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Received: 10 June 2022 | Revised: 5 October 2022 | Accepted: 21 November 2022

DOI: 10.1002/mrc.5326

RESEARCH ARTICLE

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Anomalous ^{1}H NMR chemical shift behavior of substituted benzoic acid esters

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Abstract

Benzoic acid esters represent key building blocks for many drug discovery and development programs and have been advanced as potent PDE4 inhibitors for inhaled administration for treatment of respiratory diseases. This class of compounds has also been employed in myriad industrial processes and as common food preservatives. Recent work directed toward the synthesis of intermediates for a proprietary medicinal chemistry program led us to observe that the ^{1}H NMR chemical shifts of substituents *ortho* to the benzoic acid ester moiety defied conventional iterative chemical shift prediction protocols. To explore these unexpected results, we initiated a detailed computational study employing density functional theory (DFT) calculations to better understand the unexpectedly large variance in expected versus experimental NMR chemical shifts.

KEYWORDS

^{1}H, benzoic acid esters, density functional theory (DFT), NMR

1 | INTRODUCTION

Nuclear magnetic resonance (NMR) is an invaluable tool for providing data needed for molecular structure characterization, including but not limited to chemical shifts, homonuclear coupling constants and splitting patterns, and peak integration values. It is vital to be able to correctly assign experimentally acquired spectra, and when only a 1D ^{1}H NMR spectrum is available, which is common with simple small molecules, correct NMR chemical shift assignments are especially important in confirming or identifying the chemical structure. There are a variety of available empirical tables[1,2] that can assist help in estimating proton chemical shifts and, additionally, software packages that use large repositories of experimentally determined data to gauge where a given proton will resonate, such as those implemented in the widely used ChemDraw™ software package.[3] The chemical shifts approximated by this method have the benefit of being fast, with low computational hardware demands, and can generally yield reliable results for well-behaved molecules. However, reliance solely on accumulated tables of empirical data can introduce errors in predictions.[4] In situations where the iterative or database chemical shift estimations do not accurately reflect the correct chemical shift, density functional theory (DFT) can be a viable approach to obtain more accurate calculations of troublesome ^{1}H NMR chemical shifts.

Benzoic acid esters are a commonly used scaffold in organic synthesis with applications in drug design, such as PDE4 inhibitors[5] and other commercial processes.[6] The synthesis and production of these various building blocks represent a large industrial effort and accurate

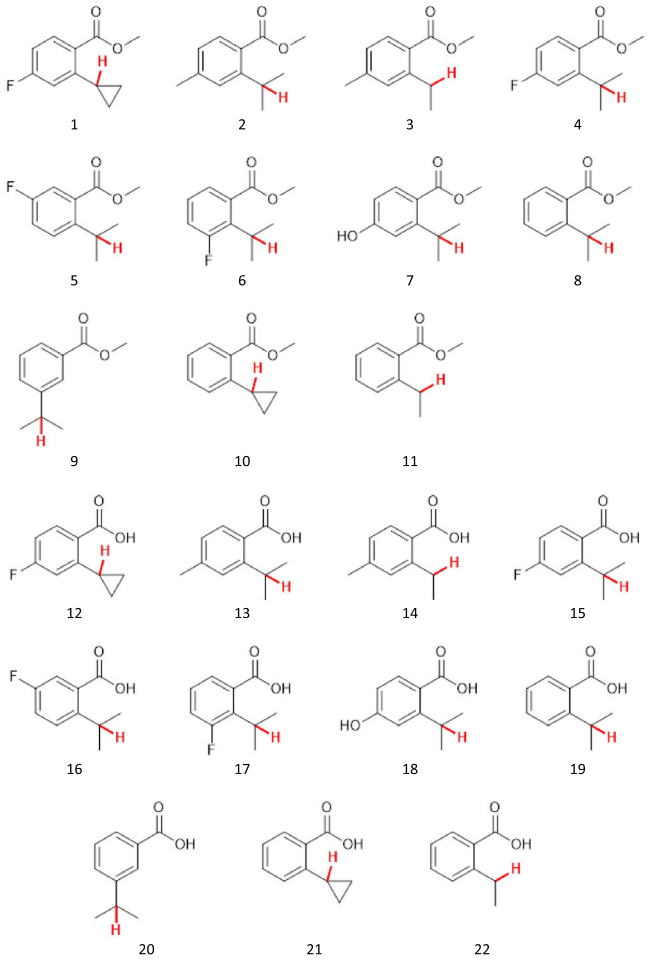

FIGURE 1 The suite of compounds and their corresponding labels of the protons of interest drawn in red

characterization of the structure, and purity of each building block is obviously important. Recently, when characterizing an array of benzoic acid and methyl benzoate derivatives, it was noted that empirically derived chemical shift calculations did not correlate well with the experimentally observed chemical shifts for the substituent protons that are bound at the *ortho* position to the carboxylic acid/methyl ester moiety. In the present contribution, a survey of DFT-predicted, empirically calculated, and experimentally determined chemical shifts of benzylic protons in 11 different benzoic acid analogs and their corresponding methyl esters (Figure 1) is presented in an effort to probe the origin of the seemingly anomalous ^{1}H NMR signature exhibited by this important class of compounds.

2 | EXPERIMENTAL AND COMPUTATIONAL DETAILS

Each compound was dissolved in 600 µl of deuterated chloroform that was then transferred to a 5 mm NMR tube, with the exception of Compounds **15** and **18**, which were dissolved in 600 µl deuterated dimethyl sulfoxide, DMSO-d_6, due to solubility issues. The proton spectra were acquired on a Bruker 600 MHz spectrometer equipped with a TXI probe, and the data were acquired at 298 K.

Monte Carlo conformational searching was performed on each molecule using the ForceGen software package, utilizing their deep search,[7] retaining conformations that were within a 10 Kcal/mol energy window from the lowest energy conformer and a 0.25 Å redundancy root-mean-square (RMS) for the conformers. Utilizing DFT calculations, the conformers were further optimized and had their vibrational modes calculated for the zero-point energy (ZPE) with the B3LYP[8,9] level of approximation and the 6–31 + G(d,p) basis set using the Gaussian 16 software package.[10] Three different pairs of DFT functionals and basis sets (Table 1), using the polarized continuum model (PCM) for solvation, were used to calculate NMR properties. The DFT functional/basis set pairs chosen, B3LYP/6–311++G(2d,p), mPW1PW91[11]/6–311 + G(2d,p),[12,13] and WP04[14]/aug-cc-pVDZ,[15] were from the listed pairs in Pierens[16] publication for conversion of NMR isotropic chemical shift tensors to chemical shift in ppm. The scaling factors were chosen from Pierens to be, for the slope and y-intercept, respectively, −1.0565 and 31.9340 for B3LYP/6–311++G(2d,p), −1.0719 and 31.8733 for mPW1PW91/6–311 + G(2d,p), and −1.0271 and 31.9316 for WP04/aug-cc-pVDZ. The chemical shifts of the conformers were Boltzmann-weighted based on the sum of their electronic energy and ZPE correction. The PCM solvent was set to chloroform for all compounds, besides **15** and **18**, which were set to DMSO, to match with the experimental solvent.

3 | RESULTS AND DISCUSSION

Structures of compounds examined in this study with their corresponding structure numbers are shown in Figure 1. The protons of interest are highlighted in red; all but two, specifically **9** and **20**, have *ortho* "benzylic" substituents. Calculated theoretical, empirical, and experimental chemical shifts are collected in Table 1. In the experimental data, the *ortho* benzylic substituent proton chemical shifts vary substantially as a function of different substitutions on the phenyl ring with a range from 2.81 to 3.99 ppm for the benzoic acid derivatives and from 2.65 to 3.87 ppm for the methyl benzoate derivatives. When comparing the experimental chemical shifts of the *ortho* versus *meta* isopropyl benzylic protons, it is seen that there is a significant difference in chemical shift (Δδ ppm) of the benzylic protons in the benzoic acid (**19**, **20**) and methyl benzoate (**8**, **9**) scaffolds being 0.93 and 0.75 ppm, respectively. This

TABLE 1 Experimental, DFT-predicted, and empirically estimated proton chemical shifts in ppm of the indicated (Figure 1) substituent protons. The DFT-calculated chemical shifts were averaged if the protons had a single resonance in the NMR spectra. The applied DFT functional is listed in the table with the corresponding basis set noted in the footnote below

Molecule	Experiment	B3LYP[a]	mPW1Pw91[b]	WP04[c]	Empirical[d]
1	2.74	3.49	3.53	3.47	1.85
2	3.87	3.88	3.93	3.85	2.88
3	2.98	3.04	3.09	3.02	2.71
4	3.82	3.94	3.98	3.91	2.88
5	3.71	3.81	3.85	3.78	2.88
6	3.52	3.96	4.00	3.91	2.88
7	3.80	4.01	4.04	3.97	2.88
8	3.70	3.82	3.88	3.79	2.88
9[ł]	2.95	2.84	2.90	2.86	2.87
10	2.65	3.27	3.33	3.26	1.85
11	2.99	3.05	3.10	3.03	2.71
12	2.89	3.39	3.43	3.39	1.85
13	3.99	4.05	4.08	4.02	2.88
14	3.19	3.08	3.11	3.07	2.71
15*	3.79	3.99	4.01	3.95	2.88
16	3.75	3.96	4.00	3.94	2.88
17	3.79	4.17	4.21	4.11	2.88
18*	3.90	4.02	4.04	3.97	2.88
19	3.93	3.99	4.03	3.95	2.88
20 [ł]	3.00	2.86	2.91	2.88	2.87
21	2.81	3.43	3.48	3.42	1.85
22	3.09	3.11	3.15	3.09	2.71

Abbreviations: DFT, density functional theory; NMR, nuclear magnetic resonance.
[a]Basis set: 6–311++G(2d,p).
[b]Basis set: 6–311 + G(2d,p).
[c]Basis set: aug-cc-pVDZ.
[d]Obtained from the ChemDraw™ software package.
*Proton spectrum was acquired in d_6-DMSO and PCM was set to DMSO in the calculations.
[ł]Meta substitutions.

observation underscores that there is a significant deshielding effect associated with the carboxylic acid/ester moieties and also possibly from steric effects,[17] which is eluded to by a series of benzyl protons in 1-isopropyl-2-methylbenzene, 1-ethyl-2-isopropylbenzene, and 1,2-diisopropylbenzene. The chemical shifts of the isopropyl methine protons are 3.18, 3.19, and 3.30 ppm,[18] which demonstrates this increase in chemical shift due to increasing the steric crowding of the methine proton. In the *mono*-substituted benzoic acid and methyl benzoate compounds, there is a trend that shows decreasing chemical shift of the benzylic proton from isopropyl (**8, 19**) to ethyl (**11, 22**) to cyclopropane (**10, 21**). The decrease in chemical shift from isopropyl to ethyl substitution can potentially be explained through steric effects[17] that make the benzylic isopropyl proton resonate at a higher frequency, and the cyclopropane moiety resonates with a lower frequency due to the ring shielding of the hydrogens due to the pseudo-aromatic nature of the ring.[19]

When comparing the empirically estimated and experimental *ortho*-substituent proton chemical shifts, which were obtained using the ChemDraw™ software package, the experimental chemical shifts are observed at a lower δ with a range between 0.27 and 0.99 ppm for the benzoic acid methyl ester derivatives (**1–8, 10, 11**) and between a similar range of 0.38 and 1.11 ppm for the benzoic acid derivatives (**12–19,21,22**). ChemDraw™ correctly predicted the benzylic substituent proton chemical shifts for the *meta*-substituted Compounds **9** and **20**, both being within 0.04 ppm of the experimental data, which shows value in these quick predictions, with other chemical shifts in the molecule being reasonable. However, caution must be

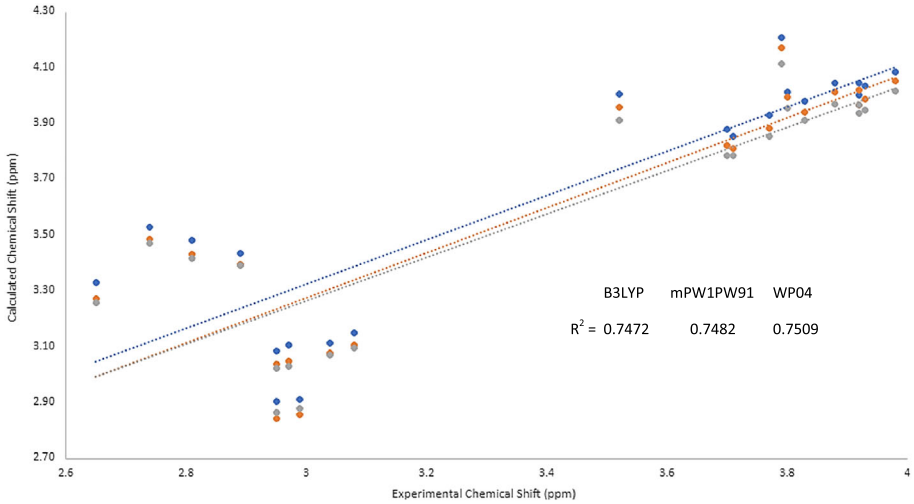

FIGURE 2 This plot shows the calculated versus experimental *ortho*-substituent proton chemical shifts. B3LYP/6–311++G(2d,p) data are shown in blue, mPW1PW91/6–311 + G(2d,p) in orange, and WP04/aug-cc-pVDZ in gray. The lines of best fit are also plotted in the same color.

exercised; the estimations for both the *ortho*- and the *meta*-substituent protons were considered "good quality" values by the ChemDraw™ software, so taking these at face value could lead to confusion as to the validity of the structure.

After examining the results from these predictions, it was clear that DFT calculations were required to prove the structural validity of the compounds in question. When comparing the experimental and DFT-calculated chemical shifts, all three of the DFT/basis set combinations showed reasonable agreement with coefficients of determination (R^2) of 0.9964, 0.9961, and 0.9968 for B3LYP/6–311++G(2d,p), mPW1PW91/6–311 + G(2d,p), and WP04/aug-cc-pVDZ, respectively, when plotting all the protons in each molecule, which is provided in the Supporting Information S1. However, when only plotting the benzylic protons (Figure 2), the correlation is not nearly as high, yielding R^2 values of 0.7472, 0.7482, and 0.7509 and average Δδ ppm of 0.25, 0.23, and 0.20 ppm, respectively. These correlations from DFT are certainly better than the empirically estimated protons, which yielded an R^2 value of 0.5392 and a mean average error (MAE) of 0.74 ppm (provided in the Supporting Information S2), but are not as closely correlated as the other DFT-calculated chemical shifts for these molecules, which shows ambiguity for the accurate calculation of protons in this type of environment. Typical MAE expected in DFT-calculated chemical shifts is between ~0.2 and 0.4 ppm.[20–22] Most of the calculated benzylic proton chemical shifts in this work lie within this range of the experimental values; however 7 out of 22 molecules are outside this range (or very close to), specifically molecules **1**, **6**, **10**, **12**, **17**,**19, and 21**. These results demonstrate that some of the most often used DFT functionals and basis sets still have some gaps even for relatively simple molecules.

The substituent protons of Structures **9** and **20**, which are the two *meta* substitutions, are both well matched by the DFT calculations and the empirical predictions. Structures **8** and **19** are both *ortho* alkyl-substituted, the former being on the methyl benzoate scaffold and the latter being the benzoic acid scaffold. Structure **8** had a slight increase in the upper range of Δδ when compared to the Δδ of Structure **9**, with the MAE range being 0.09 and 0.18 ppm from the DFT calculations and a much larger 0.82 Δδ from the empirical prediction. Molecule **19** exhibited similar Δδ, where DFT calculations have a MAE range from 0.02 to 0.11 ppm and the empirical has a Δδ of 1.05 ppm. The DFT functionals and basis sets all calculated the chemical shift well below the actual chemical shift. The remaining molecules do not exhibit any notable trends. The methyl benzoate derivatives do have a complete set of *ortho*-, *meta*-, and *para*-fluoro substitutions, relative to the alkyl substituent; however, there is no discernible pattern that arises. The chemical shifts of the benzyl proton decrease in the order of *meta*, *para*, and then *ortho*. The same comparison cannot be made for the benzoic acid derivative due to the change of solvent.

4 | CONCLUSIONS

The alkyl substituent protons demonstrated here do not follow conventional iterative chemical shift predictions. The empirically derived chemical shifts did not show a good relation to the experimental values, so DFT was employed. The chemical shifts derived from DFT calculations matched well with the overall molecule's chemical shifts but also struggled with accurately predicting some of the benzyl proton resonance chemical shifts. The reason for the proton resonance being recorded at a higher frequency is due to the close proximity of the alkyl substituent to the carboxylic acid/methyl ester moiety, which deshields the protons.

The similar trend lines for all three of the functionals shown in Figure 2 indicate an innate problem with calculating these chemical shifts. DFT has difficulty with longer range interactions and may be the cause of the poorer correlation between the predicted and the experimental chemical shifts. This is a field of high interest, and advances have been made in this area with new DFT functionals having been created to relieve this problem, and many have been tested for their effectiveness calculating chemical shifts,[23] which is a possible route for future work on this class of compounds to see if these protons can be better modeled with the inclusion of longer range interactions. The current work is a report of chemical shifts, which were found to deviate from the empirical chemical shift predictions, and expansion upon this work would include a more systematic study showing the chemical shifts of ortho, meta, and para substituents, relative to a carboxylic acid, ketone, and alkyl substituents ranging in bulkiness to get a fuller understanding of the downward chemical shifts whether they are from the electron withdrawing groups and/or steric effects.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/mrc.5326.

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How to cite this article: V. Gadikota, R. R. Govindapur, D. S. Reddy, H. J. Roseman, R. T. Williamson, J. G. Raab, *Magn Reson Chem* **2023**, *61*(4), 248. https://doi.org/10.1002/mrc.5326