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Research Article

A Straightforward Selective Acylation of Phenols over ZSM-5 towards Making Paracetamol Precursors

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Abstract

Commercially available ZSM-5 was minimally treated as the catalyst to selectively acylate phenols. The ZSM-5 was simply immersed in ammonium nitrate in order to fill the pores with Brönsted acid to concentrate the catalytic reactions inside the pores. The reactions were carried out in liquid phase at 383 K. Acetic acid and propionic acid were chosen as the acyl substrate. Gas chromatography reveals two products which are phenyl acetate and almost exclusively *para*-hydroxyacetophenone meaning no *ortho* product observed. This *para* selectivity can be attributed to the pores of ZSM-5 where the reaction is assumed to be happening via intermolecular reaction. It is a relatively straightforward method in making *para*-hydroxyacetophenone which is known as paracetamol precursor.

Keywords: Acylation of Phenol; ZSM-5; Regioselectivity; *Para*-hydroxhyacetophenone

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1. Introduction

Acylation of phenol is an important step in organic synthesis since the products are key intermediates for a number of compounds. Both *ortho*-hydroxhyacetophenone (*o*-HAP) and *para*-hydroxhyacetophenone (*p*-HAP) are used in Hoechst-Celanese process to produce drug [1]. Separately, *p*-HAP is known to be used in making paracetamol [2,3] meanwhile the *o*-HAP is an intermediate to make 4-hydroxycoumarin and warfarin, both known as anticoagulant drugs [4], and also to obtain flavanone via Claisen-Schmidt condensation [5,6]. In a similar reaction, acylation of resorcinol is also important as the product can be used for the production of valuable fine chemicals such as ipriflavone (antiosteopenic drug) and 4-O-octyl-2-hydroxybenzophenone (UV-light absorbent for polymers) [7].

Hydroxhyacetophenone could be synthesized by Fries rearrangement of phenyl acetate or Friedel-Crafts direct acylation of phenol [8]. These reactions conventionally are catalyzed with homogeneous/heterogeneous Lewis Acid and Brönsted Acid catalysts [9]. The key challenge in this reaction is to tune the selectivity of the reaction whether to obtain the ortho, the para, or even to reduce the O-acylation product

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which is usually phenyl acetate. Porous heterogeneous catalysts like zeolite have an advantage here since the pores can be engineered to selectively only allow one kind of products. Their homogeneous counterpart, usually metal halides, still have some inconvenience like the need to separate and some environmental issues because they are relatively toxic and corrosive [10].

The ratio of *o*-HAP dan *p*-HAP products depends on the reaction condition. Lower temperature usually favors the formation of *p*-HAP and higher temperature favors *o*-HAP [11]. The ratio of *p*/*o* increases with lower amount of catalyst and reaches a constant at increased amount of catalyst and by using solvent with great polarity [7]. In previous study, HZSM-5 is utilized to catalyze Fries rearrangement of phenyl acetate at 170 °C to result a *p*-HAP selective reaction (*p*/*o* ratio: 6.0) [12]. When the similar reaction is carried over the same catalyst at 265 °C, the selectivity changes to favor *o*-HAP (*o*/*p* ratio: 35.5) [13]. This shows the effect of temperature in tuning the selectivity of acylation. In the case of direct acylation, phenol is acylated with acetic anhydride over HZSM-5 that shows a very high *ortho* selectivity (72.4 % phenol conversion, 20.1 % PA yield, 47.8 % *o*-HAP yield, 0.6 % *p*-HAP yield) [14]. Guisnet *et al*. carry out the acylation of phenol with activated acetic acid in gas phase that still results in higher *ortho* selectivity (*o*/*p* ratio: 16.0) [15]. One example that shows *para* selectivity is the acylation of phenol using benzoic anhydride over HBEA zeolites with *p*/*o* at 2.1 [16].

Here, we report acylation of phenols with acetic acid and propionic acid over protonated ZSM-5 with high *para* selectivity in liquid phase and relatively mild condition. We developed the method as straightforward as possible to reduce any complexity. Nevertheless, the selectivity of the acylation was surprisingly high towards the formation of *p*-HAP and little to none of *o*-HAP was observed. This simplistic method shows promise to generate total selectivity of phenol acylation.

2. Materials and Methods

2.1 Materials and Equipments

Propionic acid, acetic acid glacial, phenol and organic solvents were purchased from Merck. ZSM-5 {pore size 4.6 Å; (0.9 ± 0.2) $H \cdot Al_2O_3 \cdot (25\text{-}50)SiO_2 \cdot 2H_2O$} was purchased from Qingdao Wish Chemical. Electron Micrograph of ZSM-5 was recorded using JEOL-JSM-6510LV Scanning Electron Microscope (SEM) under low vacuum, operated at 10-15 kV. The XRD measurements of ZSM-5 were performed on Phillips Analytical X-ray PW1835 using Cu anode with wavelength of 1.5406 Å. Quantification of products were carried out by gas chromatography (GC) using Techcomp GC-7900 with a flame ionization detector (FID) and a SGE ENX-5 capillary column (length = 15 m, inner diameter = 0.25 mm, and film thickness = 0.25 μm). Temperature program for GC analyses was set at 100 °C for 1 min and raised to 190 °C at rate of 30 °C/min and from 190 to 210 °C at rate of 10 °C/min. The temperature was finally kept for 5 min at 210 °C. The products were confirmed with ^{1}H- and ^{13}C-NMR spectra recorded on an Agilent DD2 system operating at 500 MHz (^{1}H) and 125 MHz (^{13}C).

2.2 Catalyst Preparation

To a 250 mL solution of 1 M ammonium nitrate was added 20 g of ZSM-5. The suspension was stirred at r.t. for 24 h followed by filtration. The white solid was dried in oven at 90 °C for 2 h and calcinated in the furnace at 550 °C for 6 h. This process was repeated once more to ensure the protonation of the zeolite. The protonated zeolite was characterized before and after utilized as catalyst with XRD and SEM.

2.3 Acylation of Phenol

The 2.5 g protonated ZSM-5 in three neck round bottom flask was heated at 110 °C for 2 h under N_2 atmosphere. The zeolite was cooled to r.t. before use. To the zeolite was added 21 mmol of phenol in 100 mmol of acid. The mixture was heated at 110 °C and the reaction was monitored with thin layer chromatography. After 72 h, the mixture was filtrated and purified with silica column chromatography (*n*-hexane/EtOAc = 95:5). The products were characterized with NMR and GC-MS:

p-hydroxypropiophenone (p-HPP):
^{1}H NMR (CD_3OD): δ 7.87 (2H, *d*, *J* = 8.7 Hz), 6.83 (2H, *d*, *J* = 8.7 Hz), 3.34 (1H, *s*), 2.95 (2H, *q*, *J* = 7.3 Hz), 1.15 (3H, *t*, *J* = 7.3 Hz). ^{13}C NMR: δ 202.1, 163.7, 129.8, 131.6, 129.8, 116.2, 32.1, 8.9.

Phenyl propionate (PP):
^{1}H NMR ($CDCl_3$): δ 7.40 (2H, *t*, *J* = 7.8 Hz), 7.23 (1H, *t*, *J* = 7.3 Hz), 7.11 (2H, *d*, *J* = 7.9 Hz), 2.61 (2H, *q*, *J* = 7.5 Hz), 1.29 (3H, *t*, *J* = 7.5 Hz). ^{13}C NMR: δ 172.9, 150.8, 129.3, 125.7, 121.5, 27.7, 9.0

p-hydroxyacetophenone (p-HAP):
^{1}H NMR ($CDCl_3$): δ 7.92 (2H, *d*, *J* = 8.8 Hz), 6.93 (2H, *d*, *J* = 8.6 Hz), 2.58 (3H, *s*). ^{13}C NMR: δ 198.4, 161.2, 131.3, 129.9, 115.6, 26.4

Phenyl acetate (PA):
^{1}H NMR ($CDCl_3$): δ 7.41 (2H, *t*, *J* = 8.0 Hz), 7.23 (1H, *d*, *J* = 7.2 Hz), 7.12 (2H, *d*, *J* = 7.8 Hz), 2.29 (3H,s). ^{13}C NMR: δ 169.4, 150.7, 129.3, 125.7, 121.5, 21.0.

Phenol conversion (X_p) was calculated according to Equation (1), while product selectivity (S_i) was calculated using Equation (2). In this equations, ΣY_i is total area of product, and Y_p is area of phenol, and X_i is area of product.

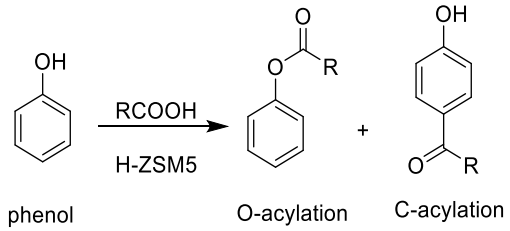
$$X_p = \frac{\sum Y_i}{\left(\sum Y_i + Y_p\right)} x100\% \quad (1)$$

$$S_i = \frac{X_i}{\sum Y_i} x100\% \quad (2)$$

3. Results and Discussion

The ZSM-5 was protonated before use to have a Brönsted acid property along with the Lewis acid property from the ZSM-5 which will be important in the catalytic process. The proton was designated only to be inside the pores of ZSM-5 by drying the zeolite after immersion in ammonium nitrate. This is to make sure that the Brönsted acids catalyze the reaction inside the pore, not outside, in order to increase selectivity. SEM images (Figure 1) show that the ZSM-5 has the shape like coffin and did not indicate any changes before and after protonation. XRD measurement also gave a similar diffractogram before and after protonation that suggests there is no significant change in morphology (Figure 2).

The acylation of phenol reactions were carried out for 72 h over ZSM-5 as the catalyst in a relatively mild condition (383 K) and liquid phase. There were two acyl substrates applied, acetic acid and propionic acid. After 24 h of reactions, the phenol was still observed and the reaction might have stopped at 24 h since no changes were observed after 24 h. This might be the indication of deactivation of the catalyst has occurred after 24 h.



Scheme 1. Acylation of phenol; R = CH_3; C_2H_5

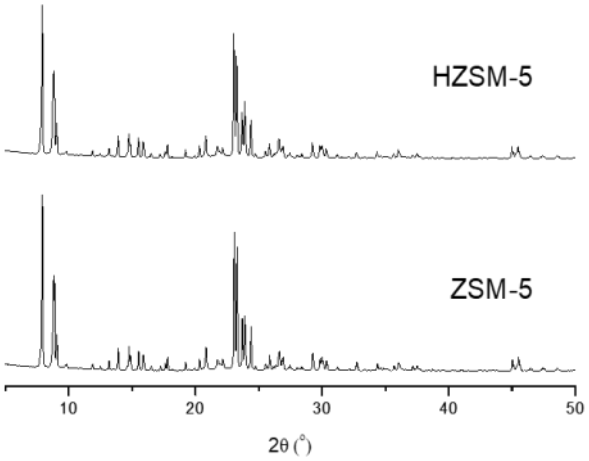


Figure 2. Difractogram of ZSM-5 before (bottom) and after (up) protonation

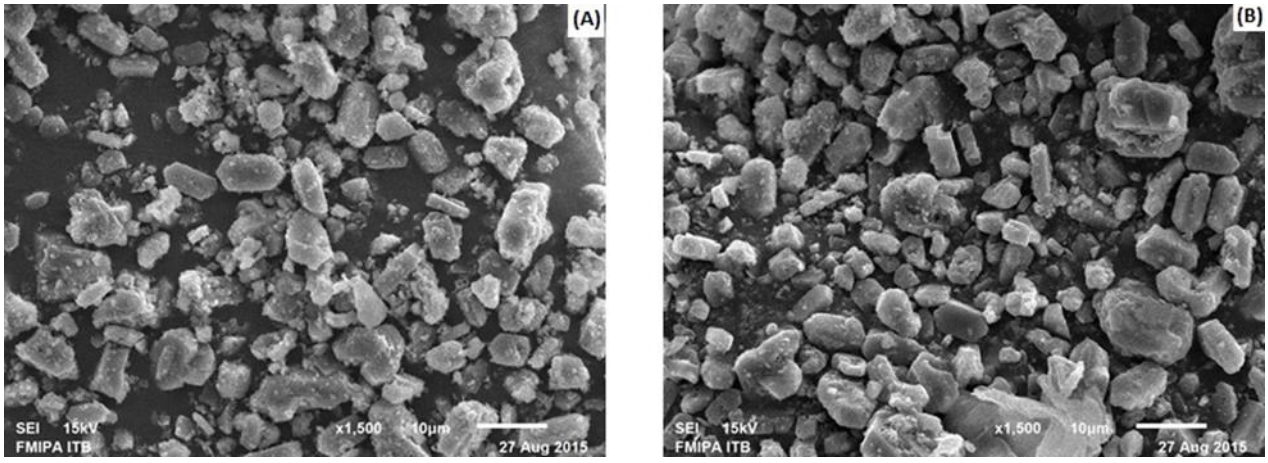


Figure 1. SEM micrographs of ZSM-5 (A) before and (B) after immersion with ammonium nitrate

Gas Chromatography measurements of the crude show both substrates gave two products (see Electronic Supporting Information). After work up and purification, the products were checked in NMR. The NMR spectra confirmed that the two products obtained are O-acylation as the major and the other is C-acylation. O-acylation products are phenylacetate (PA) and phenylpropionates (PP) meanwhile the C-acylation are *p*-hydroxyacetophenone (p-HAP) and *p*-hydroxypropiophenone (p-HPP). The reactions have moderate conversions at around 35 %. It is still a challenge to raise this conversion especially since phenyl acetate produced can also be reversed to produce phenol and ketene that reacts further with water to form acetic acid [8,17].

Table 1 shows the summary of acylation of phenol catalyzed by ZSM-5 on the two substrates. The remarkable part of the results was the selectivity of the C-acylation that only produced *para* products for both of the substrates. No *ortho* products were observed that leads to the conclusion that the selectivity is almost 99 %. The absence of *ortho* products gives a clue that the reaction might occurred inside the pore hence the exclusivity of the *para* products. The pores of ZSM-5 itself favor the insertions of *para* substituted benzenes than the *ortho* ones [18]. Inside the pores, the *para* products are formed via intermolecular reaction not intra molecular Fries rearrangement [19]. The reactions were indeed designed to occur inside the pores by removing the possible excess of Brosnted acid via drying the ZSM-5. It was also mentioned that lower temperature favor the formation para products [7]. Furthermore, *p*-hydroxyacetophenone can be formed through double acylation of the phenols followed by hydrolysis of the ester [15,20].

4. Conclusions

A very high selectivity towards *para* product of acylation of phenol with acetic acid and propionic acid over HZSM-5 was achieved. The method is relatively straightforward since it is carried out in liquid phase, mild condition, and minimum preparation of catalyst. The high selectivity can be achieved because of the use of protonated ZSM-5 which has a unique porous characteristic, as well as the Lewis acidity, that suits this selective reaction. This is really a remarkable lead to further investigate total selective acylation over HZSM-5. A high selectivity of acylation of phenol towards *ortho* products is really important in the making of paracetamol precursors.

Acknowledgments

We would like to thank *Riset Peningkatan Kapasitas* ITB program for funding this research.

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Table 1. Conversion of acylation of phenol and the selectivity of the products

Acid substrate	% phenol conversion[a]	Product Selectivity (%)[b]		
		O-acylation (Ester)	C-acylation	
			Para- product	*Ortho*- product
Acetic acid	32	74	26	0
Propionic acid	40	62	38	0

[a] determined by comparing the total peak area of products' peak on gas chromatogram over the total area of peaks (phenol + products)

[b] determined by comparing the peak area of the specified product on gas chromatogram with the total peak area of all the products

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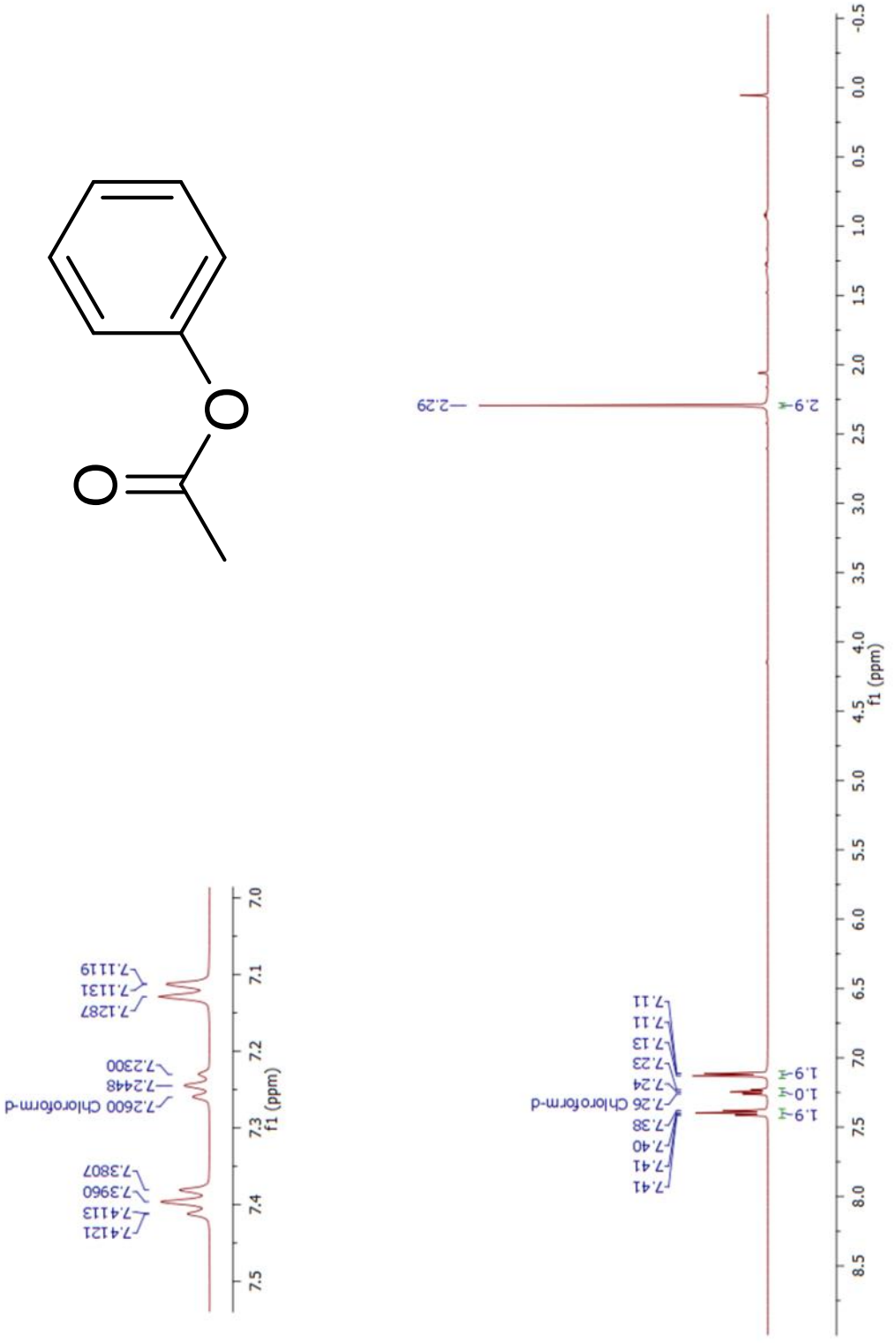
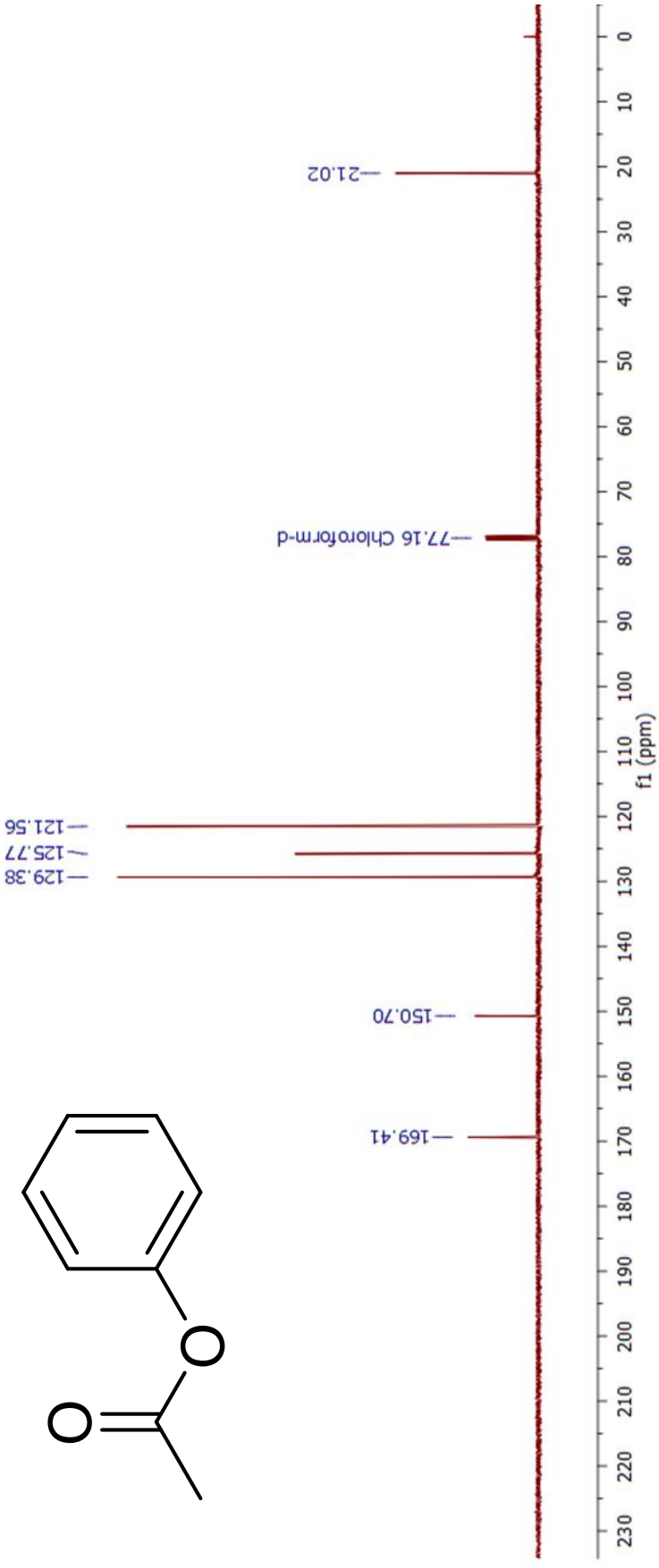
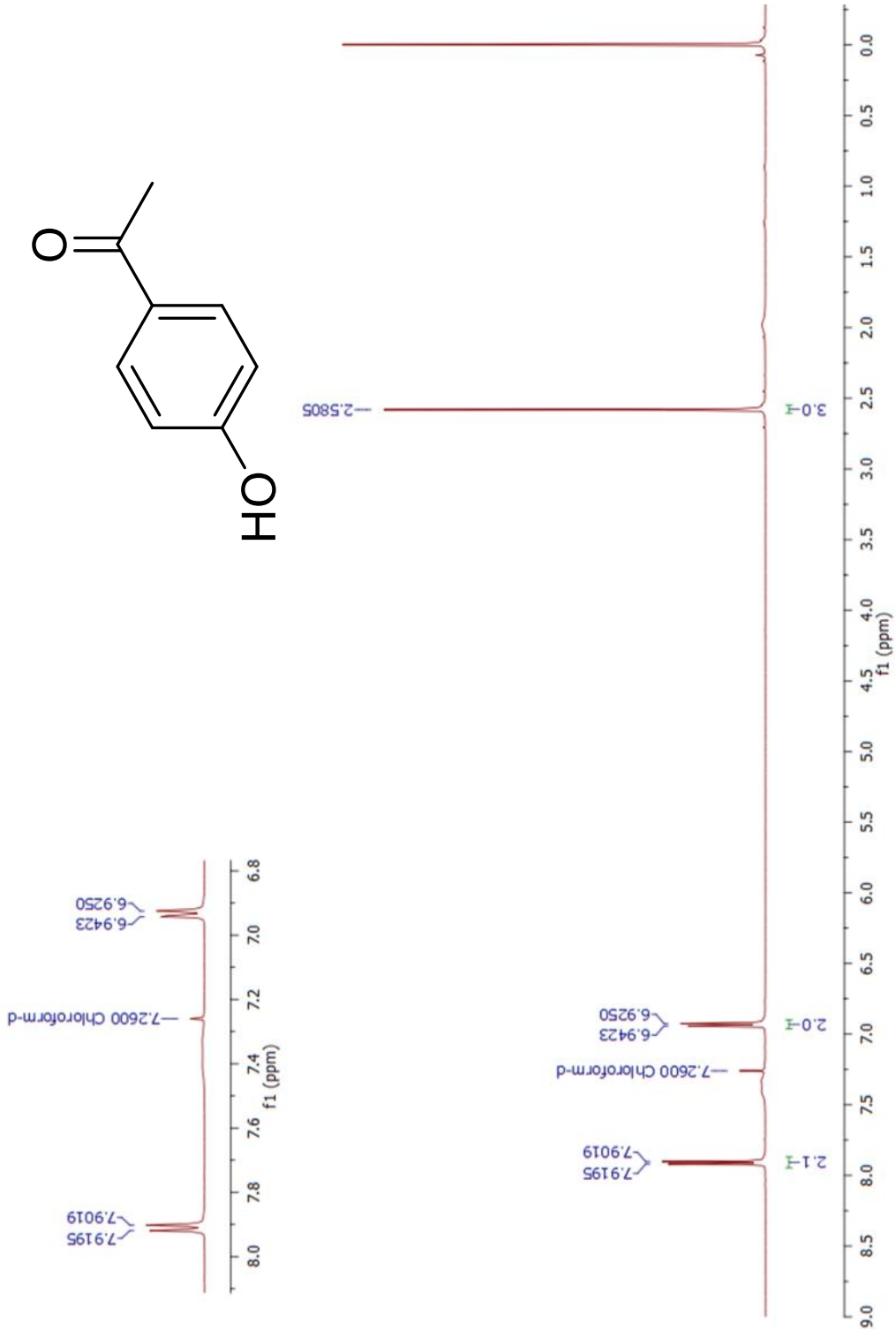
Appendix



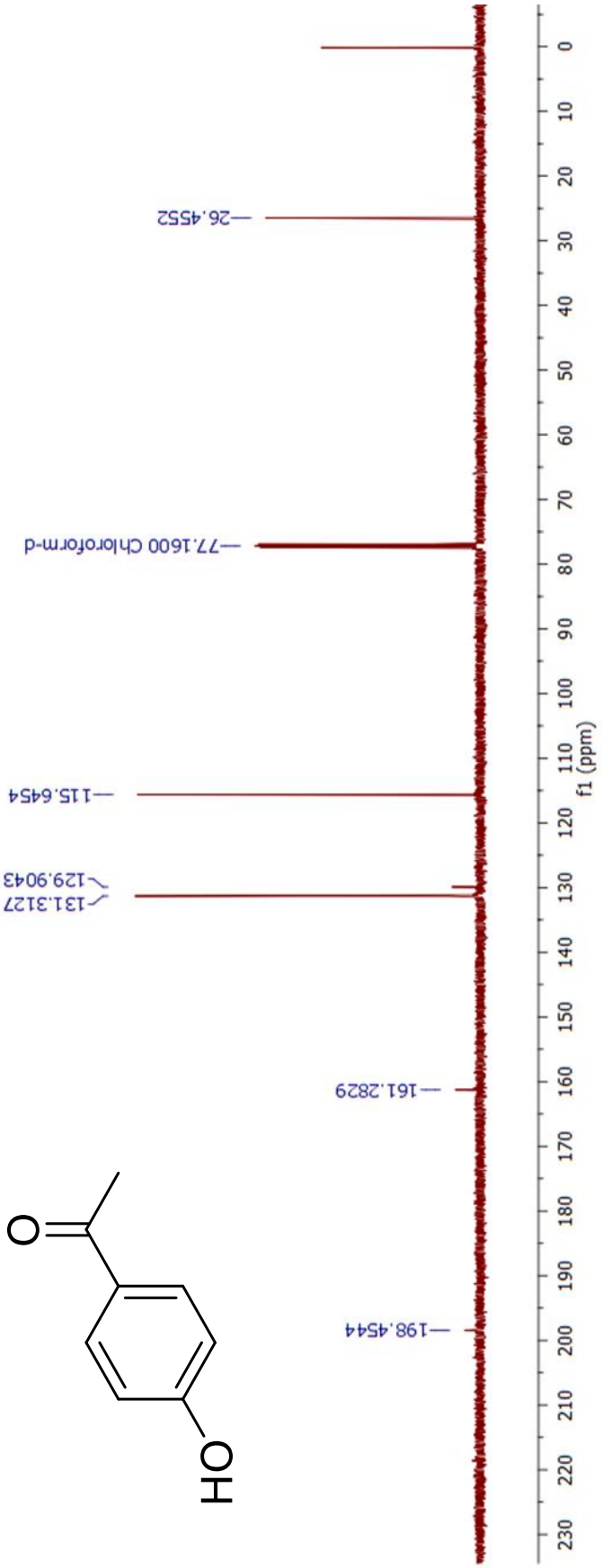
Spectrum S1. ^{1}H NMR Spectrum of Phenyl acetate (PA)



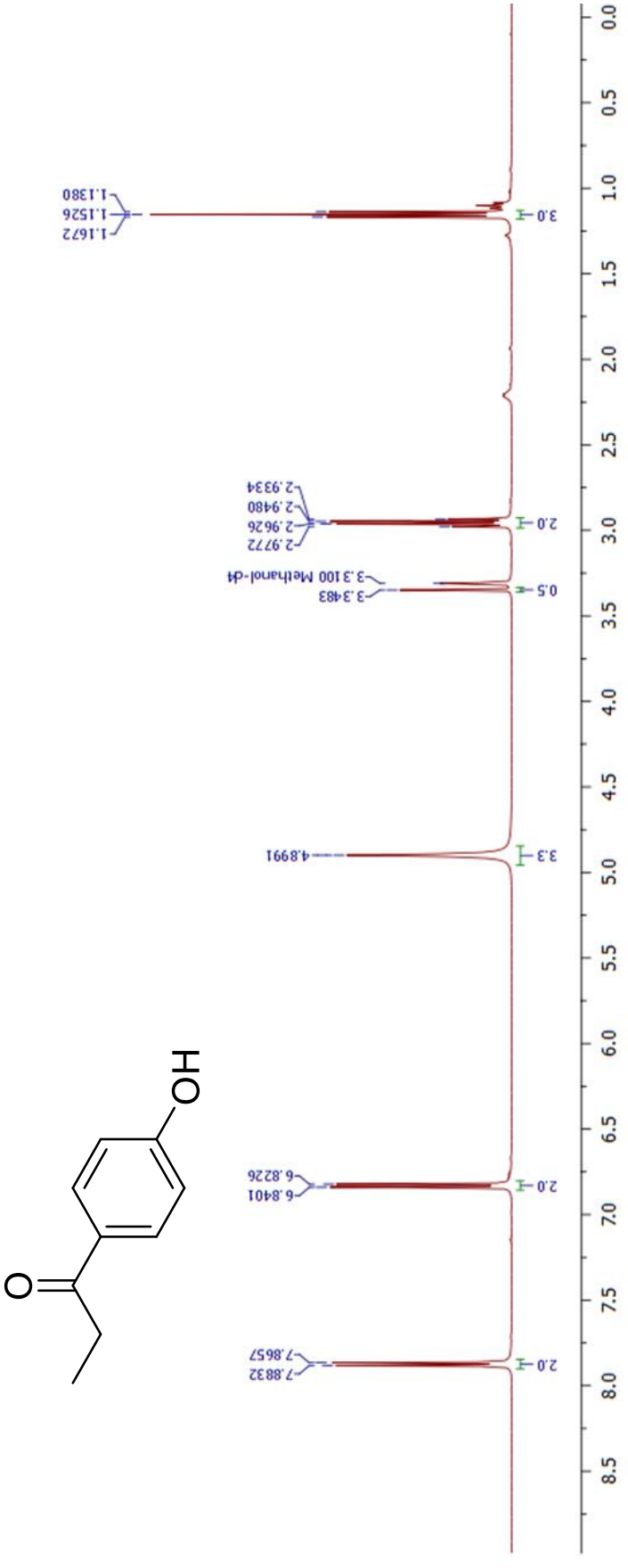
Spectrum S2. ^{13}C NMR Spectrum of Phenyl acetate (PA)



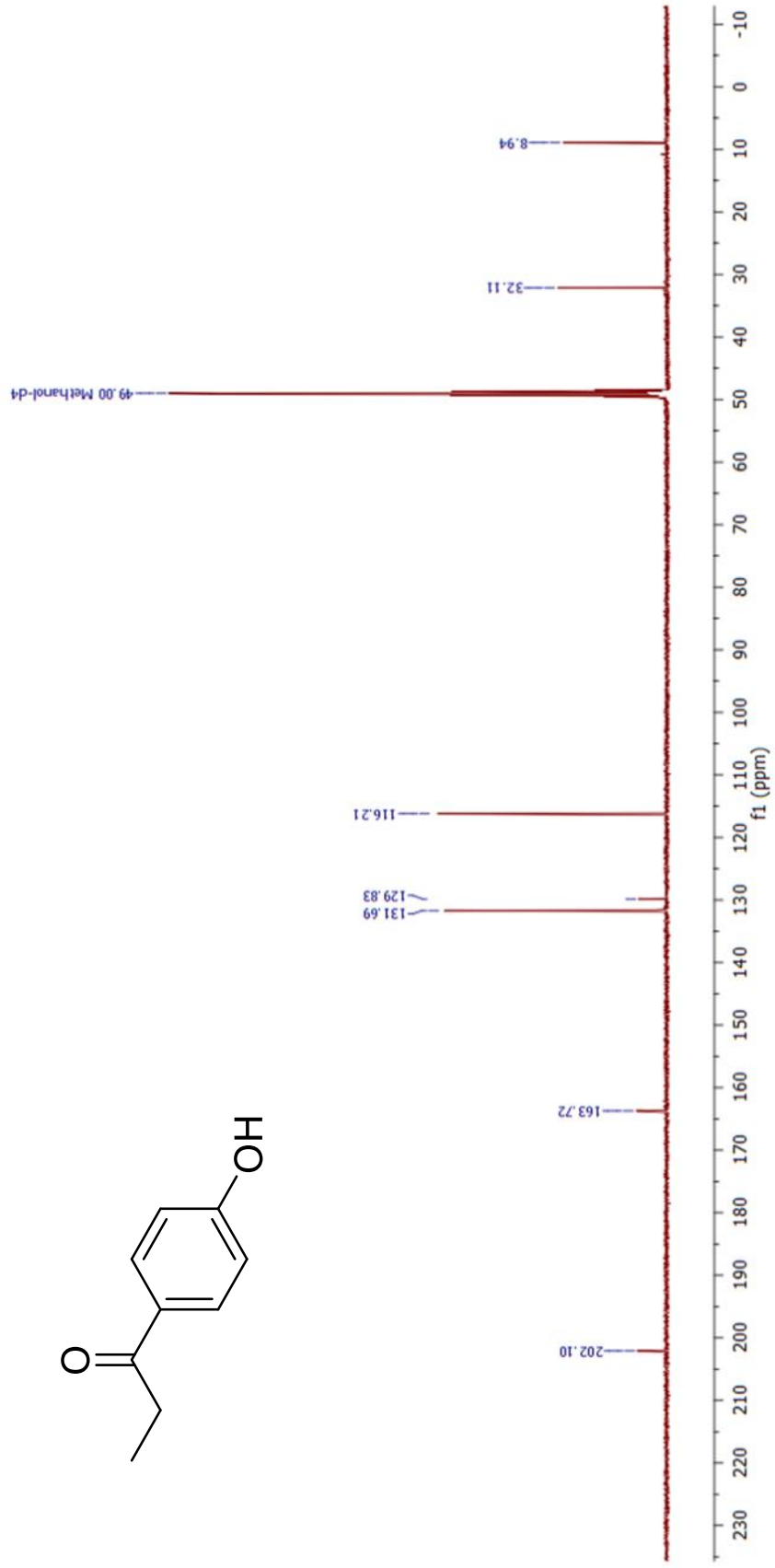
Spectrum S3. ^{1}H NMR Spectrum of *p*-hydroxyacetophenone (p-HAP)



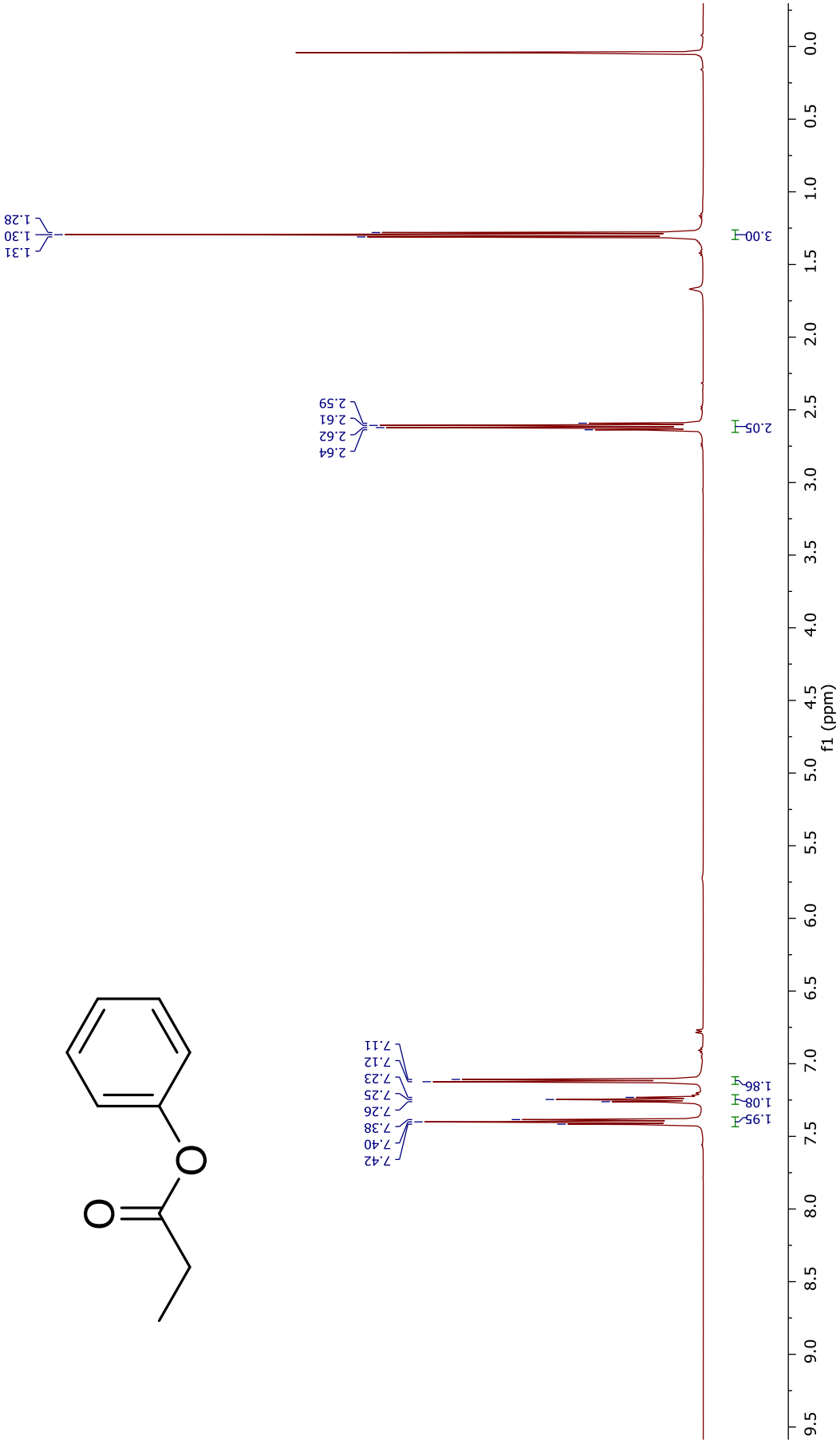
Spectrum S4. ^{13}C NMR Spectrum of *p*-hydroxyacetophenone (p-HAP)



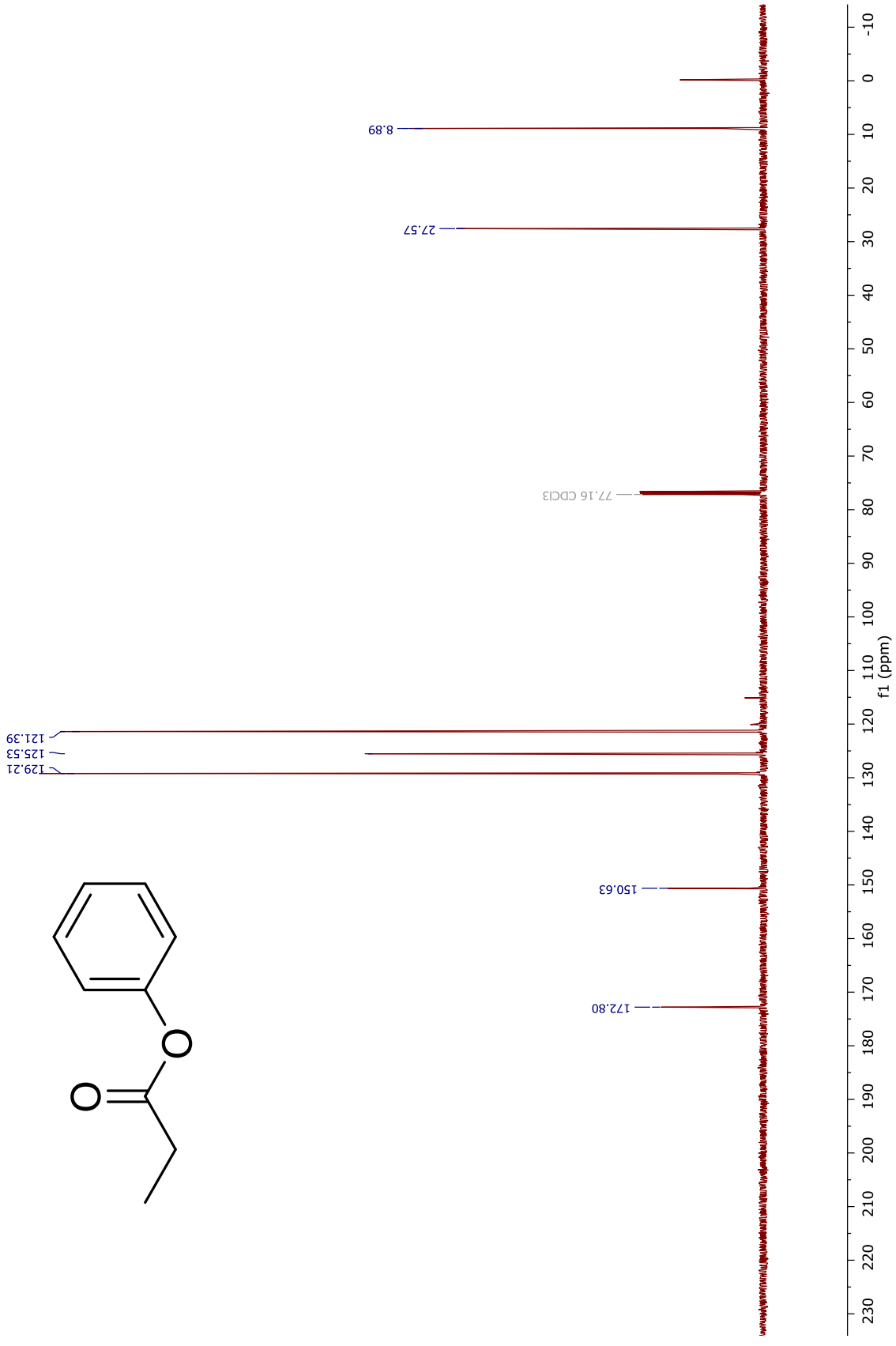
Spectrum S5. ^{1}H NMR Spectrum of *p*-hydroxypropiophenone (p-HPP)



Spectrum S6. ^{13}C NMR Spectrum of *p*-hydroxypropiophenone (p-HPP)

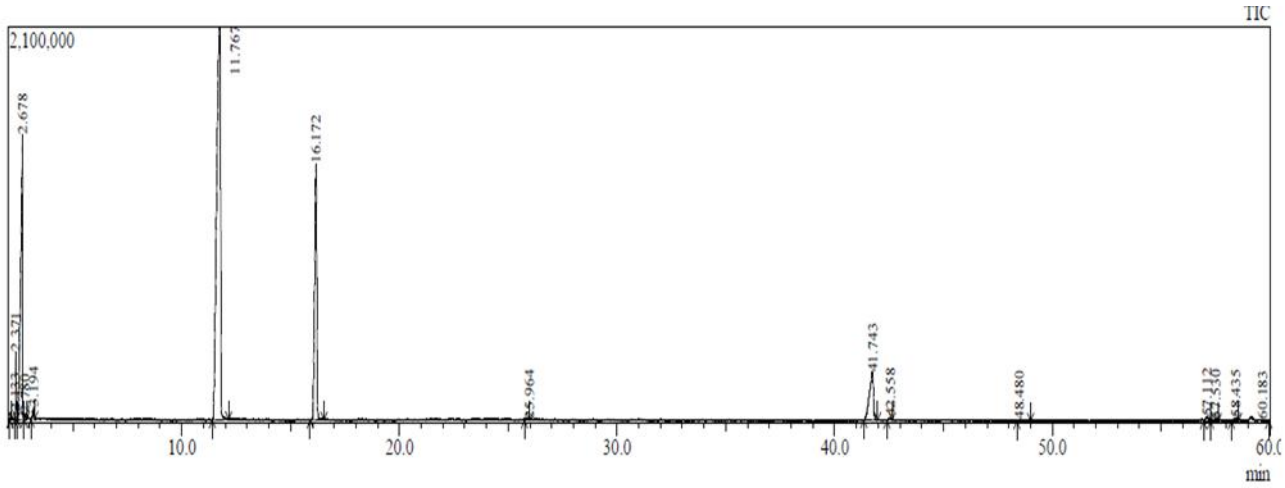


Spectrum S7. ^{1}H NMR Spectrum of Phenyl Propionate (PP)



Spectrum S8. ^{13}C NMR Spectrum of Phenyl Propionate (PP)

Chromatogram S9. Gas Chromatogram of Acetylation of Phenol



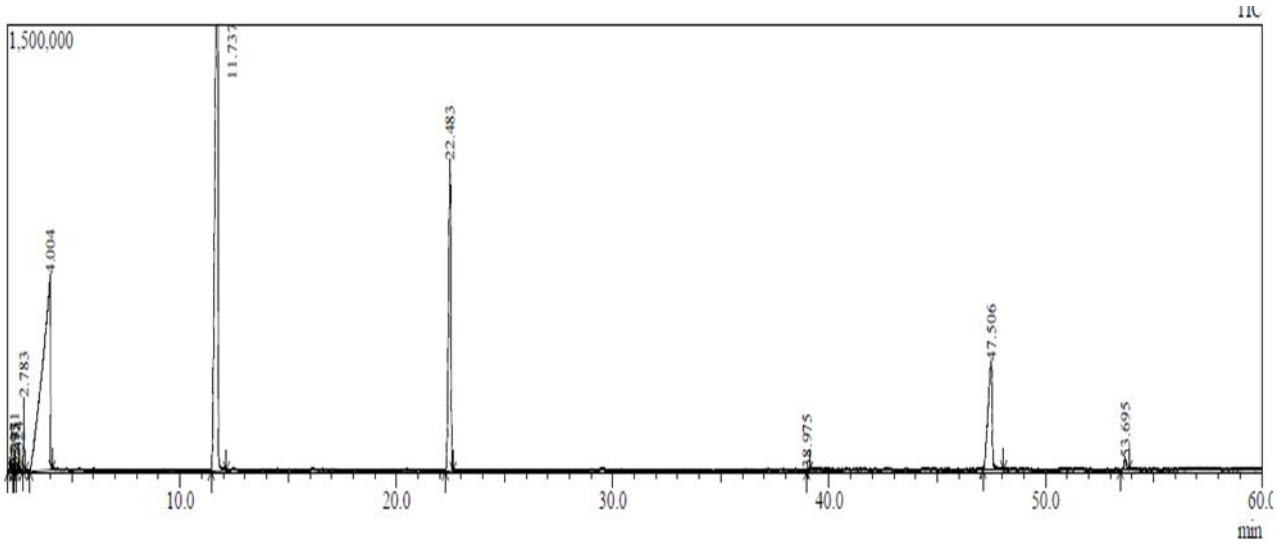
Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	2.133	2.100	2.175	78606	0.15	39697	0.65	1.98		1-Chloro-1-nitrosoethane
2	2.371	2.330	2.425	714738	1.38	360580	5.91	1.98	V	Acetic acid, methyl ester (CAS) Methyl acetate
3	2.678	2.450	2.745	9317168	18.03	1513039	24.80	6.16	V	Acetic acid (CAS) Ethylic acid
4	2.780	2.745	2.855	110660	0.21	28767	0.47	3.85	V	Propanoic acid, methyl ester (CAS) Methyl pro
5	3.194	3.070	3.250	271071	0.52	66584	1.09	4.07	V	Propanoic acid (CAS) Propionic acid
6	11.767	11.400	12.155	27655484	53.52	2428028	39.80	11.39	S	Phenol (CAS) Izal
7	16.172	15.895	16.535	9560309	18.50	1353156	22.18	7.07	SV	Acetic acid, phenyl ester (CAS) Phenyl acetate
8	25.964	25.745	25.975	50131	0.10	5290	0.09	9.48	V	Hydrazine, [4-(trifluoromethoxy)phenyl]-
9	41.743	41.345	41.980	3300107	6.39	251916	4.13	13.10		Acetophenone, 4'-hydroxy-
10	42.558	42.405	42.655	93510	0.18	13483	0.22	6.94		4-Acetoxyacetophenone
11	48.480	48.380	49.005	55257	0.11	2527	0.04	21.87		Acetic acid, 8-acetoxy-6-benzenesulfonyl-2-thi
12	57.112	56.955	57.280	162987	0.32	14681	0.24	11.10	V	Benzenebutanal, .gamma.,.gamma.,4-trimethyl
13	57.530	57.280	57.630	123632	0.24	7477	0.12	16.53	V	
14	58.435	58.230	58.555	118795	0.23	9810	0.16	12.11	V	Benzene, 1,1'-(1,1,2,2-tetramethyl-1,2-ethaned
15	60.183	59.955	60.305	58284	0.11	6215	0.10	9.38		1-Butanone, 1,4-bis(4-methylphenyl)-
				51670739	100.00	6101250	100.00			

Important Peaks

Peak	R. Time	Compound	Area
6	11.767	Phenol	27655484
7	16.172	Phenyl Acetate (PA)	9560309
9	41.743	*p*-hydroxyacetophenone (p-HAP)	3300107

Chromatogram S10. Gas Chromatogram of Propionalization of Phenol



Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	2.131	2.040	2.210	113156	0.23	46696	1.06	2.42	V	1-Chloro-1-nitrosoethane
2	2.297	2.250	2.325	30333	0.06	11615	0.26	2.61	V	2-Propanone (CAS) Acetone
3	2.375	2.325	2.400	26051	0.05	12245	0.28	2.13	V	Acetic acid, methyl ester (CAS) Methyl acetate
4	2.524	2.440	2.575	73336	0.15	17435	0.40	4.21	V	Acetic acid (CAS) Ethylic acid
5	2.783	2.740	2.845	561354	1.12	244933	5.56	2.29		Propanoic acid, methyl ester (CAS) Methyl pro
6	4.004	3.055	4.085	17005750	33.95	653354	14.83	26.03	V	Propanoic acid (CAS) Propionic acid
7	11.737	11.440	12.135	19156998	38.25	1975776	44.85	9.70	SV	Phenol (CAS) Izal
8	22.483	22.255	22.625	7963820	15.90	1041884	23.65	7.64	V	Propanoic acid, phenyl ester
9	38.975	38.965	39.095	26413	0.05	5480	0.12	4.82	V	anti11,12 syn4,12-4,4,9,10exo-Tetrachloro-11
10	47.506	47.115	48.065	4874840	9.73	360710	8.19	13.51		Propanoic acid, phenyl ester (CAS) Phenyl pro
11	53.695	53.465	53.865	254515	0.51	35083	0.80	7.25		Paroxypropione
				50086566	100.00	4405211	100.00			

Important Peaks

Peak	R. Time	Compound	Area
7	11.737	Phenol	19156998
8	22.483	Phenyl Propionate (PP)	7963820
10	47.506	*p*-hydroxypropiophenone (*p*-HPP)	4874840