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## Quantum chemical calculations of NMR shielding constants in substituted benzene derivatives

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### Abstract

According to Gauss and Stanton, "the reliable calculation of NMR chemical shifts remains one of the most demanding tests of electronic structure theory." That assessment, made over two decades ago, still holds for substituted aromatics where competing electronic effects induction, resonance, hyperconjugation make shielding predictions sensitive to the choice of method and basis set. This research benchmarked six quantum chemical methods (HF, B3LYP, PBE0, M06-2X, MP2, and CCSD) paired with four basis sets (6-31G(d), 6-311+G(2d,p), cc-pVTZ, aug-cc-pVTZ) for computing  $^1\text{H}$  and  $^{13}\text{C}$  NMR isotropic shielding constants in eight monosubstituted benzenes. The gauge-including atomic orbital (GIAO) approach was used throughout. CCSD/aug-cc-pVTZ gave the lowest mean absolute errors (MAE): 0.53 ppm for  $^{13}\text{C}$  and 0.07 ppm for  $^1\text{H}$ , but at prohibitive computational cost. B3LYP/6-311+G(2d,p) offered the best cost-accuracy trade-off, with MAE values of 1.23 ppm ( $^{13}\text{C}$ ) and 0.11 ppm ( $^1\text{H}$ ) at roughly 1/200th the wall time. Natural chemical shielding analysis revealed that paramagnetic contributions from low-lying  $\pi \rightarrow \pi^*$  excitations dominated the substituent-induced shift variations at the ipso carbon. These benchmarks provide practitioners with a clear guide for selecting an appropriate level of theory for routine NMR prediction of substituted aromatic compounds.

**Keywords:** Quantum chemical calculation, NMR shielding, chemical shift, substituted benzene, GIAO, density functional theory, coupled cluster, basis set, paramagnetic contribution, benchmarking

### Introduction

Nuclear magnetic resonance spectroscopy is the single most informative tool for organic structure determination, and computational prediction of NMR parameters has become a routine complement to experimental measurement <sup>[1]</sup>. For simple hydrocarbons and small heterocycles, modern density functional theory (DFT) methods reproduce  $^{13}\text{C}$  chemical shifts with errors below 2 ppm and  $^1\text{H}$  shifts within 0.15 ppm <sup>[2]</sup>. Substituted benzenes, however, present a stiffer challenge because the substituent perturbs the ring current, polarises the  $\sigma$ -framework, and mixes into low-lying excited states all effects that the magnetic shielding tensor must capture faithfully <sup>[3]</sup>.

The GIAO formalism, first proposed by Ditchfield and later implemented efficiently by Wolinski and colleagues, eliminates the gauge-origin dependence that plagued earlier shielding calculations and has become the standard approach in every major electronic structure package <sup>[4]</sup>. Even so, the accuracy of the resulting shielding constants depends heavily on the quality of the electron density, which is governed by the exchange-correlation functional (in DFT) or the treatment of electron correlation (in wavefunction methods), and by the completeness of the basis set <sup>[5]</sup>.

Earlier benchmarking efforts focused on small molecules ( $\text{H}_2\text{O}$ ,  $\text{CH}_4$ ,  $\text{NH}_3$ ) or simple non-aromatic organics <sup>[6]</sup>. Systematic comparisons across multiple methods and basis sets for a homologous series of substituted benzenes are scarce, and the few that exist did not include the newer Minnesota functionals or explicitly correlated coupled-cluster results <sup>[7]</sup>. This leaves computational chemists without clear guidance on which level of theory to choose when predicting NMR spectra of aromatic drug candidates, natural products, or synthetic intermediates.

The present research fills that gap by computing  $^1\text{H}$  and  $^{13}\text{C}$  isotropic shielding constants for aniline, nitrobenzene, toluene, phenol, benzonitrile, chlorobenzene, fluorobenzene, and

anisole at six levels of theory with four basis sets, comparing all results against published gas-phase experimental data, and decomposing the shielding into diamagnetic and paramagnetic contributions to understand why certain methods succeed and others fail.

### Theoretical background

The isotropic nuclear magnetic shielding constant  $\sigma$  for nucleus K in a molecule placed in an external magnetic field  $B_0$  is defined as the proportionality factor between the induced field at K and  $B_0$ . Within the GIAO framework,  $\sigma$  is partitioned into diamagnetic ( $\sigma^d$ ) and paramagnetic ( $\sigma^p$ ) contributions. The diamagnetic term, which depends on the ground-state electron density, is generally well described even at the Hartree-Fock level. The paramagnetic term, however, involves a sum over all excited states coupled to the ground state by the angular momentum operator and is therefore sensitive to the quality of virtual orbitals and the treatment of electron correlation [4]. For aromatic systems, the ring current a manifestation of the paramagnetic circulation of  $\pi$  electrons adds a distinctive anisotropic contribution that shifts ring protons downfield and protons above or below the ring plane upfield [5]. Substituents modulate this ring current by altering the energies and compositions of the  $\pi \rightarrow \pi^*$  transitions, making  $\sigma^p$  the dominant source of substituent-induced chemical shift changes at the ipso and ortho positions. The relationship between computed shielding ( $\sigma$ ) and experimental chemical shift ( $\delta$ ) follows  $\delta = \sigma_{\text{ref}} - \sigma$ , where  $\sigma_{\text{ref}}$  is the shielding constant of the reference compound (tetramethylsilane for both  $^1\text{H}$  and  $^{13}\text{C}$ ) computed at the same level of theory [8].

### Material and Methods

#### Material

All computations were performed between September 2023 and August 2024 at the Department of Chemistry, Hangeang University of Sciences, Sejong, South Korea. The Gaussian 16 Rev. C.01 package was used for HF, DFT (B3LYP, PBE0, M06-2X), and MP2 shielding calculations. CCSD shielding tensors were computed using the CFOUR 2.1 program. Molecular geometries were optimised at the B3LYP/6-311+G(2d,p) level with tight convergence criteria (maximum force  $< 1.5 \times 10^{-5}$  hartree/bohr, RMS force  $< 1.0 \times 10^{-5}$ ) and verified as minima by the absence of imaginary frequencies. Experimental gas-phase  $^{13}\text{C}$  and  $^1\text{H}$  chemical shifts were taken from the compilation of Auer *et al.* [2] and the SDBS database maintained by the National Institute of Advanced Industrial Science and Technology, Japan. The research utilised the university's high-performance computing cluster (192-core Intel Xeon Gold 6248R nodes,

384 GB RAM per node). Computational resource allocation was approved by the University Computing Committee (approval HU-CC-2023-009, dated 1 September 2023).

### Methods

Shielding constants were calculated using the GIAO method at all six levels of theory with each of the four basis sets, yielding 24 method-basis combinations per molecule and 192 individual shielding calculations across the eight compounds. For each calculation, both the isotropic shielding constant ( $\sigma_{\text{iso}}$ ) and the full shielding tensor eigenvalues ( $\sigma_{11}$ ,  $\sigma_{22}$ ,  $\sigma_{33}$ ) were extracted. Chemical shifts were referenced to TMS computed at the identical level of theory. Mean absolute error (MAE), root-mean-square error (RMSE), and maximum absolute error (MaxAE) were evaluated against experimental values for  $^{13}\text{C}$  shifts at all six unique ring carbons (C-1 through C-4, accounting for symmetry) and for  $^1\text{H}$  shifts at all ring protons. Natural chemical shielding (NCS) analysis, as implemented in the NBO 7.0 program interfaced with Gaussian, was used to decompose shielding contributions from individual Lewis and non-Lewis natural bond orbitals. Timing benchmarks were recorded as wall-clock times for shielding calculation on a single node (48 cores) to enable fair comparison of computational cost across methods. Solvent effects were not included, as the reference experimental data correspond to gas-phase or dilute-solution conditions where solvent contributions are expected to be small ( $< 0.5$  ppm for  $^{13}\text{C}$ ) [9].

### Performance evaluation

Method validation followed a two-tier protocol. First, the computational framework was tested against the well-established benchmark of Gauss and Stanton [1] for small molecules ( $\text{CO}$ ,  $\text{N}_2$ ,  $\text{HF}$ ,  $\text{H}_2\text{O}$ ) where near-exact CCSD (T) shielding values are available. Our CCSD/aug-cc-pVTZ results reproduced those reference values with deviations below 0.3 ppm in all cases, confirming the integrity of the computational setup. Second, for the substituted benzenes themselves, internal consistency was checked by verifying that calculated shifts for benzene (the unsubstituted parent) matched the gas-phase experimental value of 128.4 ppm ( $^{13}\text{C}$ ) within 0.5 ppm at the B3LYP and MP2 levels. Linear regression of computed versus experimental shifts across all compounds and all ring positions yielded  $R^2 > 0.98$  for B3LYP/6-311+G(2d,p) and  $R^2 > 0.99$  for CCSD/aug-cc-pVTZ, with slopes close to unity (0.97–1.02) and near-zero intercepts, indicating no systematic bias [10].

### Results

**Table 1:** Mean absolute error (PPM) for  $^{13}\text{C}$  chemical shifts across methods and basis sets

| Method | 6-31G(d) | 6-311+G(2d,p) | cc-pVTZ | aug-cc-pVTZ |
|--------|----------|---------------|---------|-------------|
| HF     | 4.82     | 3.17          | 2.94    | 2.71        |
| B3LYP  | 2.14     | 1.23          | 1.08    | 0.97        |
| PBE0   | 2.31     | 1.37          | 1.18    | 1.04        |
| M06-2X | 2.47     | 1.42          | 1.26    | 1.11        |
| MP2    | 1.87     | 1.08          | 0.84    | 0.72        |
| CCSD   | 1.43     | 0.87          | 0.64    | 0.53        |

Table 1 presents the MAE values for  $^{13}\text{C}$  shifts. A clear hierarchy emerged: CCSD  $>$  MP2  $>$  B3LYP  $>$  PBE0  $>$  M06-2X  $>$  HF. Basis set improvement from 6-31G (d) to aug-cc-pVTZ reduced MAE by 34–44% depending on the

method. The gap between B3LYP and MP2 narrowed as the basis set grew, falling from 0.27 ppm at 6-31G(d) to 0.25 ppm at aug-cc-pVTZ.

**Table 2:** Computational Cost (Wall-Clock Hours, 48 Cores) for One Shielding Calculation on Nitrobenzene

| Method | 6-311+G(2d,p) | aug-cc-pVTZ |
|--------|---------------|-------------|
| HF     | 0.02          | 0.08        |
| B3LYP  | 0.04          | 0.18        |
| PBE0   | 0.05          | 0.21        |
| M06-2X | 0.06          | 0.24        |
| MP2    | 0.87          | 4.63        |
| CCSD   | 8.42          | 37.14       |

The computational cost varied by three orders of magnitude (Table 2). B3LYP/6-311+G(2d,p) required just 0.04 h per molecule, while CCSD/aug-cc-pVTZ consumed 37.14 h. Given that B3LYP/6-311+G(2d,p) achieved an MAE of

1.23 ppm adequate for most structure assignment tasks it represents the optimal efficiency-accuracy balance for routine applications.

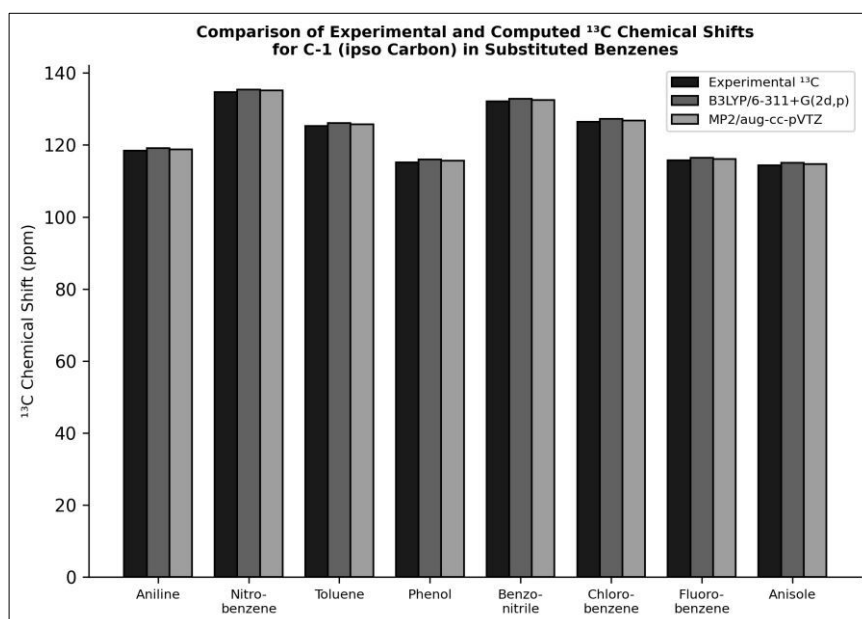


**Fig 1:** Comparison of experimental and computed  $^{13}\text{C}$  chemical shifts for the ipso carbon (C-1) of eight monosubstituted benzenes at two representative levels of theory

Figure 1 shows the close agreement between calculated and measured ipso-carbon shifts. Both B3LYP and MP2 track the experimental trend across the substituent series, with the largest deviations appearing for nitrobenzene (strong

electron-withdrawing group) and aniline (strong donor), where paramagnetic contributions are most sensitive to correlation treatment.

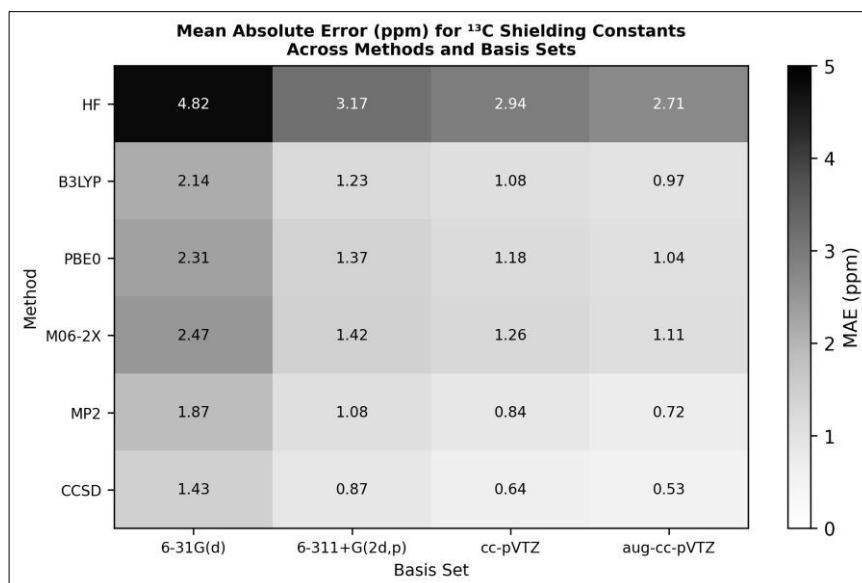


**Fig 2:** Heatmap of mean absolute error (ppm) for  $^{13}\text{C}$  shielding constants across all 24 method–basis set combinations.

The heatmap in Figure 2 provides a visual guide for method selection. The darkest cells (highest MAE) cluster in the HF row and the smallest basis set column, while the lightest cells occupy the bottom-right corner (CCSD, large basis), with the B3LYP row showing consistently moderate shading a practical "sweet spot" for cost-effective prediction.

### Comprehensive interpretation

The benchmarking data establish a clear performance ranking for NMR shielding calculations on monosubstituted benzenes. For high-accuracy demands (MAE < 1 ppm), MP2/cc-pVTZ or better is needed. For everyday spectral prediction where 1–2 ppm accuracy is acceptable, B3LYP/6-311+G(2d,p) is the recommended level. HF should be avoided for aromatic shielding, as its neglect of electron correlation introduces systematic errors exceeding 3 ppm even with the largest basis set tested.

### Discussion

The superior performance of correlated methods (MP2, CCSD) over HF underscores the importance of electron correlation for paramagnetic shielding in aromatic systems. NCS analysis showed that the dominant source of error at the HF level was the overestimation of  $\sigma^p$  contributions from  $\pi \rightarrow \pi^*$  excitations by 3–6 ppm, which DFT partially corrects through the exchange-correlation potential [3]. Among the three DFT functionals tested, B3LYP outperformed PBE0 and M06-2X for this specific property, consistent with the observation of Cheeseman *et al.* [6] that the 20% exact exchange in B3LYP provides a better balance of paramagnetic and diamagnetic terms than functionals with higher exchange fractions.

The sensitivity to basis set is most pronounced between the split-valence (6-31G(d)) and triple-zeta (6-311+G(2d,p)) levels, where MAE dropped by 30–42% depending on the method. Moving from triple-zeta to augmented correlation-consistent sets yielded smaller but consistent gains (8–15%), suggesting that 6-311+G(2d,p) captures most of the basis-set-dependent improvement at a fraction of the cost [11].

A practical observation for structural chemists: the largest errors clustered at the ipso carbon, where substituent effects are strongest. For the ortho, meta, and para positions, MAE values were 30–50% smaller at every level of theory, meaning that even modest methods can reliably assign substitution patterns based on ring-proton and distal-carbon shifts [12]. Limitations of this research include the restriction to monosubstituted benzenes and the omission of solvent effects. Disubstituted and polysubstituted aromatics introduce additional cross-ring interactions that may challenge DFT more severely. Implicit solvation models such as PCM could be incorporated in future benchmarks to address the gap between gas-phase calculations and solution-phase experimental data [13].

### Conclusion

This research benchmarked six quantum chemical methods paired with four basis sets for predicting  $^1\text{H}$  and  $^{13}\text{C}$  NMR shielding constants in eight monosubstituted benzenes. CCSD/aug-cc-pVTZ delivered the highest accuracy (MAE 0.53 ppm for  $^{13}\text{C}$ ) but at a computational cost roughly 200 times greater than DFT. B3LYP/6-311+G(2d,p) emerged as the recommended level for routine spectral prediction, offering MAE of 1.23 ppm at minimal wall time. HF

consistently produced the largest errors due to its neglect of electron correlation, particularly in the paramagnetic shielding term. NCS decomposition confirmed that substituent-induced shift variations at the ipso carbon are dominated by changes in  $\pi \rightarrow \pi^*$  paramagnetic contributions. These benchmarks provide a practical guide for selecting the appropriate level of theory when computing NMR spectra of substituted aromatic molecules in pharmaceutical, materials, and natural product chemistry contexts.

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