cm⁻¹) band show is agreement with experimental data (1760 cm⁻¹).

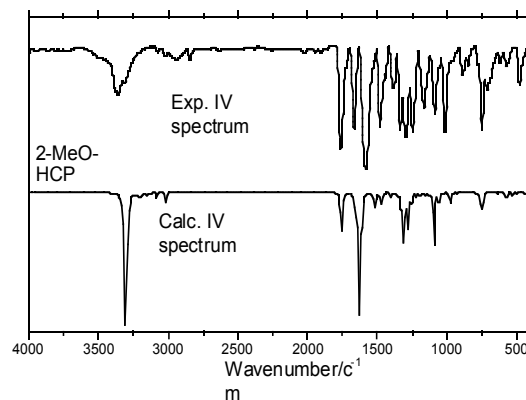


Figure 3. Experimental and calculated IR spectra of 2-MeO-HCP.

Experimental vibration frequencies were in agreement with that theoretically calculated, see Table 4.

Conclusion

In conclusion, 2-MeO-HCP purity was determined for DSC and structural elucidation was made by MS, NMR and IR. Theoretical infrared spectra was calculated and compared with experimental data. The difference between the observed and scaled wavenumbers values of most of the fundamentals is very small. Any discrepancy noted between the observed and the calculated frequencies may be due to the fact that the calculations have been actually done on a single molecule contrary to the experimental values recorded in the presence of intermolecular interactions. Therefore, the assignments made at higher levels of theory with only reasonable deviations from the experimental values, seem to be correct.

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Table 4. Wavenumbers (cm⁻¹), intensities and assignments of bands occurring in the IR spectra of 2-MeO-HCP. The theoretical wavenumbers were calculated in B3LYP/6-311g level.

	Wavenumber /cm ⁻¹	Vibrational assignments		Wavenumber /cm ⁻¹	Vibrational assignments
IR	476 _m	β (CCC), β	IR	1246 _m	β _s (CH ₃)
Theor.	430 _w	(CO ^a C), β (COO)	Theor.	1220 _w	
IR	-	β (CO ^a C), β	IR	1296 _m	ν (CH ₃ O-C _{ar}), β (CH)
Theor.	530 _w	(CCO)	Theor.	1280 _m	
IR	574 _w	β (CCC), α	IR	1335 _m	ν(CC)
Theor.	570 _w	(CCC)	Theor.	1310 _m	
IR	-	β (CCC), α	IR	1385 _m	β (CH), β (OH)
Theor.	580 _w	(CCC)	Theor.	1400 _w	
IR	615 _m	α (CCC)	IR	1438 _w , 1479 _m	ν(C _{co} -C _{coo})
Theor.	640 _w		Theor.	1470 _w	
IR	710 _m	β _{as} (COO)	IR	1580 _s	ν(CC) _{ar} , δ(CH ₃)
Theor.	750 _m		Theor.	1520 _m , 1610 _m	
IR	847 _w , 885 _w	γ (CH)	IR	1665 _m	ν(CC) _{ar}
Theor.	-		Theor.	1630 _s	
IR	957 _w	γ(OH)	IR	1760 _s	ν(C=O)
Theor.	970 _w		Theor.	1750 _m	
IR	1013 _s	γ(CH)	IR	2842 _w , 2936 _w , 3018 _w	ν _s (CH ₃)
Theor.	1050 _m		Theor.	3020 _w	
IR	1055 _w	ν (-O-CH ₃)	IR	3074 _w	ν _{as} (CH ₃)
Theor.	1053 _w		Theor.	3080 _w	
IR	1084 _m	ν(-C-CO-)	IR	-	ν(CH)
Theor.	1090 _m		Theor.	3150 _w	
IR	1161 _m	β (CH)	IR	3309 _m , 3358 _m	ν(OH)
Theor.	1130 _w , 1150 _w		Theor.	3300 _{vs}	

^aoxygen methoxy group

ν, stretching; ν_s, sym. stretching; ν_{as}, asym. stretching; β, in-plane-bending; γ, out-of-plane bending;

C. T. de Carvalho, A. B. Siqueira, E. Y. Ionashiro, M. Pivatto, M. Ionashiro. Síntese e caracterização do ácido 2-metoxicinamalpirúvico.

Resumo: O ácido 2-metoxicinamalpirúvico (2-MeO-HCP) foi sintetizado e caracterizado por ressonância magnética nuclear (¹H and ¹³C NMR), espectrometria de massas (MS), espectroscopia na região do infravermelho (FTIR) e calorimetria exploratória diferencial (DSC). A técnica DSC foi usada para determinação da pureza do composto e as principais bandas de absorção na região do infravermelho foram atribuídas utilizando-se o programa GaussView 3.0.

Palavras-chaves: ácido 2-metoxicinamalpirúvico; síntese; MS; NMR; IR.

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