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April 27, 2010

RE: **An Examination of 3,4-substitution Effects on Acidity of Methoxy- and Chloro-Substituted Benzoic Acid Derivatives**
By Joey Spicer and Kyle Marks*

Dear Professor Glaser:

We greatly appreciate your response on April 14, 2010, with regard to our paper on benzoic acid derivatives. We were pleased with the positive responses provided by our three reviewers. All three were confident that our paper was up to the standards of publication in *JOC* after only minor revisions. In response to the reviewers' suggestions, we have made the necessary corrections along with a few additions of our own for this revision. Following are our responses to the individual reviewers.

Response to Reviewer 1:
[1.1] As "bubbling oxygen" is a common laboratory technique, it was unnecessary to clarify the procedure in the synthesis of 3,4-dimethoxybenzoic acid.
[1.2] An explanation for the difference in benzoic acid acidity of the meta-substituted compared to the para-substituted benzoic acids was added.

Response to Reviewer 2:
[2.1] The conclusion was made more explicit in the abstract of the paper.
[2.2] The hypothesis was strengthened in the introduction.
[2.3] The significance of the particular selection of benzoic acid derivatives was described in the last paragraph of the introduction, so no additional explanation was added.

[2.4] Furthermore, the distinction between our expectations for both mono- and di-substituted benzoic acids was clearly outlined in the Results and Discussion section.
[2.5] The method used in pK_a determination was added to the introduction.

Response to Reviewer 3:
[3.1] The depiction of 3,4-dimethoxybenzoic acid was corrected to better represent its lowest energy conformation.
[3.2] Figures 1 and 2 were relabeled to Schemes 1 and 2.
[3.3] Per ACS style guide, the article titles were not moved in front of the authors list in the reference citations.

Additional Changes:
[A.1] A graphic of the equilibrium reaction of the two new benzoic acid derivatives was added to the abstract.
[A.2] A figure depicting the HOMOs of benzoate and the corresponding benzoates of the selected di-substituted benzoic acids was added along with an interpretation of this data.
[A.3] Placement of Schemes 1 and 2 was switched.
[A.4] Specific group electronegativity values were added.
[A.5] Errors in reference formatting were corrected.
[A.6] Minor formatting errors were corrected throughout the paper.

Again, we are grateful to the reviewers and the editor for their consideration of our paper and the suggestions that were made. We are confident that we have made all necessary changes so that our paper may have the privilege of being published in *The Journal of Organic Chemistry*.

Sincerely,
Joey Spicer and Kyle Marks

JOC Article
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An Examination of 3,4-substitution Effects on Acidity of Methoxy- and Chloro-Substituted Benzoic Acid Derivatives

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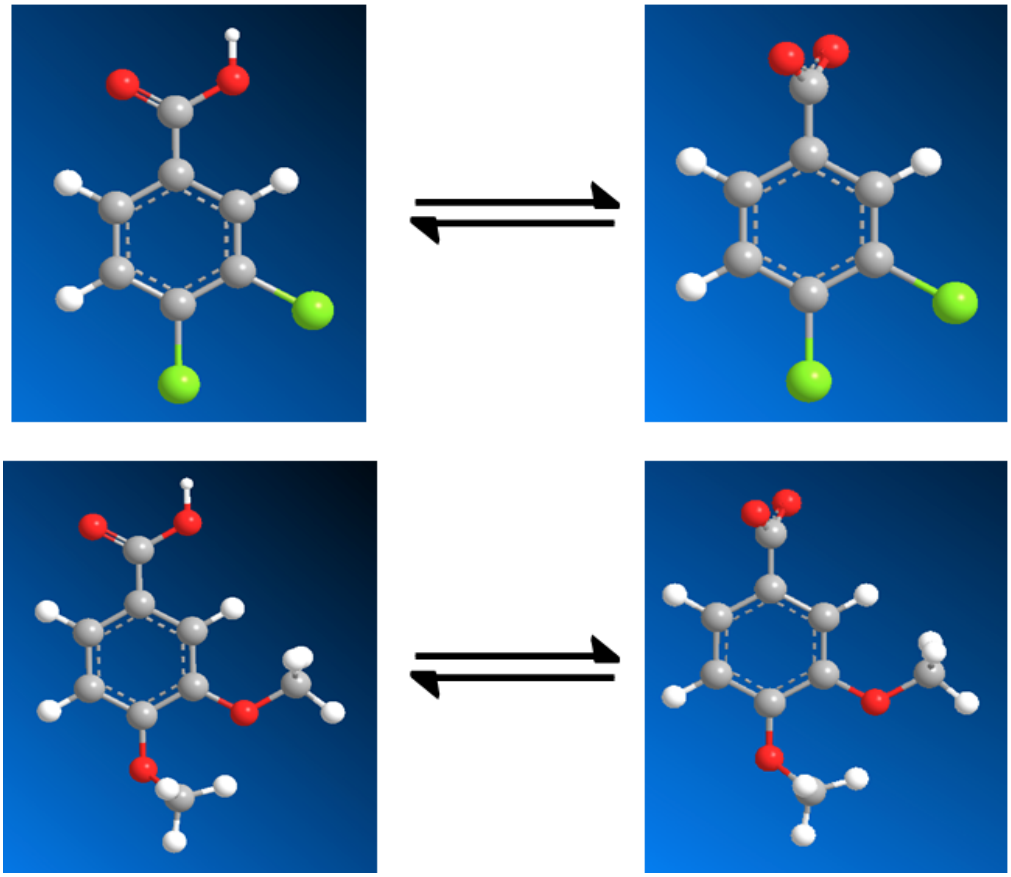


Abstract

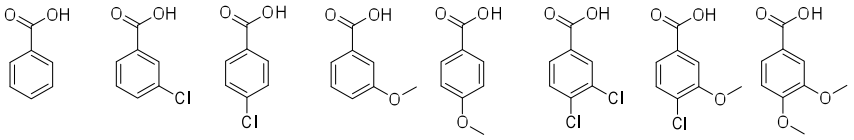
Two new benzoic acid derivatives were synthesized and their pK_as measured in DMSO. The two compounds were 3,4-dimethoxybenzoic acid with a pKa of 11.40 and 3,4 -dichlorobenzoic acid with a pK_a of 9.60. Substituent affects on benzoic acid derivatives will be discussed in terms of both electronegativity and molecular orbital theory to account for the observed pK_as. In this experiment it was found that substitution at the meta position of benzoic controls the acidity of much more than substitution at the para position. Furthermore the 3,4-disubstitutued benzoic acid derivatives showed

intermediate acidity between that of benzoic acid and the monosubstituted form due to steric hindrance.

Introduction

The study of acids is age-old in the field of chemistry. It is so prevalent that there continues to be three definitions of the word acid all measuring the same thing but with different types of molecules. It is important to consider pH for the rate at which reactions proceed.[1,2] It is well know that acidity has major implications when it comes to solubility. Acids are also used widely as catalysts and buffers. Acidity has ties to several structural molecular components including both electronegativity and covalent bond energies.[3]

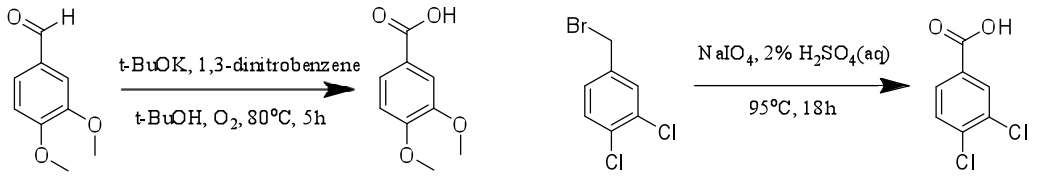
Benzoic acid consists of a carboxylic acid connected directly to a phenyl group. Benzoic acid and its derivatives have a wide variety of uses. For example, benzoic acid was used as an acidic standard because of the ease with which it can be obtained in high purity.[4] Also there is the more known example of a substituted benzoic acid NSAID called aspirin.[5] Due largely to these applications, the pK_a of benzoic acids and their derivatives are important to know. Even more important is the knowledge of how the substituents in a benzoic acid derivative affect the pK_a.



Scheme 1. Benzoic acid and the monosubstituted and disubstituted benzoic acid derivatives discussed in this paper

In this paper the results of the synthesis of two new benzoic acid derivatives are reported. Additionally, the pK_as of the compounds were measured and spectra recorded using UV Vis spectral titration. The substituent effects on pK_a will be discussed in relation to 3,4-substitution patterns with the methoxy group and the chloro group. These groups were chosen in order to observe the effects of ring activators and ring deactivators paired with themselves and each other in comparison with their monosubstituted analogues. It was our belief that an additional identical substituent placed at the para position would have an additive effect on the acidity of the benzoic acid derivative in the same direction as the first and that a combination of chloro and methoxy substituents would resemble cause a pK_a similar to that of benzoic acid. The various benzoic acids studied in this paper are shown in **Scheme 1**.

Materials and Methods



Scheme 2. Syntheses of two benzoic acid derivatives

All starting materials were purchased from Sigma Aldrich, and all reactions were performed using standard laboratory glassware. In the interest of studying the substituent effects on the pK_a of benzoic acid derivatives, two new compounds were synthesized: 3,4-dimethoxybenzoic acid and 3,4-dichlorobenzoic acid. The 3,4-dimethoxybenzoic acid was synthesized by oxidation of 3,4-dimethyoxybenzaldehyde in a solution of tert-

butanol with potassium tert-butoxide and a catalytic amount of 1,3-dinitrobenzene. This reaction had a yield of 93.0%. The 3,4-dicholrobenzoic acid was synthesized by oxidation of 3,4-dichlorobenzyl bromide using $NaIO_4$ and 2% aqueous H_2SO_4. This reaction had a yield of 88%. The two new benzoic acid derivatives and their synthesis is shown in **Scheme 2**. For detailed information about the syntheses of these products, see the supplemental material.

The pK_a values of our new benzoic acid derivatives were determined using a UV-vis spectrometric titration. The end point was considered when the addition of titrant did not change the spectra. The Spectrometer was a Perkin-Elmer Lambda 2S UV-Vis spectrophotometer. Fused silica cells with a path length of 1cm were used. The reference used was pure DMSO.[6] The resulting pKa values can be found in Table 1.

Table 1: pK_a values of methoxy and chloro disubstituted benzoic acids, the corresponding monosubstituted benzoic acids, and benzoic acid. All pK_a values were measured in DMSO.

Compound Number	Compound Name	pK_a Value	Source
1	3,4-dimethoxybenzoic acid	11.40	This Work
2	3,4-dichlorobenzoic acid	9.60	This Work
3	4-chloro-3-methoxybenzoic acid	10.39	7
4	3-chlorobenzoic acid	9.51	8
5	4-chlorobenzoic acid	10.10	7
6	3-methoxybenzoic acid	11.10	7
7	4-methoxy benzoic acid	11.80	7
8	Benzoic acid	11.00	6

Results and Discussion

The relative acidity of molecules is due largely to how well the conjugate base is stabilized through a variety of effects like inductive, resonance, and steric effects. Both of the monochloro substituted benzoic acids are more acidic than benzoic acid itself, due to the inductive effects of the chloro substituent. The chloro group has a high electronegativity of 7.65 eV.[9] As a result, electron density is pulled away from the ring, pulling density through the conjugated pi system and away from the carboxylate site, which stabilizes the full negative charge distributed between the two oxygen atoms of the carboxyl group. Similarly, both monomethoxy substituted benzoic acids are less acidic than benzoic acid due to the resonance donation from oxygen, which pushes electron density into the ring and destabilizes the negative charge on the carboxyl oxygen atoms. As the methoxy group has an electronegativity value of 5.73 eV, it is better able to share electron density than the more electronegative chloro group.[9] A more thorough examination of resonance and inductive effects can be achieved by application of the Hammett equation.[10]

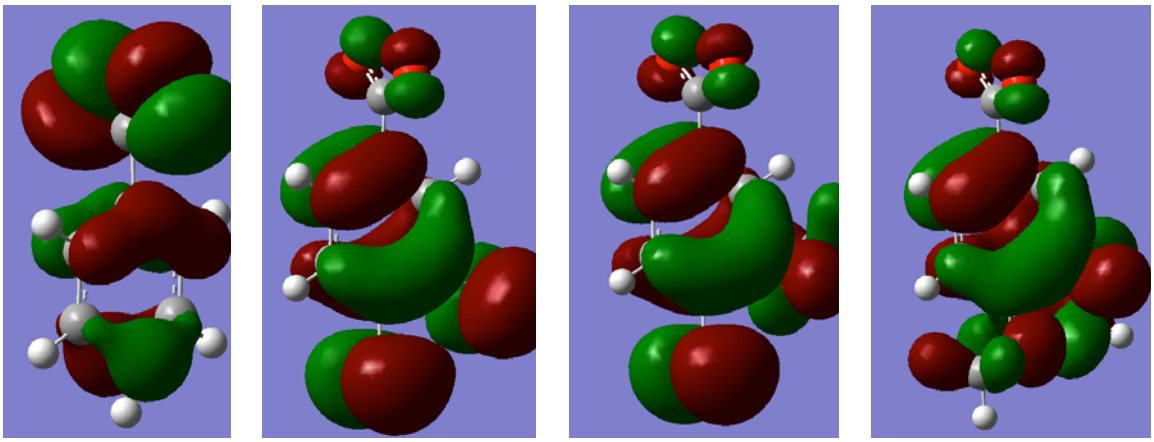
It is interesting to note that mono-substitution at the meta position, whether chloro or methoxy, gives a more acidic molecule than substitution at the para position. The situation is analogous to electrophilic aromatic substitution of benzene. Addition to benzoic acid preferentially occurs at the meta position due to the meta-directing carboxyl group because this forms the more stable carbocation intermediate. Upon examination of the resonance structures for meta and para substitution of benzoic acid, it can be seen that meta substitution results in the more stable carboxylate. While the para substituted

benzoate places more electron density near and on the carboxyl group, the meta substituted benzoate more effectively maintains electron density evenly distributed along the ring.

With these things in mind, it was hypothesized that a second and identical second substituent at the para position would have an additive effect on the acidity of the benzoic acid derivative in the same direction as the first and that the combination of one chloro and one methoxy substituent would even the acidity out to near the level of benzoic acid itself. However, this was not the case in any of the disubstituted situations. The dimethoxy benzoic acid derivative was intermediate in acidity between the two monomethoxy derivatives, closer to the 3-methoxy. In the same way, the dichloro benzoic acid derivative was intermediate in acidity between the two monochloro derivatives but much closer to the 3-chloro in acidity. From this, it seems that the meta position has a much stronger influence on the acidity than does the para, and that having 3,4-substitution is slightly destabilizing relative to 3-substituion, likely due to electron-electron repulsion between electron dense substituents.

When considering the 4-chloro-3-methoxybenzoic acid, it is important to note that even though the methoxy substituent occupies the important meta position, this derivative more closely resembles the analogous monochloro derivative in acidity. Examining the mono-substituted derivatives it is seen that monochloro substituents yield a greater increase in acidity than monomethoxy substituents yield decreases in acidity. This explains the dominance of the 4-chloro over the 3-methoxy substituent in 4-chloro-3-methoxybenzoic acid.

Upon comparison of the highest occupied molecular orbitals of the various disubstituted benzoate derivatives to benzoate, the role of stabilization of the anionic conjugate base in acidity can be seen more clearly (**Figure 1**). In benzoic acid, there is a large concentration of electron density on the carboxylate ions. The 3,4-dichlorobenzoate has significantly less electron density surrounding the carboxyl group. Instead it is more uniformly distributed along the benzene ring, which results in a comparatively lower energy. Although the 4-chloro-3-methoxybenzoate and 3,4-dimethoxybenzoate have significantly less electron density around the carboxyl group, there is successively more electron density being pushed into the ring by the methoxy groups, having a destabilizing effect on the ion. Additionally, each methoxy group has large regions of electron density associated with it, causing destabilization by electron-electron repulsion. In this way, the molecular orbital interpretation of the benzoate derivatives supports the relative acidities described above.



Benzoate | 3,4-dichlorobenzoate | 4-chloro-3-methoxybenzoate | 3,4-dimethoxybenzoate

Figure 1. HOMOs of benzoate and disubstituted benzoate derivatives (Isovalue = 0.02)

Conclusion

In this experiment it was found that substitution at the meta position of benzoic acids has a much stronger effect on acidity than para substitution and that chloro substituents increase acidity more than methoxy substituents decrease acidity. However, 3,4-disubstituted benzoic acid derivatives had acidities intermediate between their respective mono-substituted counterparts, likely due to steric factors from the proximity of the electron dense substituents.

Supplemental Material Available: the appendix contains detailed procedures for the syntheses of 3,4-dichlorobenzoic acid and 3,4-dimethoxybenzoic acid as well as the spectroscopic data for these two compounds including carbon and proton NMR, IR, mass spectrometry, and melting points. This material is available from the authors upon request.

References

(1) DeWolfe, Robert H.; Newcomb, Clark. *Hydrolysis of Formanilides in Alkaline Solutions. J. Org. Chem.* **1971**, 25, 3870-3878.

(2) Stadlbauer, J.; Barnbas, M.; Walker, D. Muonium Reactions with Oxalic Acid and Oxalate Ions in Water: Huge Kinetic Isotope Effects When compared with H. *J. Phys. Chem. A.* **1997**, *101*, 2442-2444.

(3) Plumley, J.; Jeffery, E. Periodic Trends and Index of Boron Lewis Acidity. *J.Phys. Chem. A.* **2009,** 113, 5985-5992.

(4) Morey, G. Benzoic Acid as an Acidimetric Standard. *J. Am. Chem. Soc.* **1912**, *34*, 550-552.

(5) Moriatry, L.; Lally, M.; Carolan, C.; Jones, M.; Clancy, J.; Gilmer, J. Discovery of a "True" Aspirin Prodrug. *J. Med. Chem.* **2008,** *51*, 7991-7999.

(5) Yagupolskii, L. et. al. The immense acidifying effect of the supersubstituent NSO2CF3 on the acidity of amides and amidines of benzoic acids in acetonitrile. *J.*

Chem. Soc., Perkin Trans. **2002,** *2*, 1950–1955.

(7) Pytela, O.; Kulhanek, J.; Ludwig, M.; Riha, V. Chemometircal Analysis of Substituent Effects. *Collect. Czech. Chem. Commun*. **1994**, *59*, 627-638.

(8) Jover, J.; Bosque, R.; Sales, J. QSPR Prediction of pK_a for Benzoic Acids in Different Solvents. *QSAR Comb. Sci.* **2008**, *27*, 563-581.

(9) Profit, F.; Langenaeker, W.; Geerlings, P. Ab Initio Determination of Substituent Constants in a Density Functional Theory Formalism: Calculation of Intrinsic Group Electronegativity, Hardness, and Softness. *J. Phys. Chem.* **1993**, *97*, 1826-1831.

(10) Hansch, C.; Leo, A.; Taft, R. A Survey of Hammett Substituent Constants and Resonance and Field Parameters. *Chem. Rev*. **1991**, *91*, 165-195.

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Supporting Information for

An Examination of 3,4-substitution Effects on Acidity of Methoxy- and Chloro-Substituted Benzoic Acid Derivatives

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Table of Contents

1. Synthesis of 3,4-dimethoxybenzoic acid	3
2. Synthesis of 3,4-dichlorobenzoic acid	3-4
3. Carbon NMR of 3,4-dimethoxybenzoic acid	4
4. Proton NMR of 3,4-dimethoxybenzoic acid	5
5. IR of 3,4-dimethoxybenzoic acid	6
6. Mass Spectrometry of 3,4-dimethoxybenzoic acid	6
7. Carbon NMR of 3,4-dichlorobenzoic acid	7
8. Proton NMR of 3,4-dichlorobenzoic acid	8
9. IR of 3,4-dichlorobenzoic acid	9
10. Mass Spectrometry of 3,4-dichlorobenzoic acid	9

Syntheses:

3,4-dimethoxybenzoic:

In order to synthesize 3,4-dimethoxybenzoic acid, 2.4 mmol of 3,4-dimethoxybenzaldehyde, 8.0 mmol of potassium *tert*-butoxide, and 0.12-0.24 mmol of 1,3-dinitrobenzene were added to 12.0 mL of *tert*-butanol. While stirring with a magnetic stir bar, the reaction mixture was heated to 74-80 ^{o}C and held for 5 h at atmospheric pressure while bubbling oxygen through the mixture. The reaction mixture became dark red after a few minutes, and later changed to orange-brown. After the five hours of heating, the reaction mixture was diluted with 100 mL of water and extracted with three portions of 80 mL ethyl acetate. This ethyl acetate organic phase contained the unreacted substrate, the unconsumed 1,3-dinitrobenzene, and the reaction products. The basic water phase is acidified using concentrated H_2SO_4 to a pH of 1-2 and extracted with ethyl acetate three portions of 80 mL ethyl acetate. This ethyl acetate organic phase contained essentially only the 3,4-dimethoxybenzoic acid product with 93.0% yield with 97.4% selectivity.

3,4-dichlorobenzoic acid:

For preparation of 3,4-dichlorobenzoic acid, 15 mL of 2% aqueous H_2SO_4 was added to a mixture of 3 mmol of 3,4-cholrobenzyl bromide and 3 mmol of $NaIO_4$. The reaction mixture was heated using an oil bath for 18 hours at 95 °C. Then the reaction mixture was cooled to room temperature and extracted with three portions of 40 mL of ethyl acetate. The combined organic phas was washed with saturated sodium thiosulfate solution and water, dried over anhydrous Na_2SO_4, and concentrated under reduced

pressure. The crude product was washed with cold *n*-hexane and recrystallized from suitable solvents to give pure 3,4-dichlorobenzoic acid with 88% yield.

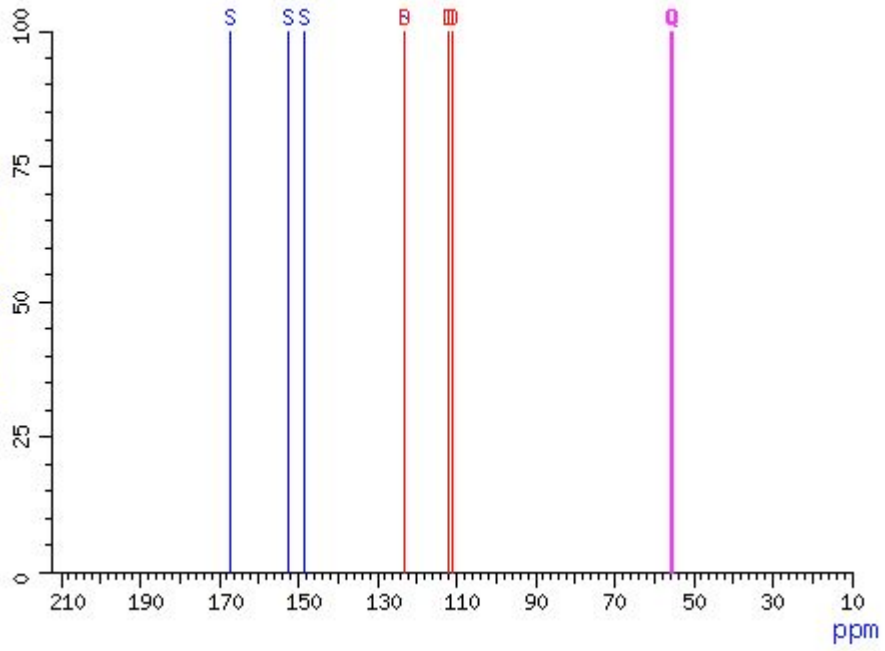

Figure 1. ^{13}C NMR of 3,4-dimethoxybenzoic acid. Spectrum taken using a Bruker WM-360 spectrometer with DMSO as the solvent and TMS standard.

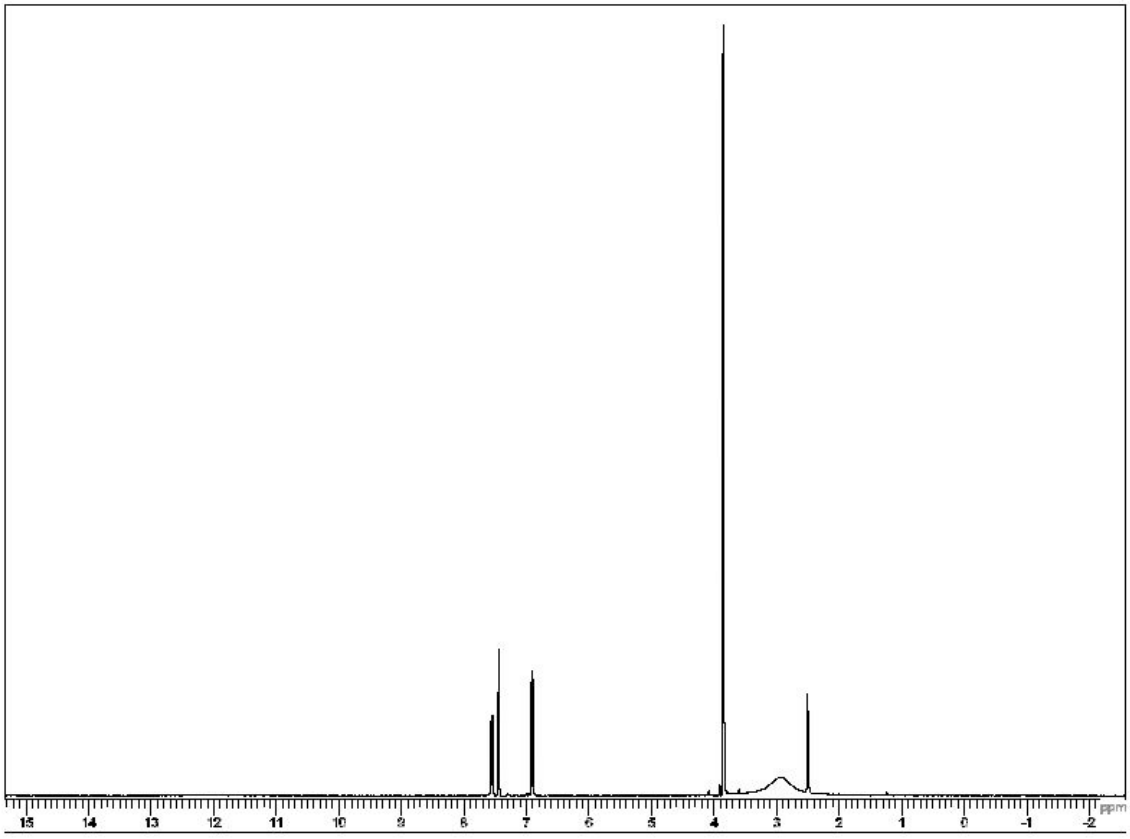

Figure 2. ^{1}H NMR of 3,4-dimethoxybenzoic acid. Spectrum was taken with a frequency of 300 MHz at a temperature of 45 ^{o}C with DMSO as the solvent.

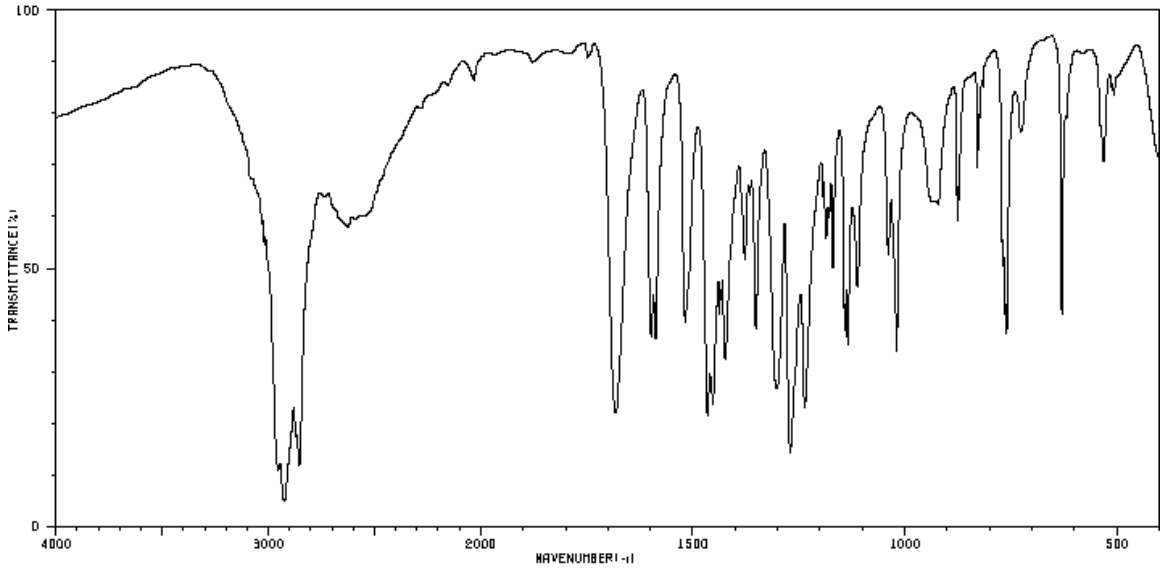

Figure 3. IR spectrum of 3,4-dimethoxybenzoic acid taken with a Nicolet 170SX spectrometer.

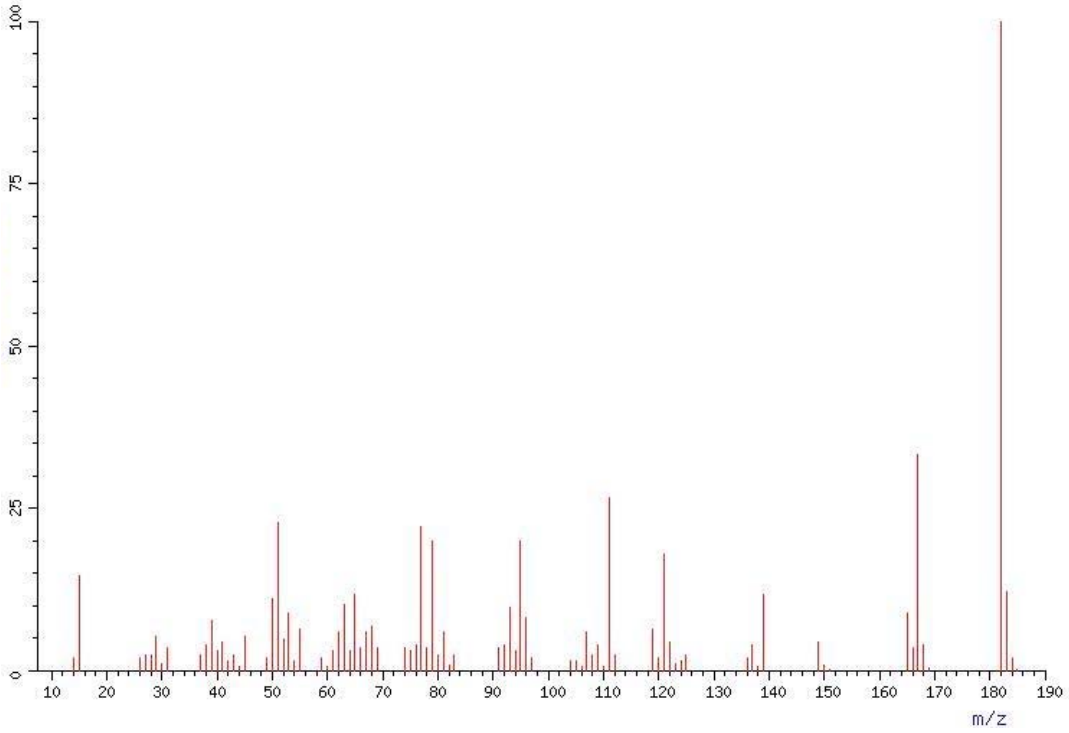

Figure 4. Mass spectrometry of 3,4-dimethoxybenzoic acid

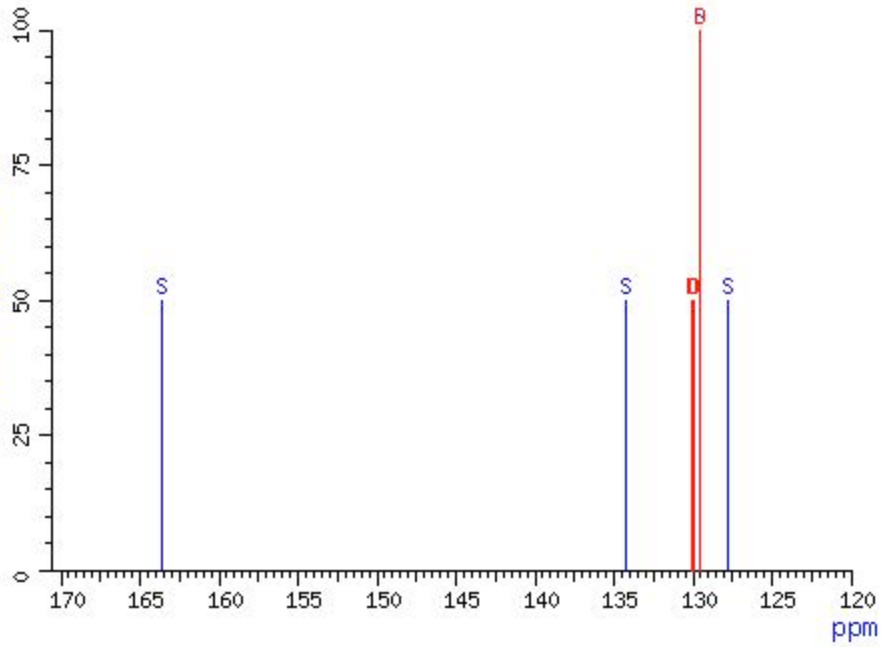

Figure 5. ^{13}C NMR of 3,4-dichlorobenzoic acid. Spectrum was taken using a Bruker WH-90 spectrometer with DMSO as the solvent and TMS standard.

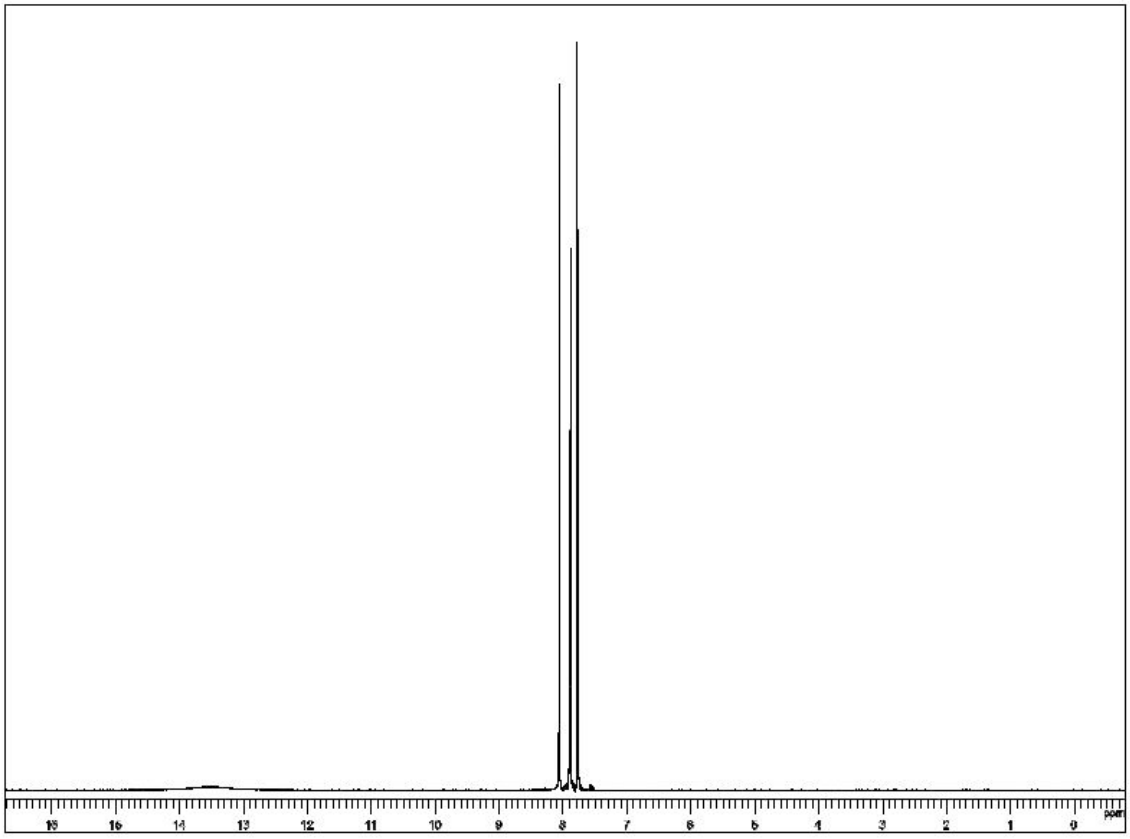

Figure 6. ^{1}H NMR of 3,4-dichlorobenzoic acid

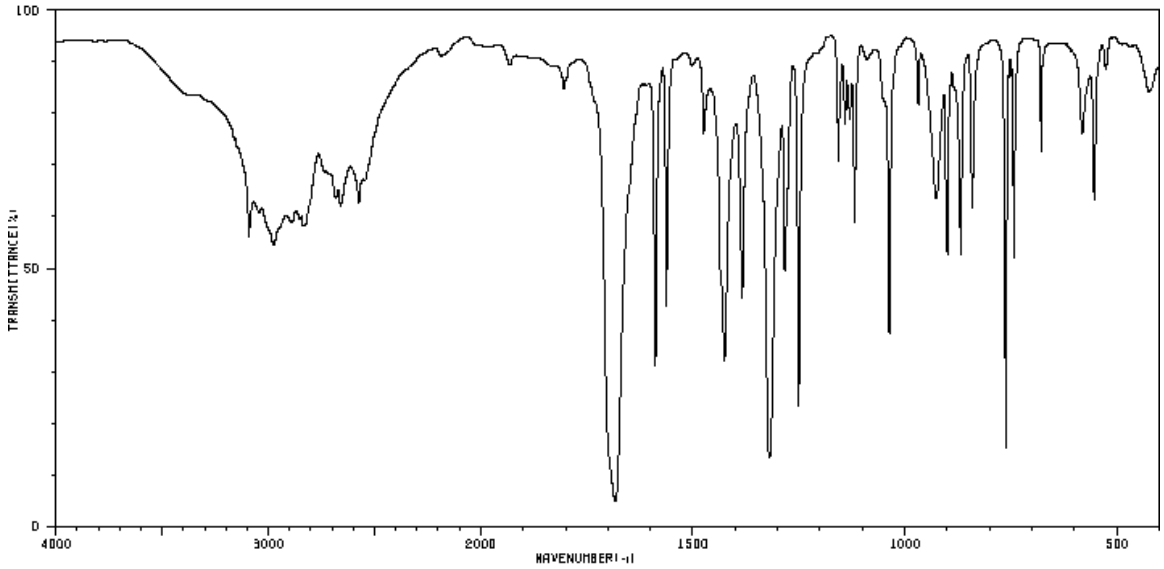

Figure 7. IR spectrum for 3,4-dichlorobenzoic acid. The spectrum was obtained using a Nicolet 170SX spectrometer.

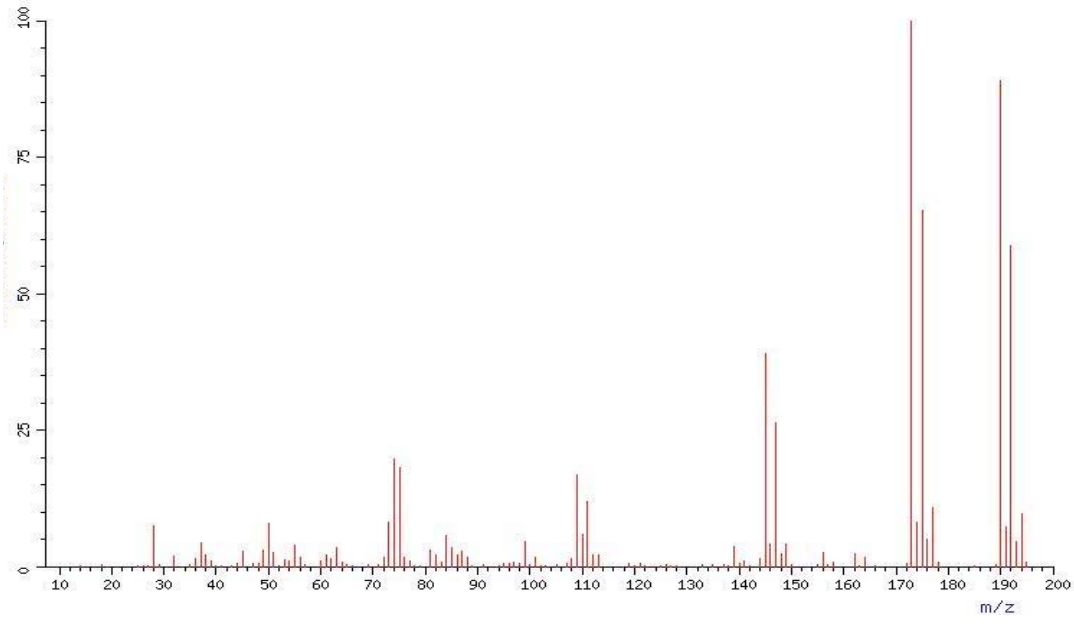

Figure 8. Mass spectrometry for 3,4-dichlorobenzoic acid

Extra References

Bjorsvik, H.; Liguori, L.; Vedia Merinero, J. A Highly Selective Aerobic Oxidation Process Catalyzed by Electron-Deficient Nitroarenes via Single Electron Transfer Processes. *J. Org. Chem.* **2002**, *67*, 7493-7500.

Shaikh, T; Emmanuvel, L.; Sudalai, A. $NaIO_4$ Mediated Selective Oxidation of Alkylarenes and Benzylic Bromides/Alcohols to Carbonyl Derivatives Using Water as Solvent. *J. Org. Chem.* **2006**, *71*, 5043-5046.

American Chemical Society. ^{13}C NMR Spectrum. CNCC-93692-081S. 2010.

American Chemical Society. Proton NMR Spectrum. JEOL GX-400. 2010.

American Chemical Society. IR Absorption Spectrum. NIDA66114. 2010.

American Chemical Society. Mass Spectrum. ID_WID-DLO-020580-1. 2010.

American Chemical Society. ^{13}C NMR Spectrum. CNCC-32042-807F. 2010.

American Chemical Society. Proton NMR Spectrum. SBI_1911643. 2010.

American Chemical Society. IR Absorption Spectrum. NIDA15745. 2010.

American Chemical Society. Mass Spectrum. ID_WID-DLO-018611-8. 2010.